Neuroanesthesia and Intensive Care

A meta-analysis of noninvasive weaning to facilitate liberation from mechanical ventilation

[Une méta-analyse d'un sevrage non effractif pour faciliter le retrait de la ventilation mécanique]

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Purpose: To summarize the evidence comparing noninvasive positive pressure ventilation (NPPV) and invasive positive pressure ventilation (IPPV) weaning on mortality, ventilator associated pneumonia and the total duration of mechanical ventilation among invasively ventilated adults with respiratory failure.

Source: Meta-analysis of randomized and quasi-randomized studies comparing early extubation with immediate application of NPPV to IPPV weaning. We selected randomized studies that 1) included adults, with respiratory failure, invasively ventilated for at least 24 hr; 2) compared extubation with immediate application of NPPV to weaning using IPPV; and 3) reported at least one clinically important outcome.

Principal findings: We searched MEDLINE (1966 to 2003), EMBASE (1980 to 2003) and the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 2, 2003) for randomized controlled trials comparing NPPV and IPPV weaning. Additional data sources included personal files, conference proceedings and author contact. Two reviewers independently assessed trial quality and abstracted data. Five studies enrolling 171 patients demonstrated that compared to IPPV, noninvasive weaning decreased mortality (relative risk, 0.41 [95% confidence interval [CI] 0.22–0.76]), ventilator associated pneumonia (relative risk, 0.28 [95% CI 0.09–0.85]) and the total duration of mechanical ventilation (weighted mean difference, -7.33 days [95% CI -11.45 to -3.22 days]).

Conclusions: In the absence of a large randomized controlled trial, this meta-analysis demonstrated a consistent positive effect of noninvasive weaning on mortality. Notwithstanding, the use of NPPV to facilitate weaning, in mechanically ventilated patients, with predominantly chronic obstructive pulmonary disease, is associated with promising, but insufficient, evidence of net clinical benefit at present.

***Objectif** : Résumer les données comparatives sur le sevrage de la ventilation à pression positive non effractive (VPPNE) et de la ventilation à pression positive effractive (VPPE) sur la mortalité, la pneumonie associée à la ventilation et la durée totale de la ventilation mécanique chez des adultes atteints d'insuffisance respiratoire placés sous ventilation effractive.*

***Source** : Une méta-analyse d'études randomisées et quasi-randomisées comparant l'extubation précoce, suivie de l'application immédiate de VPPNE, au sevrage de la VPPE. Les études sélectionnées 1) incluaient des adultes atteints d'insuffisance respiratoire, placés sous ventilation effractive pendant au moins 24 h ; 2) comparaient l'extubation, suivie immédiatement de VPPNE, au sevrage de la VPPE et 3) reportaient au moins un résultat clinique important.*

***Constatations principales** : Les études randomisées et contrôlées comparant la VPPNE et le sevrage de la VPPE ont été repérées dans MEDLINE (1966 à 2003), EMBASE (1980 à 2003) et Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 2, 2003). Des fichiers personnels, les comptes rendus de conférences et des collègues ont complété nos sources. Deux réviseurs indépendants ont évalué la qualité des études et les données résumées. Cinq études, sur 171 patients, ont démontré que le sevrage de la VPPNE, comparé à celui de la VPPE, a réduit la mortalité (risque relatif (RR), 0,41 [intervalle de confiance de*

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95 % [IC] 0,22–0,76]), la pneumonie associée à la ventilation (RR, 0,28 [IC de 95 % 0,09–0,85]) et la durée totale de la ventilation mécanique (différence moyenne pondérée, -7,33 jours [IC de 95 % -11,45 à -3,22 jours]).

***Conclusion** : En l'absence d'une grande étude randomisée et contrôlée, cette méta-analyse a démontré un effet positif, régulièrement obtenu, du sevrage non effractif sur la mortalité. Néanmoins, l'usage de la VPPNE pour faciliter le sevrage de la ventilation mécanique, chez des patients atteints surtout de maladie pulmonaire obstructive chronique, est associé à des indices prometteurs, mais insuffisants, de bénéfices cliniques évidents.*

PATIENTS with acute respiratory failure (ARF) frequently require endotracheal intubation (ETI) and mechanical ventilation to sustain life. While invasive ventilation is effective, it has been associated with the development of complications including respiratory muscle weakness,[1] upper airway pathology,[1] ventilator associated pneumonia (VAP)[1] and sinusitis.[2] Ventilator associated pneumonia, in turn, is associated with increased morbidity and a trend toward increased mortality.[3] For these reasons, minimizing the duration of invasive mechanical ventilation is an important goal of critical care medicine.[4]

Use of noninvasive positive pressure ventilation (NPPV) may provide a means of reducing the duration of invasive ventilation for intubated patients recovering from ARF. Noninvasive positive pressure ventilation, unlike conventional invasive ventilation, is achieved with an oronasal, nasal or total facemask (covering the entire face) connected to a ventilator and does not require an artificial airway. Noninvasive positive pressure ventilation has been shown to augment tidal volume, reduce breathing frequency, rest the muscles of respiration and improve gas exchange.[5] The effectiveness of NPPV as an initial treatment modality in decreasing mortality and ETI rates in acute exacerbations of chronic obstructive pulmonary disease (COPD) has been demonstrated in randomized controlled trials and meta-analyses.[6,7]

Noninvasive positive pressure ventilation can provide partial ventilatory support to patients recovering from respiratory failure who require mechanical support but have regained the ability to breathe spontaneously and can be extubated. Since no tracheal prosthesis is used with NPPV and the cough reflex is preserved, the risk for development of VAP is reduced.[8,9] Other potential benefits of noninvasive weaning include a reduced requirement for sedation,[10] decreased psychological distress[11] and preservation of important functions including speech and eating.[12] A study of COPD patients with acute hypercapneic respiratory failure demonstrated that while the physiologic and clinical responses to the delivery of noninvasive and invasive pressure support were similar, significantly lower dyspnea scores and higher tidal volumes were achieved with noninvasive pressure support.[13] Noninvasive positive pressure ventilation has been identified by professional organizations including the American College of Chest Physicians, American Association for Respiratory Care and American College of Critical Care Medicine as a promising weaning modality that may decrease the duration of intubation and improve patient outcomes.[14] Potential limitations of NPPV include the need to relinquish a protected airway, desiccation of oral secretions and the ability to provide partial ventilatory support.

The first report to describe the successful use of NPPV in liberating patients with weaning failure from invasive positive pressure ventilation (IPPV) was published in 1992.[15] Thereafter, four uncontrolled prospective studies were reported in which patients with tracheostomies,[16] tracheostomies and translaryngeal airways[17] and those not meeting conventional discontinuation criteria[18,19] were weaned using NPPV. More recently, randomized controlled trials (RCTs) comparing the alternative weaning strategies have been published. The purpose of this review was to summarize the evidence comparing the effect of the alternative weaning strategies on mortality, VAP, the total duration of mechanical ventilation and other important clinical outcomes.

Methods

We searched MEDLINE (January 1966 – July 2003), EMBASE (January 1980 – July 2003) and the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 2, 2003) using the following Mesh headings: *respiratory insufficiency (explode), respiratory failure (explode), positive pressure respiration (explode), positive end-expiratory pressure, artificial ventilation (explode)* and *ventilator weaning (explode)*. No language restrictions were applied. The search was conducted independently and in duplicate. Citations were screened on the basis of the title and abstract and potentially eligible studies were retrieved in full. One reviewer (K.B.) manually searched abstracts published in conference proceedings of the *American Journal of Respiratory and Critical Care Medicine*, *Intensive Care Medicine, Critical Care Medicine* and *Chest* from January 1995 – December 2002. Bibliographies of retrieved articles were reviewed to identify potentially relevant trials. Authors of included studies and review articles were contacted to identify unpublished work.

We identified randomized or quasi-randomized (allocation based on order) RCTs involving adults, invasively ventilated for at least 24 hr with acute respiratory failure. We selected trials that compared extubation with immediate application of NPPV to continued weaning using IPPV. We included trials that reported at least one of mortality, VAP, weaning failures, intensive care unit (ICU) or hospital length of stay (LOS), the total duration of mechanical ventilation (including invasive and noninvasive ventilation), duration of endotracheal mechanical ventilation (ETMV; time wherein mechanical ventilation was delivered through an artificial airway using author's definitions), duration of ventilation related to weaning, adverse events or quality of life. We excluded studies comparing NPPV and IPPV in the immediate postoperative setting and application of NPPV and supplemental oxygen to unassisted oxygen following elective or unplanned extubation. Two reviewers (K.B., N.A.) independently selected articles meeting inclusion criteria. Disagreements were resolved by consensus.

Two authors (K.B., N.A.) independently evaluated studies for the following validity features: random allocation, allocation concealment, similarity at baseline (with regard to age, gas exchange, spirometric indices and illness severity), blinded outcomes assessment, control of cointerventions, (including bronchodilator, corticosteroid, antibiotic and sedation administration), completeness of follow-up and adherence to the intention-to-treat principle. In addition, we assessed for the following study design characteristics specific to weaning trials: use of daily screening to identify patients capable of spontaneous breathing, inclusion of permissive weaning criteria and/or conduct of a spontaneous breathing trial (SBT), *a priori* criteria for SBT failure, explicit weaning protocols or guidelines and discontinuation and reintubation criteria. Permissive weaning criteria included formal assessment of any of the following: minute ventilation, tidal volume, vital capacity, respiratory rate, rapid shallow breathing index, Glasgow coma scale, presence of spontaneous breathing and a cough reflex, requirement for positive end-expiratory pressure and ability to maintain arterial oxygen saturation $\geq 90\%$ with a fractional concentration of oxygen (FiO_2) ≤ 0.50. At each stage, reviewers compared results and differences were resolved by consensus. We contacted authors of the primary research if additional data were required to assess validity.

Categorical and continuous data were summarized using relative risk (RR) and the weighted mean difference (WMD) as summary estimates of effect, respectively. We used the random effects model to pool data quantitatively if studies were similar with regard to the populations studied, interventions applied and outcomes reported and where we could reasonably expect a similar direction and magnitude of treatment effect.[20] An evaluation of the heterogeneity of the data, using the Q-test,[21] with a threshold of *P*-value < 0.10, was conducted to determine the appropriateness of pooling the results. RevMan analyses 1.0.1 was used for all analyses. If an outcome was reported at two time points, we included the later measurement in the pooled analyses. An *a priori* sensitivity analysis was planned to assess the effect of excluding quasi-randomized studies from analyses of mortality and the incidence of VAP. Subgroup analyses were planned to assess the impact of the etiology of respiratory failure (COPD *vs* mixed populations) on mortality and the proportion of weaning failures. For these outcomes, we tested the difference in RR between subgroups to assess whether potential explanations of heterogeneity identified sets of studies with significantly different estimates of treatment effect using a Z-test. We considered a *P*-value ≤ 0.05 to be statistically significant. We assessed interobserver agreement for study inclusion by the kappa (κ) statistic.[22] A κ of < 0.40 was considered to represent poor agreement, while values between 0.40 and 0.75 and > 0.75 represented moderate and excellent agreement, respectively.

Results

Using the multifaceted search strategy, we identified ten potentially relevant articles for more detailed evaluation. Five publications[23–27] fulfilled the inclusion criteria, including one abstract publication[27] and one article published in Chinese.[25] The two reviewers achieved complete agreement upon independent assessments of study eligibility ($\kappa = 1.0$).

The five identified studies enrolling 171 patients represent an international experience using NPPV for weaning (Italy, France, Spain, China and the United States). Two studies[23,25] included exclusively COPD patients and three included mixed patient populations.[24,26,27] In the latter studies, COPD was diagnosed in approximately 75% of patients in two studies[24,26] and in one third of patients in the remaining study.[27] Patients were considered difficult-to-wean in one study[24] and persistent weaning failures in another study.[26] Two trials were multicentre.[23,26] Table I presents the method of identification of participants, inclusion and exclusion criteria, interventions applied (including the mode of NPPV administration, patient-ventilator interfaces used, methods for delivering support [continuous *vs* intermittent] and outcomes reported) in individual studies.

TABLE I Patient populations and interventions

Study Year (n)	*Eligibility criteria*	*Inclusion criteria*	*Exclusion criteria*	*Interventions*		*Outcomes reported*
				Extubation and NPPV	*IPPV*	
Nava 1998 (50)	COPD (AE) MV > 36–48 hr pH ≤ 7.33 Elevated bicarbonate PaO_2 ≤ 45 mmHg Severe dyspnea No other etiology	Permissive criteria Failure of a 1-hr T-piece trial	Cardiac arrest Cardiogenic edema Aortic aneurysm Neurologic diseases Cancer Myocardial infarction GI perforation Postoperative Sepsis Trauma Coagulopathy	PS mode with face mask Initial PS set to achieve prior $PaCO_2$, pH, RR < 25 to 30 beats·min^{-1} and satisfactory ABGs PS delivered 20–22 hr·day^{-1} during first 48 hr separated by periods of SB with supplemental oxygen PS decreased by 2 to 4 cm H_2O·day^{-1} with at least 2 periods of SB·day^{-1} of increasing duration Discontinued: criteria + successful 3 hr SB period	Initial PS set to achieve prior $PaCO_2$ and pH and RR < 30 beats·min^{-1} PS titrated to RR < 25 beats·min^{-1} and SBT performed twice daily using T-piece or CPAP < 5 cm H_2O Discontinued: criteria + successful 3 hr SBT	60-day mortality Successful weaning at 60 days Incidence VAP Total duration of MV in ICU ICU length of stay Adverse events Tracheostomy
Girault 1999 (33)	ACRF Obstructive and restrictive difficult to wean MV ≥ 48 hr	Screening after 48 hr MV Permissive criteria Failure of a 2-hr T-piece trial	Ineffective cough Difficult intubation Swallowing disorder Bronchial congestion Lack of cooperation Recent GI surgery Intestinal ileus	PS or flow mode delivered by face or nasal mask EPAP adjusted to offset iPEEP NPPV delivered intermittently separated by at least 2 periods of SB·day^{-1} of gradually increasing duration starting at 1–2 hr At least 2 periods of observation per day Discontinued: physician observation of SB	Initial PS set to maintain RR 20 to 30 beats·min^{-1} with initial flows 0.1–0.25 sec PEEP to offset iPEEP PS titrated by 3–5 cm H_2O according to tolerance At least 2 periods of observation per day Discontinued: physician observation of 2 periods of decreased PS Extubation permitted when PS ≤ 8 cm H_2O	90-day mortality Hospital mortality Successful weaning Incidence VAP Duration MV related to weaning Duration of ETMV Mean daily period of support ICU length of stay Hospital length of stay Adverse events Reintubation Tracheostomy
Chen 2001 (24)	COPD (AE) pH ≤ 7.35 PaO_2 ≤ 45 torr RR > 30 beats·min^{-1} MV > 48–60 hr	Permissive criteria	NA	PS mode titrated to RR and ABGs Gradual decrease in PS and PEEP Discontinued: criteria + successful 3 hr SB period	Initial PS titrated to RR and ABGs Gradual decrease in PS and PEEP Discontinued: criteria + successful 3 hr SBT	Mortality Incidence VAP Duration MV related to weaning Hospital length of stay
Ferrer 2003 (43)	ARF Persistent weaning failure MV > 72 hr	Daily screening Permissive criteria Failure of 2 hr T-piece trial on 3 consecutive days	Cranial/facial trauma or surgery Recent gastric or esophageal surgery Tracheotomy Upper GI bleeding Excessive secretions Lack of cooperation	Bilevel ventilation in ST mode delivered continuously during first 24 hr Periods of SB of gradually increasing duration	AC or PS titrated at physician discretion Daily T-piece trials until extubation Discontinued: after successful 2 hr SBT	ICU mortality, 90–day mortality Incidence VAP Duration MV related to weaning Duration of ETMV Total duration of MV ICU length of stay Adverse events Reintubation Tracheostomy
Hill* 2000 (21)	ARF Not restricted to COPD	Daily screening Failure of 30-min T-piece trial	Excessive secretions Difficult intubation Unable to tolerate PS < 15 cm H_2O Unable to breathe spontaneously	VPAP – PS in ST mode by face and nasal mask delivered continuously Titrated to RR and V_T At least one period of SB/d of gradually increasing duration	PS titrated to RR and V_T T-piece trials permitted	Mortality Successful weaning Duration of ETMV Reintubation

COPD = chronic obstructive pulmonary disease; AE = acute exacerbation; ACRF = acute on chronic respiratory failure; ARF = acute respiratory failure; MV = mechanical ventilation; PaO_2 = arterial partial pressure of oxygen; $PaCO_2$ = arterial partial pressure of carbon dioxide; GI = gastrointestinal; NPPV = noninvasive positive pressure ventilation; IPPV = invasive positive pressure ventilation; AC = assist control; PS = pressure support; RR = respiratory rate; V_T = tidal volume; CPAP = continuous positive airway pressure; VPAP = ventilator (delivered) positive airway pressure; ST = spontaneous timed; SBT = spontaneous breathing trial; SB = spontaneous breathing; ABGs = arterial blood gases; VAP = ventilator associated pneumonia; ETMV = endotracheal mechanical ventilation; NA = not available; ICU = intensive care unit; PEEP = positive end-expiratory pressure; EPAP = intermittent positive end-expiratory pressure; iPEEP = expiratory positive airway pressure. *Trial published in abstract form only. To convert torr to kPa, multiply by 0.13333.

TABLE II Quality assessment of trials

Study Year (n)	*Allocation concealed*	*Blinded outcome assessment*	*Baseline similarity*	*Control of cointerventions*	*Daily screening*	*Permissive criteria*	*Criteria for initial SBT failure*	*Weaning guideline or protocol*	*Reintubation criteria*
Nava[23] 1998 (50)	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes
Girault[24] 1999 (33)	Yes	No	Yes	Partial	Yes	Yes	Yes	Yes	No
Chen†[25] 2001 (24)	No	No	Yes	Partial	No	Yes	NA	No	No
Ferrer[26] 2003 (43)	Yes	No	Yes	Partial	Yes	Yes	Yes	No	Yes
Hill*[27] 2000 (21)	Yes	Yes	Yes	Yes	Yes	Uncertain	Yes	Yes	Yes

SBT = spontaneous breathing trial; NA = not applicable. *Trials published in abstract form only. †Trial reported randomization by order; may be truly randomized (consecutive patients) or quasi-randomized (assignment to treatment groups based on order of presentation).

Screening of invasively ventilated patients for eligibility occurred daily[26,27] and after 48 hr of mechanical ventilation.[24] Candidates for weaning were identified following 36 to 48 hr of invasive ventilation, including six to eight-hours of paralysis,[23] 48 to 60 hr of ventilation[25] or after three days of invasive ventilation.[26] Eligibility for study inclusion and randomization was based upon meeting predefined permissive weaning criteria[23–26] and failure of either a single 30-min,[27] one-hour[23] or two-hour[24] T-piece trial, or alternatively, two-hour T-piece trials conducted on three consecutive days.[25] Details of the methods used to initiate, titrate and discontinue NPPV and IPPV are summarized in Table I.

We attempted to contact all authors to confirm and supplement information pertaining to study methods; four authors responded.[23,24,26,27] Overall, the included studies were of moderate to good quality and fulfilled the validity criteria to a similar extent. In all studies, allocation to treatment group was by random assignment, with one study randomizing by order.[25] All trials adhered to the intention-to-treat principle, had complete follow-up and used discontinuation criteria. Table II summarizes the remaining validity features and study design characteristics of the included trials. Due to the nature of the interventions, blinding of caregivers and patients was not possible; however, one study blinded data analysts. Features, including the use of daily screening of patients receiving invasive support (three studies), criteria to proceed with a SBT (four studies) and for prerandomization SBT failure (four studies) were incorporated into the study design to limit bias in the identification of weaning candidates. Bias in the administration of the interventions was limited through use of protocols or guidelines to reduce mechanical support in both treatment groups (three studies), discontinuation criteria (all studies) and objective criteria for reintubation following a failed attempt at extubation (three studies).

Mortality was reported at 60 days,[23] 90 days[24,26] and at an undisclosed time point.[25,27] While point estimates from each trial favoured NPPV, no study reported a significant difference. The pooled data demonstrated a strong mortality benefit favouring noninvasive weaning (RR 0.41, [95% confidence interval (CI) 0.22 to 0.76], $P = 0.005$) with a nonsignificant test for heterogeneity ($P = 0.83$), (Figure 1). While four studies reported the proportion of patients developing VAP,[23–26] only three reported criteria for diagnosing VAP.[23,25,26] The definitions were similar among trials with respect to the requirement for a new and persistent radiographic infiltrate and additional supportive criteria. In two studies,[23,25] additional criteria included fever or peripheral leukocytosis or a positive Gram stain from an endotracheal aspirate. In the remaining study,[26] additional criteria included fever or hypothermia, leukopenia or leukocytosis or isolation of at least one potentially pathogenic microorganism

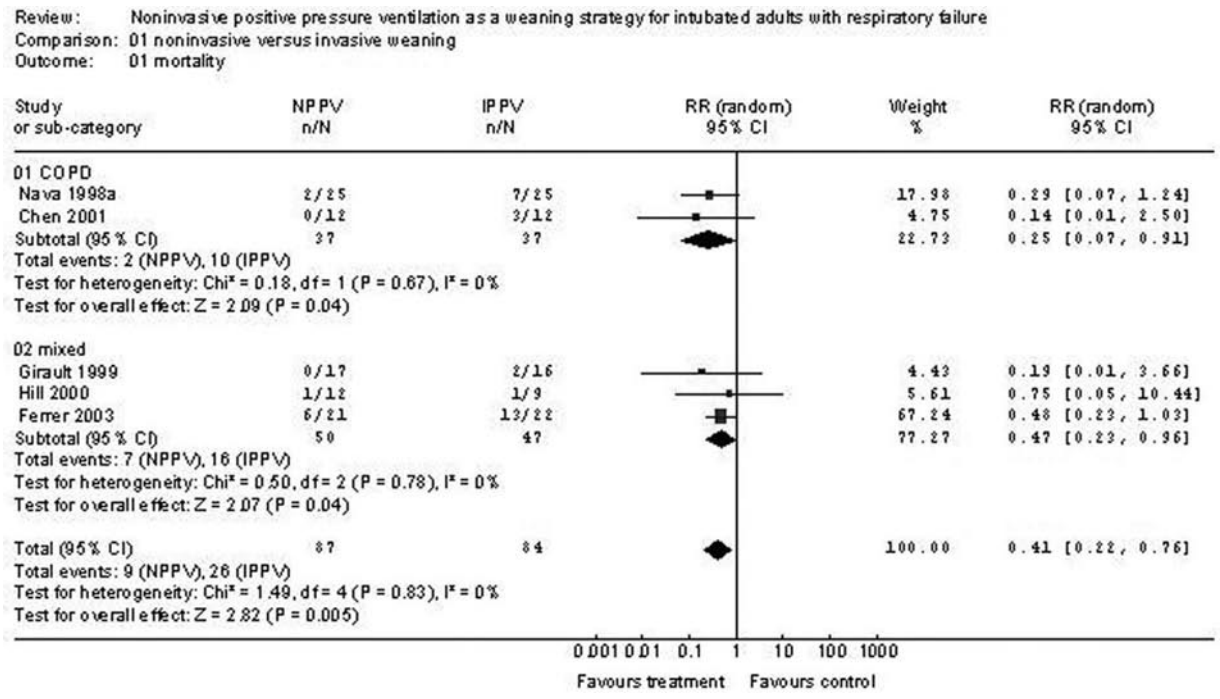

FIGURE 1 Forest plot of mortality in studies comparing invasive and noninvasive weaning.

from a respiratory sample, blood or pleural fluid. When data from these four studies were pooled, a beneficial effect of the noninvasive strategy in decreasing VAP was demonstrated (RR 0.28, [95% CI 0.09 to 0.85], $P = 0.03$), (Figure 2). The test for heterogeneity was not significant ($P = 0.27$). We pooled two studies[23,26] with estimates of the total duration of mechanical ventilation. The aggregate estimate demonstrated a significantly shorter duration of mechanical ventilation using noninvasive weaning (WMD -7.33 days, [95% CI -11.45 to -3.22], $P = 0.0005$). The test for heterogeneity was nonsignificant ($P = 0.59$).

Table III presents additional outcomes reported in the included studies. Three trials reported hospital LOS.[24–26] The pooled estimate revealed a significant reduction in hospital LOS using noninvasive weaning (WMD -7.33 days, [95% CI -14.05 to -0.61], $P = 0.03$). Similarly, three trials reported the ICU LOS[23,24,26] and favoured noninvasive weaning (WMD -6.88 days, [95% CI -12.60 to -1.15], $P = 0.02$), however, results were heterogeneous across studies ($P = 0.05$). The duration of ventilation related to weaning was available for three studies,[24–26] with one study[24] reporting this outcome in successful patients. There was no effect of noninvasive weaning on the duration of duration of invasive mechanical ventilation (WMD -2.72 days, [95% CI -15.58 to 10.14], $P = 0.68$) however a significant reduction in the duration of ETMV favouring noninvasive weaning (WMD -6.32 days, [95% CI -12.12 to -0.52], $P = 0.03$) was apparent in three trials[24,26,27] reporting this outcome. Significant heterogeneity was noted in aggregating results from trials reporting the duration of ventilation related to weaning and ETMV (Table III).

Three trials reported the proportion of patients successfully weaned.[23,24,27] Successful weaning was defined as not requiring initiation of NPPV or reintubation within 72 hr[23] or not requiring reintubation within 48 hr.[27] The remaining trial[24] defined weaning failure as the need for reintubation by day five following extubation or when extubation was not possible within five days of initiation of weaning efforts in the IPPV group; however, all patients considered weaning failures were reintubated within five days. In the absence of significant heterogeneity, the pooled data showed no effect of NPPV on the proportion of weaning failures (RR 0.82, [95% CI 0.29 to 2.32], $P = 0.71$). Adverse events during weaning were reported in three studies.[23,24,26] One study reported adverse events related to the noninvasive approach, including cutaneous irritation, nasal abrasions and gastric distension.[23] Other studies reported the incidence of general

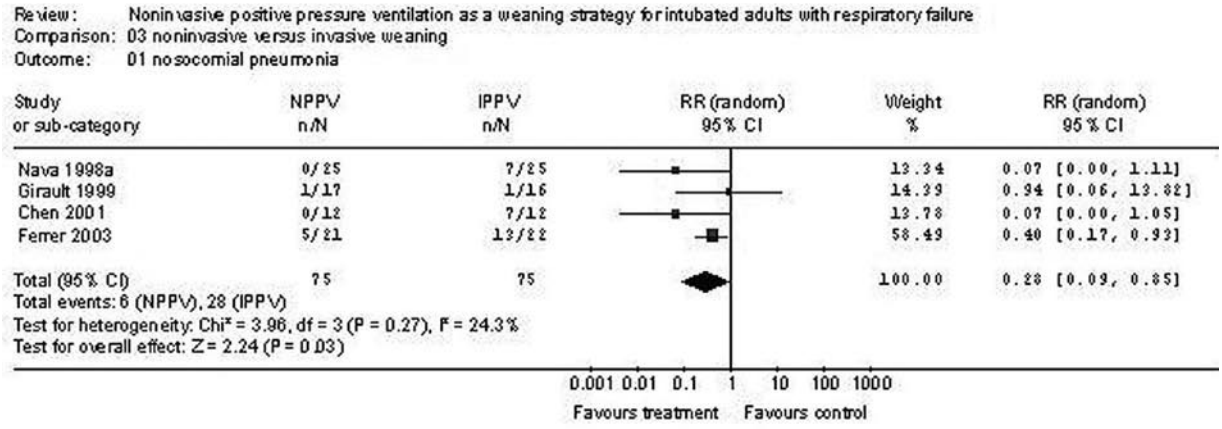

FIGURE 2 Forest plot of ventilator associated pneumonia in studies comparing noninvasive and invasive weaning.

TABLE III Comparison of noninvasive and invasive weaning on outcomes

Outcome	*Number of trials (participants)*	*Test of heterogeneity P-value*	*Summary estimate RR or WMD (95% CI)*	*P-value*
Mortality	5 (171)	$P = 0.83$	RR 0.41 (0.22, 0.76)	$P = 0.005$‡
Incidence of VAP	4 (150)	$P = 0.27$	RR 0.28 (0.09, 0.85)	$P = 0.03$‡
Weaning failure	3 (104)	$P = 0.20$	RR 0.82 (0.29, 2.32)	$P = 0.71$
ICU LOS	3 (126)	$P = 0.05$†	WMD -6.88 (-12.60, -1.15)	$P = 0.02$‡
Hospital LOS	3 (100)	$P = 0.20$	WMD - 7.33 (-14.05, -0.61)	$P = 0.03$‡
Total duration of MV	2 (93)	$P = 0.59$	WMD -7.33 (-11.45, -3.22)	$P = 0.0005$‡
Duration of MV related to weaning	3 (92)	$P < 0.00001$†	WMD -2.72 (-15.58, 10.14)	$P = 0.68$
Duration of ETMV	3 (97)	$P = 0.08$†	WMD -6.32[-12.12, -0.52]	$P = 0.03$‡

RR = relative risk; WMD = weighted mean difference; RE = random effects; CI = confidence interval; VAP = ventilator associated pneumonia; ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; ETMV = endotracheal mechanical ventilation.
†Significant statistical heterogeneity; ‡Statistically significant treatment effect. Continuous outcomes are represented in days.

medical[24,26] and intervention-related complications including sinusitis,[24] sepsis,[26] pneumonia,[26] and barotrauma.[26] The incidence of reintubation was reported separately from the proportion of weaning failures in three studies[24,26,27] while three studies[23,24,26] reported the requirement for tracheostomy. Variability in the selection and reporting of adverse events in the included studies precluded pooling of this data. No study reported quality of life.

Excluding a quasi-randomized trial[25] maintained the statistically significant reductions in mortality (RR 0.43, [95% CI 0.23 to 0.81], $P = 0.010$) and VAP (RR 0.37, [95% CI 0.15 to 0.93], $P = 0.03$) favouring noninvasive weaning. While reductions in mortality using NPPV were noted for both COPD ($n = 2$) and mixed population ($n = 3$) subcategories (RR 0.25, [95% CI 0.07 to 0.91], $P = 0.04$ and RR 0.47, [95% CI 0.23 to 0.96], $P = 0.04$), the magnitude of benefit was larger for patients with COPD with a nonsignificant between group difference ($z = 0.84$, $P = 0.40$). Similarly, we noted a nonsignificant between group difference ($z = 1.49$, $P = 0.14$) in weaning failures in COPD ($n = 1$) compared to mixed population ($n = 2$) subcategories. While summary estimates for weaning failures were qualitatively different (RR 0.38, 95% CI 0.11 to 1.25, $P = 0.11$ and RR 1.28, 95% CI 0.45 to 3.60, $P = 0.64$), neither summary RR was statistically significant. When studies enrolling at least 50% COPD ($n = 4$) were compared those enrolling < 50% COPD ($n = 1$), a possible mortality benefit favouring the NPPV approach in COPD patients was noted (RR 0.39, [95% CI 0.21 to 0.75], $P = 0.004$ and RR 0.75,

[95% CI 0.05 to 10.44], $P = 0.83$). A nonsignificant trend toward fewer weaning failures in COPD patients weaned noninvasively was apparent (RR 0.38, [95% CI 0.11 to 1.25], $P = 0.11$ and RR 1.28, [95% CI 0.45 to 3.60], $P = 0.64$); however the between group difference was not significant ($z = 0.47$; $P = 0.64$).

Discussion

We identified five, small studies comparing noninvasive and invasive weaning among 171 patients with predominantly COPD. Compared to invasive weaning, noninvasive weaning significantly decreased mortality, VAP, the total duration of mechanical ventilation and hospital LOS. The noninvasive approach to weaning also significantly decreased ICU LOS and the duration of ETMV amidst statistically significant between-study variation. There was no effect of noninvasive weaning on the duration of mechanical ventilation related to weaning or the proportion of weaning failures and insufficient data to pool adverse events or quality of life. Subgroup analyses suggested fewer weaning failures and the potential for a greater mortality benefit in COPD patients compared to mixed populations, although differences were nonsignificant.

Our study has several strengths. First, we used a clearly defined, multimodal strategy (including electronic searches of computerized databases, hand searching abstracts from conference proceedings and bibliographies of selected and review articles and direct author contact) to identify relevant literature. Second, we conducted duplicate, independent screening of citations, evaluation of studies for inclusion, data abstraction and validity assessment to limit bias in the identification, selection and appraisal of relevant literature.[28] Third, in addition to established criteria to appraise RCT quality,[29] we used criteria, specific to the weaning process, in our validity assessment. Additional criteria (for the identification of weaning candidates and titration, discontinuation and reinitiation of mechanical support) were included because of their potential to influence the duration of mechanical ventilation in unblinded weaning trials.

The major threat to the validity of this systematic review is the decision to pool studies that differed slightly with regard to eligibility criteria, modes of ventilation and in the methods for delivering support (continuous *vs* intermittent). We used clinical judgment to decide *a priori* to combine studies that were more similar than different and where we could reasonably expect a similar direction and magnitude of treatment effect. We used a random-effects model to pool data, which usually generates more conservative confidence limits for estimates of treatment effect.[30] Figures 1 and 2 demonstrate that the confidence intervals of the individual studies overlap. This suggests that random error is a reasonable explanation for between-study variance and that pooling was appropriate.[31] In addition, the small number of events in the included studies limits the strength of the inferences that can be made from this review. While nonpharmacologic treatments are seldom studied as extensively as pharmacologic agents prior to widespread implementation, a large RCT is required to confirm the direction and increase the precision of estimates of treatment effect in our meta-analysis.

The included studies highlight the use of NPPV to advance extubation and wean selected patients with predominantly COPD. While a consistent direction of treatment effect of noninvasive weaning on mortality was demonstrated in all studies, subgroup analyses suggested that the mortality benefit of noninvasive weaning may be best realized in patients with COPD. Patients with COPD may be ideal candidates for noninvasive support, whether applied as an initial treatment or during weaning, as NPPV counteracts respiratory muscle fatigue due to expiratory flow limitation, tachypnea and the development of intrinsic positive end-expiratory pressure.[5] Notwithstanding, the physiologic derangements of other etiologies of respiratory failure may be less amenable to noninvasive support during weaning. While the literature supports that patients with cardiogenic pulmonary edema benefit from initial treatment with continuous positive airway pressure and NPPV, limited RCT evidence exists to support NPPV as an initial treatment for other etiologies of hypoxemic respiratory failure including acute lung injury, pneumonia, respiratory failure following lung resection and in immunocompromised hosts.[32] Since hypoxemic respiratory failure includes conditions with diverse pathophysiology and of mixed severity,[32] patient response to initial treatment with NPPV or application of NPPV to facilitate weaning can be expected to be more variable and may depend not only on the timing of NPPV application but on the extent, density and rate of resolution of the air space consolidation.

For safety reasons, blinding of clinicians and participants was not feasible in the included RCTs. Under these circumstances, the importance of limiting bias related to differential implementation of study interventions or cointerventions cannot be overstated. Explicit criteria were used in most studies to identify candidates early in the weaning process. To this end, several studies included daily screening,[33] with or without conduct of a SBT, to minimize delayed identification of patients ready to wean. However, failure to include

these prerandomization study design considerations would not be expected to systematically influence the total duration of mechanical ventilation or time to discontinuation between study arms but may contribute to between study heterogeneity. Conversely, differential application of post-randomization weaning strategies, including mechanical ventilation titration and discontinuation may introduce intervention bias. All studies, in this review adopted at least one strategy to limit intervention bias. Comparable reductions in mechanical support between treatment strategies were achieved through the use of protocols or guidelines to reduce mechanical support in both treatment groups (three studies), objective discontinuation criteria (all studies) and reintubation criteria (three studies). Future weaning trials should consider standardizing important cointerventions such as sedation administration since protocolized sedation has been shown to decrease the duration of mechanical ventilation and ICU LOS.[34]

Variability was present in the definitions used for VAP and the duration of mechanical support and in the description of adverse events in the included studies. Including microbiologic confirmation as a criterion for VAP diagnosis may result in increased VAP detection in the invasive weaning strategy as the endotracheal tube facilitates specimen collection. Similarly, in the absence of a high reintubation rate, the duration of ETMV would be expected to be shorter in patients randomized to noninvasive weaning by design. Consequently, the more important outcomes to be compared are the total duration of any mechanical support and the duration of ventilation related to weaning. While we noted a significant decrease in the total duration of mechanical ventilation favouring NPPV, no effect of the noninvasive strategy was noted on the duration of mechanical ventilation related to weaning. Variability in the selection and reporting of outcomes may have contributed to between study heterogeneity during pooling of outcomes pertaining to the duration of mechanical support. Further study is required to clarify the impact of noninvasive weaning on these outcomes. No study reported the impact of the alternative weaning strategies on quality of life or the implications of reintubation on mortality[35–37] and ICU LOS.[37]

Notwithstanding the limitations of the included trials, several important observations can be made from our systematic review and meta-analysis. First, noninvasive weaning reduced mortality and hospital LOS in the populations studied. We hypothesize that the decrease in mortality with NPPV may be attributable, in part, to the decreased incidence of VAP, resulting from a reduced duration of ETI[38] or reduced requirement for tracheostomy.[39] Similarly, the reduction in hospital LOS of approximately seven days may be related to the decreased incidence of VAP and duration of ventilation. Second, exploratory analyses suggested that the mortality benefit of noninvasive weaning may be greater in patients with COPD. However, the small number of patients with events and studies limits the strength of the conclusions that can be made from these analyses. Third, the methods used to identify weaning candidates and to titrate and discontinue mechanical support varied among the included studies. Daily screening minimizes delayed identification of patients 'ready to wean'.[40–42] Whereas failure to include daily screening prior to randomization would not be expected to bias ventilation outcomes between study arms, it may increase the duration of mechanical support and limit study interpretability. Conversely, differential titration and discontinuation of mechanical ventilation following randomization could bias the duration of ventilation between study arms. These features represent important study design considerations for unblinded weaning trials to minimize biased estimates of the duration of mechanical support.

Similar to trials assessing the role of NPPV in post-extubation respiratory failure,[43–45] trials assessing NPPV as a weaning modality aim to decrease the period of invasive mechanical support; but differ in two critical ways. First, when used to facilitate weaning, NPPV is applied immediately following extubation without the expectation of resuming completely autonomous breathing. Second, application of NPPV to facilitate weaning precedes a decline in clinical status. Conversely, application of NPPV for post-extubation respiratory failure follows development of recurrent respiratory distress. While our results suggest a beneficial role for NPPV following intubation in decreasing mortality in patients with predominantly COPD, RCTs investigating NPPV in patients with postextubation respiratory failure have not demonstrated analogous benefits. This suggests that timing of application of NPPV following extubation may influence outcomes and highlights the importance of early NPPV application.

In their efforts to expeditiously wean patients from mechanical ventilation, clinicians are challenged by an implicit trade-off between the deleterious effects of ETI and the risks associated with premature extubation. While no individual study mortality estimate achieved statistical significance, summary estimates from five small studies of moderate to good quality demonstrated a consistent positive effect on overall mortality. However, the small number of patients with

events and studies limits the strength of the inferences that can be made. Our meta-analysis also highlights that the net benefits, risks and consequences associated with noninvasive weaning remain to be fully elucidated. Realization of these promising outcomes in the future will require broader feasibility assessments, clinician acceptance of the noninvasive approach to weaning and demonstration of acceptable weaning failure, reintubation and adverse event rates. Noninvasive weaning is a promising approach to achieve liberation in selected patients recovering from ARF. A large RCT is required to confirm the clinical effectiveness of noninvasive weaning and to delineate the patient population who will benefit most from this approach.

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