Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review

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Competing interests: None declared.

This article has been peer reviewed.

This article is based on a Cochrane review published in the *Cochrane Database of Systematic Reviews* 2013; issue 12, DOI: 10.1002/14651858.CD004127.pub3

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***CMAJ* 2014. DOI:10.1503/cmaj.130974**

ABSTRACT

Background: Noninvasive ventilation has been studied as a means of reducing complications among patients being weaned from invasive mechanical ventilation. We sought to summarize evidence comparing noninvasive and invasive weaning and their effects on mortality.

Methods: We identified relevant randomized and quasirandomized trials through searches of databases, conference proceedings and grey literature. We included trials comparing extubation and immediate application of noninvasive ventilation with continued invasive weaning in adults on mechanical ventilation. Two reviewers each independently screened citations, assessed trial quality and abstracted data. Our primary outcome was mortality.

Results: We identified 16 trials involving 994 participants, most of whom had chronic obstructive pulmonary disease (COPD). Compared with invasive weaning, noninvasive weaning significantly reduced mortality (risk ratio [RR] 0.53, 95% confidence interval [CI] 0.36 to 0.80), weaning failures (RR 0.63, 95% CI 0.42 to 0.96), ventilator-associated pneumonia (RR 0.25, 95% CI 0.15 to 0.43), length of stay in the intensive care unit (mean difference [MD] −5.59 d, 95% CI −7.90 to −3.28) and in hospital (MD −6.04 d, 95% CI −9.22 to −2.87), and total duration of mechanical ventilation (MD −5.64 d, 95% CI −9.50 to −1.77). Noninvasive weaning had no significant effect on the duration of ventilation related to weaning, but significantly reduced rates of tracheostomy (RR 0.19, 95% CI 0.08 to 0.47) and reintubation (RR 0.65, 95% CI 0.44 to 0.97). Mortality benefits were significantly greater in trials enrolling patients with COPD than in trials enrolling mixed patient populations (RR 0.36 [95% CI 0.24 to 0.56] v. RR 0.81 [95% CI 0.47 to 1.40]).

Interpretation: Noninvasive weaning reduces rates of death and pneumonia without increasing the risk of weaning failure or reintubation. In subgroup analyses, mortality benefits were significantly greater in patients with COPD.

Patients with acute respiratory failure often require endotracheal intubation and mechanical ventilation to sustain life. Although it is effective, invasive ventilation is associated with complications including respiratory muscle weakness, upper airway pathology, ventilator-associated pneumonia[1] and sinusitis.[2] Ventilator-associated pneumonia has been associated with increased morbidity and a trend toward increased mortality.[3] Consequently, minimizing the duration of invasive mechanical support without increasing the risk of adverse events is an important goal for critical care clinicians.[4]

Noninvasive ventilation may provide a means of reducing the duration of invasive mechanical support for patients with acute respiratory failure. Unlike invasive ventilation, noninvasive ventilation is delivered with an oronasal, nasal or total face mask, or a helmet, connected to a ventilator, and does not require an artificial airway. One can then administer oxygen, augment inhaled volume and apply extrinsic positive end-expiratory pressure to counteract intrinsic positive end-expiratory pressure, similar to invasive ventilation.[5] Noninvasive ventilation has been shown to augment tidal volume, reduce breathing frequency, rest the muscles of respiration and improve gas exchange.[6] Randomized controlled trials (RCTs) and meta-analyses have shown that noninvasive ventilation decreases mortality and intubation rates compared with standard medical treatment alone in the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD).[7,8]

Many patients undergo intubation when noninvasive ventilation has failed or is contraindicated. To mitigate complications associated with protracted invasive ventilation, researchers have investigated the role of noninvasive ventilation in weaning; that is, replacing invasive support with noninvasive support in patients who are ready to be weaned but not yet ready for mechanical ventilation to be removed. Because no artificial airway is used with noninvasive ventilation and the cough reflex is preserved, the risk for ventilator-associated pneumonia is reduced.[9,10] Additionally, noninvasive weaning may reduce the requirement for sedation,[11] decrease psychological distress[12] and permit speech and oral intake.[13] However, with noninvasive weaning, clinicians must anticipate drying of secretions, accept that only partial ventilatory support can be provided and forfeit a protected airway. Since its initial description as a weaning modality,[14] RCTs and meta-analyses[15,16] have compared noninvasive ventilation with alternative weaning strategies. A recent guideline suggested that noninvasive ventilation could be used to facilitate early liberation from mechanical ventilation in patients who have COPD at centres with expertise in its use.[17] The purpose of this review was to critically appraise, summarize and update a systematic review and meta-analysis of the effect of noninvasive weaning compared with invasive weaning on important outcomes in light of new evidence.

Methods

Data sources and search criteria

We updated a previously conducted search of MEDLINE (January 1966 to May 2013) and Embase (January 1980 to May 2013) via OvidSP, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 5, 2013) without language restrictions (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130974/-/DC1). Two reviewers (KB, NA) independently screened citation titles and abstracts. Two reviewers (KB, MM) updated manual searches of abstracts from conference proceedings published in the *American Journal of Respiratory and Critical Care Medicine*, *Intensive Care Medicine*, *Critical Care Medicine* and *Chest* from April 2009 to May 2013. We reviewed the reference lists of retrieved articles to identify potentially relevant trials, contacted authors to obtain additional information regarding study methods where needed and searched for ongoing trials at Controlled-trials.com and ClinicalTrials.gov. Ethics approval was not required for this systematic review.

Study selection

We included randomized and quasirandomized trials that enrolled adults with respiratory failure who required invasive mechanical ventilation for at least 24 hours, compared extubation with immediate application of noninvasive ventilation with continued invasive weaning and reported at least one of the following outcomes: mortality (primary outcome), ventilator-associated pneumonia, weaning failure (using authors' definitions), length of stay in the intensive care unit (ICU) or hospital, total duration of ventilation, duration of ventilation related to weaning, duration of invasive ventilation, adverse events or quality of life. We excluded trials that compared noninvasive weaning with invasive weaning in the immediate postoperative setting, compared noninvasive ventilation with unassisted oxygen supplementation or investigated noninvasive ventilation after unplanned extubation.

Data extraction and quality assessment

Two authors (KB, NA), unblinded to the source of the reports, abstracted data regarding study methods (randomization, allocation concealment, completeness of follow-up, selective outcomes reporting) using a standardized form. Disagreements regarding study selection and data abstraction were resolved by consensus and arbitration with a third author (MM).

Data synthesis and statistical analysis

We pooled data across studies using random effects models. We derived summary estimates of risk ratio (RR) and mean difference (MD) with 95% confidence intervals (CIs) for binary and continuous outcomes, respectively, using Review Manager 5.1.6.[18] If an outcome was reported at 2 different times, we included the more protracted measure in pooled analyses.

We evaluated the effect of statistical heterogeneity among pooled studies for each outcome using the Cochran Q statistic (threshold $p < 0.10$)[19,20] and the I^2 test[21,22] with threshold values of 0%–40% (representing heterogeneity that might not be important), and 30%–60%, 50%–90%, and ≥ 75% (representing moderate, substantial or considerable heterogeneity, respectively).[22] If a heterogeneity value overlapped 2 categories, we assigned it the higher rating. In sensitivity analyses, we assessed the effect of excluding quasirandomized trials on estimates of mortality and ventilator-associated pneumonia. We planned subgroup analyses to compare the effects of noninvasive weaning on mortality and weaning failure in studies including only patients with COPD with the effects seen in studies involving patients without COPD or mixed populations. In addition, we compared the effects seen in studies in which at least 50% of the participants had COPD with the effects seen in studies in which less than 50% of participants had COPD. We assessed for differences between subgroup summary estimates using the χ^2 test.[23] We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) principles[24] to assess the quality of evidence associated with specific outcomes (mortality, weaning failure, ventilator-associated pneumonia, duration of ventilation related to weaning and reintubation).

Results

Trial identification

We identified 1506 records in our updated search. Of the 961 unique records we found, we assessed 15 new articles for eligibility (Figure 1).[16] Although we identified 6 additional trials from our updated search, 1 author confirmed that his trial had been aborted and never published, and 1 trial had not been consistently randomized (see Appendix 2 for a list of the excluded studies, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130974/-/DC1). Consequently, we included 4 newly identified trials in our analysis,[25–28] in addition to the 12 trials included in our previous review.[16]

Of the 16 included trials, 2 were published only in abstract form,[29,30] 4 were published in Chinese,[31–34] 1 was a dissertation subsequently published in full,[35] and one was a pilot RCT.[28] We excluded 20 studies (11 identified through our updated search [Figure 1] and 9 excluded previously; Appendix 2), including 9 newly identified publications, 1 abstract and the aborted trial (Figure 1).

Of the 16 included RCTs (involving a total of 994 patients), 9 trials exclusively involved patients with COPD,[26,30–37] and 7 trials[25,27,28,29,38–40] included mixed or non-COPD populations (Table 1). In the trials involving mixed or non-COPD patient populations, COPD was diagnosed in about 75% of patients in 3 trials,[25,38,39] in about 30% of patients in 2 trials[29,40] and in more than 20% of patients in 1 trial;[27] COPD was an exclusion criterion in 1 trial.[28] Patients were considered difficult to wean in 2 trials[25,38] and had persistent weaning failures in 1 trial.[39] Four trials[32–34,37] included patients with COPD whose respiratory failure was due to pulmonary infection. The 2 reviewers achieved complete agreement on study selection.

Quality assessment

Overall, the quality of the included trials was moderate to good (Tables 2 and 3). In most of the trials, allocation to the treatment group was by random assignment, with 1 quasirandomized trial

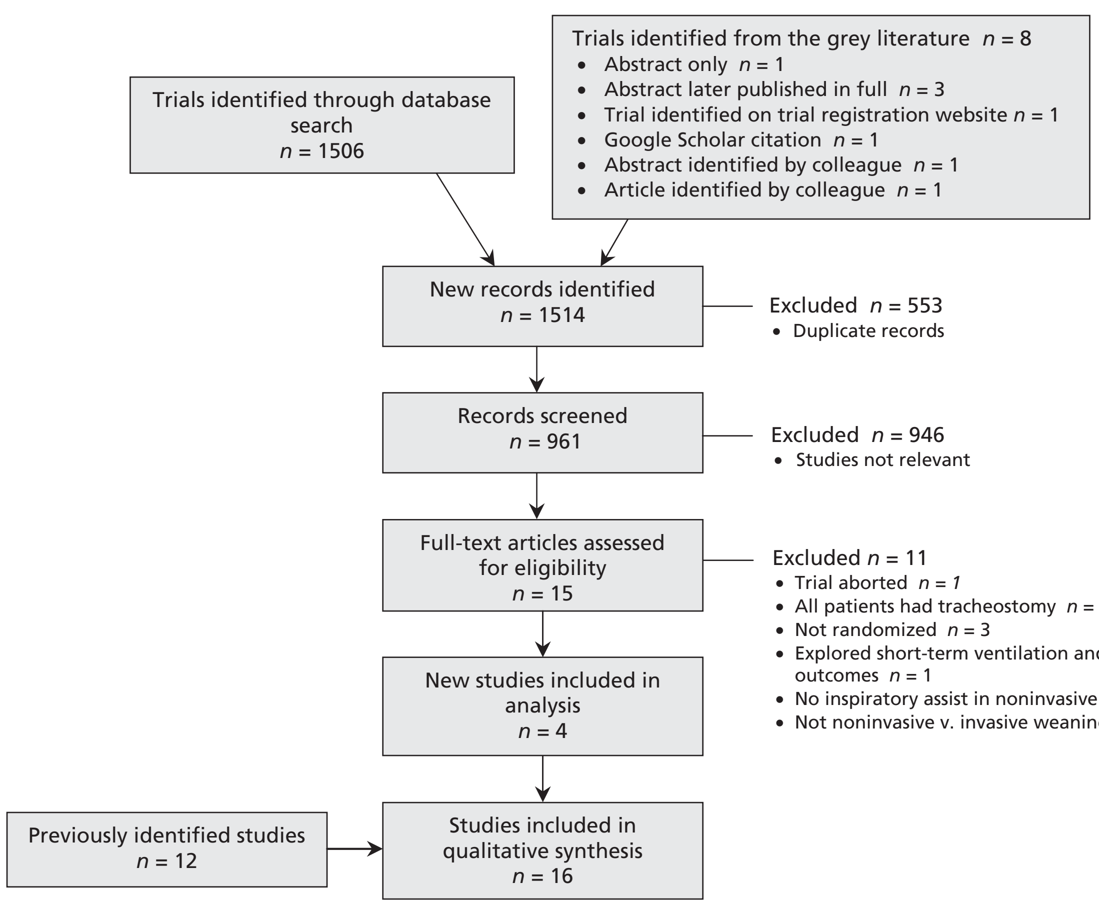

Figure 1: Selection of included studies. This review represents an update of a previously conducted systematic review and meta-analysis.[16]

Table 1: Populations and interventions in studies of noninvasive ventilation in adults with critical illness

Study	No. of patients	Inclusion criteria		Experimental strategy	Control strategy
		Patient characteristics	Weaning eligibility		
Girault et al. 2011[25]	138	Chronic hypercapnic respiratory failure; invasive mechanical ventilation for at least 48 h	2 h SBT failure	Noninvasive pressure support ± PEEP or bilevel NIV with face mask (initial choice)	Invasive pressure support with once daily SBT with T-piece or pressure support ± PEEP
Rabie Agmy et al. 2012[26]	264	Acute-on-chronic exacerbation of COPD	2 h SBT failure	NIV (pressure, ST mode)	Invasive pressure support
Tawfeek et al. 2012[27]	42	Invasive mechanical ventilation > 48 h	2 h SBT failure	Noninvasive PAV delivered by face mask	SIMV
Vaschetto et al. 2012[28]	20	Hypoxemic respiratory failure; invasive mechanical ventilation for at least 48 h	Pressure support with PEEP + inspiratory support, ≤ 25 cm H_2O and PEEP 8–13 cm H_2O; PaO_2:FiO_2 200–300 mm Hg with FiO_2 ≤ 0.6	Helmet NIV	Invasive pressure support with SBT when PaO_2:FiO_2 > 250 mm Hg
Hill et al. 2000[29]	21	Acute respiratory failure	30 min SBT failure	NIV using VPAP in ST-A mode	Invasive pressure support
Rabie Agmy et al. 2004[30]	37	Exacerbation of COPD	2 h SBT failure	NIV (proportional assist in timed mode) delivered by face or nasal mask	Invasive pressure support
Chen et al. 2001[31]	24	Exacerbation of COPD; mechanical ventilation for at least 48–60 h; O_2 saturation ≥ 88% on FiO_2 40%	Day 3+ weaning criteria	Bilevel NIV (pressure mode)	Invasive pressure support
Wang et al. 2004[32]*	28	COPD; bronchopulmonary infection	PIC window	NIV (pressure mode) delivered by mask (unspecified)	SIMV + pressure support
Zheng et al. 2005[33]*	33	COPD; severe pulmonary infection	PIC window	Bilevel NIV (pressure mode) delivered by face or nasal mask	Invasive pressure support
Zou et al. 2006[34]*	76	COPD with severe respiratory failure; pulmonary infection	PIC window	Bilevel NIV (pressure, ST mode) delivered by nasal or oronasal mask	SIMV + pressure support
Prasad et al. 2009[35]	30	COPD; hypercapnic respiratory failure	2 h SBT failure	Bilevel NIV (pressure mode) delivered by full face mask	Invasive pressure support
Nava et al. 1998[36]	50	Exacerbation of COPD; mechanical ventilation for at least 36–48 h	Simple weaning criteria, 1 h SBT failure	Noninvasive pressure support on conventional ventilator delivered with face mask	Invasive pressure support
Collaborating Research Group for Noninvasive Mechanical Ventilation 2005[37]*	90	COPD with severe hypercapnic respiratory failure; pneumonia or purulent bronchitis; age ≤ 85 y; capable of self-care during previous year	PIC window	Bilevel NIV (pressure mode)	SIMV + pressure support
Girault et al. 1999[38]	33	Acute-on-chronic respiratory failure (COPD, restrictive or mixed populations); mechanical ventilation for at least 48 h	Simple weaning criteria, 2 h SBT failure	Flow or pressure mode with nasal or face mask	Flow or pressure mode (pressure support)
Ferrer et al. 2003[39]	43	Acute respiratory failure and persistent weaning failure; intubation for at least 72 h	2 h SBT failure on 3 consecutive days	Bilevel NIV in ST mode delivered with face or nasal mask	Assist control or invasive pressure support
Trevisan et al. 2008[40]	65	Invasive mechanical ventilation > 48 h	30 min SBT failure	Bilevel NIV (pressure mode) delivered by facemask	Invasive mechanical ventilation

Note: COPD = chronic obstructive pulmonary disease, FiO_2 = fraction of inspired oxygen, NIV = noninvasive ventilation, PaO_2 = partial pressure of oxygen, PAV = proportional assist ventilation, PEEP = positive end-expiratory pressure, PIC = pulmonary infection control, SBT = spontaneous breathing trial, SIMV = synchronized intermittent mandatory ventilation, ST = spontaneous/timed, VPAP = variable positive airway pressure.
*Trials evaluating patients with COPD and pulmonary infection, which enrolled patients who achieved PIC window criteria or after infection control was achieved. These criteria included an improved radiograph, temperature and leukocyte count (or percentage of neutrophils), in addition to reduced secretion volume and tenacity. Two trials also specified improved hemodynamics, expectoration and level of consciousness;[34,36] 1 trial[57] specified minimum ventilator settings (SIMV rate 10–12 breaths/min, pressure support 10–12 cm H_2O).

allocating patients according to order of hospital admission.[31] We judged allocation concealment to be adequate in 8 trials,[25–30,36,39] unclear in 7 trials[32–35,37,38,40] and inadequate in 1 quasirandomized trial.[31] In 2 trials,[32,34] denominators were not provided in binary outcomes to ensure complete

Table 2: Risk of bias in the included trials

Study	Selection bias: Random sequence generation	Selection bias: Allocation concealment	Attrition bias (incomplete data)	Reporting bias (selective reporting)
Girault et al. 2011[25]	Low	Low	Low	Low
Rabie Agmy et al. 2012[26]	Low	Low	Low	Low
Tawfeek et al. 2012[27]	Unclear	Low	Low	Low
Vaschetto et al. 2012[28]	Low	Low	Low	Low
Hill et al. 2000[29]	Unclear	Low	Low	Low
Rabie Agmy et al. 2004[30]	Unclear	Low	Low	Low
Chen et al. 2001[31]	High	High	Low	Unclear
Wang et al. 2004[32]	Unclear	Unclear	Low	Low
Zheng et al. 2005[33]	Unclear	Unclear	Unclear	Low
Zou et al. 2006[34]	Low	Unclear	Unclear	Low
Prasad et al. 2009[35]	Low	Unclear	Low	Low
Nava et al. 1998[36]	Unclear	Low	Low	Low
Collaborating Research Group for Noninvasive Mechanical Ventilation 2005[37]	Unclear	Unclear	Low	Low
Girault et al. 1999[38]	Unclear	Unclear	Low	Low
Ferrer et al. 2003[39]	Low	Low	Low	High
Trevisan et al. 2008[40]	Unclear	Unclear	Low	Low

Table 3: Summary estimates of effect of noninvasive ventilation in adults with critical illness

Outcome	No. of studies (no. of patients*)	Summary estimate (95% CI)	Heterogeneity, I^2, %
Death	16 (994)	0.53‡ (0.36 to 0.80)	37
VAP	14 (953)	0.25‡ (0.15 to 0.43)	38
Weaning failure	8 (605)	0.63‡ (0.42 to 0.96)	39
Length of stay			
Intensive care unit	13 (907)	–5.59§ (–7.90 to –3.28)	77
Hospital	10 (803)	–6.04§ (–9.22 to –2.87)	78
Duration of mechanical ventilation			
Total	7 (385)	–5.64§ (–9.50 to –1.77)	86
Related to weaning	9 (645)	–0.25§ (–2.06 to 1.56)	90
Endotracheal†	12 (717)	–7.44§ (–10.34 to –4.55)	87
Adverse events			
Reintubation	10 (789)	0.65‡ (0.44 to 0.97)	41
Tracheostomy	7 (572)	0.19‡ (0.08 to 0.47)	10
Arrhythmia	3 (201)	0.89‡ (0.34 to 2.34)	0

Note: CI = confidence interval, VAP = ventilator-associated pneumonia.
*For weaning failure, reintubation and tracheostomy, the numbers of patients in the denominators differ from sums of numbers in Table 1 because one study[38] reported these outcomes differently (i.e., weaning failure included reintubation or death within 7 d; reintubation included only reintubation within 7 d; tracheostomy was reported in 105 surviving patients at discharge).
†Invasive ventilation.
‡Risk ratio.
§Mean difference.

reporting. The possibility of selective outcomes reporting was not excluded in 1 trial[31] that reported clinically important outcomes, but did not specify primary and secondary outcomes. Another trial[39] did not report weaning outcomes in the full publication, but did report them in a previously published abstract; the authors affirmed that they had not continued to collect these data (Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130974/-/DC1).

Primary outcome

All of the trials provided mortality data, which was reported at 30, 60 and 90 days,[27,35,36,38,39] at discharge from the ICU[25,28] or hospital[26,28,30,33,34,37,38,40] or at an undefined time.[29,31,32] There was strong evidence that noninvasive weaning reduced mortality (RR 0.53, 95% CI 0.36 to 0.80; 994 patients) with moderate heterogeneity ($I^2 = 37\%$; $p = 0.07$) (Figure 2 and Appendix 4, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130974/-/DC1).

Secondary outcomes

Eight trials involving 605 patients, using variable definitions, reported the proportion of patients successfully weaned.[25–30,36,38] The pooled data showed a significant reduction in the proportion of weaning failures using noninvasive weaning (RR 0.63, 95% CI 0.42 to 0.96) with moderate heterogeneity ($I^2 = 38\%$; $p = 0.1$) (Figure 3).

Pooled data from 14 trials (involving 953 patients)[25–27,30–40] that reported ventilator-associated pneumonia (for which criteria for the diagnosis were provided in 10 trials[27,31–37,39,40]) showed that noninvasive weaning was associated with decreased ventilator-associated pneumonia (RR 0.25, 95% CI 0.15 to 0.43), with moderate heterogeneity ($I^2 = 38\%$; $p = 0.07$) (Figure 4, Appendix 4).

Noninvasive weaning significantly reduced the length of stay in both the ICU (MD −5.59 d, 95% CI −7.90 to −3.28) and the hospital (MD −6.04 d, 95% CI −9.22 to −2.87), the total

Subgroup and study	Noninvasive No. of events	Noninvasive No. of patients	Invasive No. of events	Invasive No. of patients	RR (95% CI)
COPD					
Chen et al. 2001[31]	0	12	3	12	0.14 (0.01 to 2.50)
Nava et al. 1998[36]	2	25	7	25	0.29 (0.07 to 1.24)
Prasad et al. 2009[35]	5	15	9	15	0.56 (0.24 to 1.27)
Rabie Agmy et al. 2004[30]	1	19	2	18	0.47 (0.05 to 4.78)
Rabie Agmy et al. 2012[26]	7	134	26	130	0.26 (0.12 to 0.58)
Wang et al. 2004[32]	1	14	2	14	0.50 (0.05 to 4.90)
CRGNMV 2005[37]	1	47	7	43	0.13 (0.02 to 1.02)
Zheng et al. 2005[33]	3	17	3	16	0.94 (0.22 to 4.00)
Zou et al. 2006[34]	3	38	11	38	0.27 (0.08 to 0.90)
Subtotal		321		311	0.36 (0.24 to 0.56)
Total events	23		70		
$I^2 = 0\%$					
Mixed					
Ferrer et al. 2003[39]	6	21	13	22	0.48 (0.23 to 1.03)
Girault et al. 1999[38]	0	17	2	16	0.19 (0.01 to 3.66)
Girault et al. 2011[25]	16	69	9	69	1.78 (0.84 to 3.75)
Hill et al. 2000[29]	1	12	1	9	0.75 (0.05 to 10.44)
Tawfeek et al. 2012[27]	2	21	6	21	0.33 (0.08 to 1.47)
Trevisan et al. 2008[40]	9	28	10	37	1.19 (0.56 to 2.53)
Vaschetto et al. 2012[28]	2	10	3	10	0.67 (0.14 to 3.17)
Subtotal		178		184	0.81 (0.47 to 1.40)
Total events	36		44		
$I^2 = 35\%$					
Total		499		495	0.53 (0.36 to 0.80)
Total events	59		114		
$I^2 = 37\%$					
Test for subgroup differences $p = 0.02$, $I^2 = 80.5\%$					

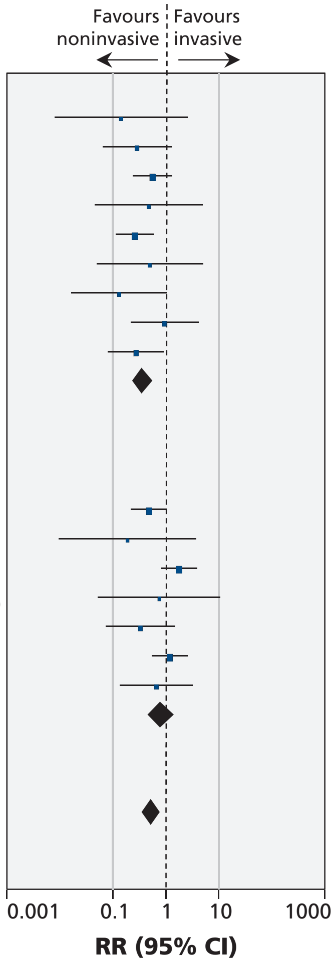

Figure 2: Effect of noninvasive weaning on mortality. CI = confidence interval, COPD = chronic obstructive pulmonary disease, CRGNMV = Collaborating Research Group for Noninvasive Mechanical Ventilation, RR = risk ratio.

duration of mechanical ventilation (MD −5.64 d, 95% CI −9.50 to −1.77) and the duration of invasive ventilation (MD −7.44 d, 95% CI −10.34 to −4.55), all with considerable heterogeneity. Noninvasive weaning had no effect on the duration of mechanical ventilation related to weaning (MD −0.25 d, 95% CI −2.06 to 1.56). None of the included studies reported on quality of life (Table 3).

Adverse events

The pooled result showed no difference in arrhythmias (RR 0.89, 95% CI 0.34 to 2.34; 3 trials, 201 patients),[25,35,38] but significantly lower rates of reintubation (RR 0.65, 95% CI 0.44 to 0.97; 10 trials, 789 patients)[25–29,34,37–40] and tracheostomy (RR 0.19, 95% CI 0.08 to 0.47; 7 trials, 572 patients)[25–28,38–40] with variable heterogeneity (Table 3).

Sensitivity and subgroup analyses

The exclusion of a quasirandomized trial[31] maintained significant reductions in mortality (RR 0.60, 95% CI 0.40 to 0.90) and the rate of ventilator-associated pneumonia (RR 0.27, 95% CI 0.16 to 0.45), favouring noninvasive weaning.

We noted a significant difference in RR between subgroups (p = 0.02) evaluating the effect of noninvasive weaning on mortality in COPD (RR 0.36, 95% CI 0.24 to 0.56; 9 trials) compared with the effect in a mixed population (RR 0.81, 95% CI 0.47 to 1.40; 7 trials). A subgroup analysis comparing trials in which at least 50% of the enrolled participants had COPD (RR 0.47, 95% CI 0.29 to 0.76; 12 trials) with trials in which less than 50% of participants had COPD (RR 0.86, 95% CI 0.47 to 1.58; 4 trials) showed a greater reduction in mortality in the COPD-predominant trials. However, the difference was not significant (p = 0.1). The effect of noninvasive weaning on weaning failure did not differ significantly between trials involving patients with COPD or mixed populations.

Interpretation

We identified 16 trials of moderate to good quality comparing noninvasive and invasive weaning among 994 patients, most of whom had COPD. Compared with invasive weaning, noninvasive weaning significantly decreased mortality, the rates

Subgroup and study	Treatment: No. of events	Treatment: No. of patients	Control: No. of events	Control: No. of patients	RR (95% CI)
COPD					
Nava et al. 1998[36]	3	25	8	25	0.38 (0.11 to 1.25)
Rabie Agmy et al. 2004[30]	4	19	6	18	0.63 (0.21 to 1.88)
Rabie Agmy et al. 2012[26]	28	134	52	130	0.52 (0.35 to 0.77)
Subtotal		178		173	0.52 (0.36 to 0.74)
Total events	35		66		
I^2 = 0%					
Mixed					
Girault et al. 1999[38]	4	17	4	16	0.94 (0.28 to 3.14)
Girault et al. 2011[25]	23	69	22	69	1.05 (0.65 to 1.69)
Hill et al. 2000[29]	4	12	1	9	3.00 (0.40 to 22.47)
Tawfeek et al. 2012[27]	3	21	10	21	0.30 (0.10 to 0.94)
Vaschetto et al. 2012[28]	1	10	5	10	0.20 (0.03 to 1.42)
Subtotal		129		124	0.73 (0.35 to 1.50)
Total events	35		42		
I^2 = 47%					
Total		307		298	0.63 (0.42 to 0.96)
Total events	70		108		
I^2 = 39%					
Test for subgroup differences p = 0.40, I^2 = 0%					

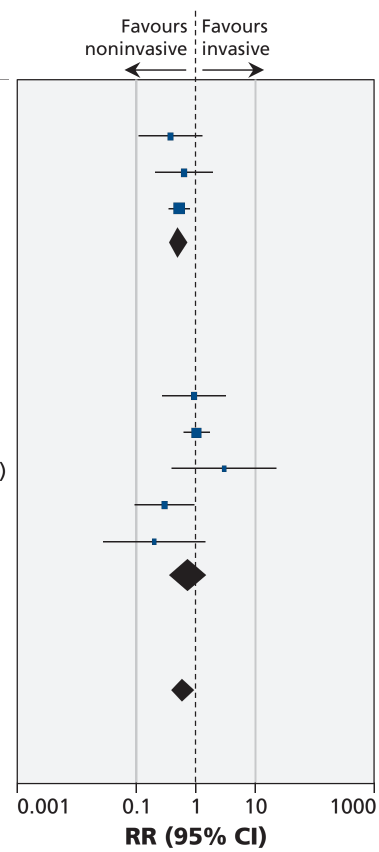

Figure 3: Effect of noninvasive weaning on weaning failures. CI = confidence interval, COPD = chronic obstructive pulmonary disease, CRGNMV = Collaborating Research Group for Noninvasive Mechanical Ventilation, RR = risk ratio.

of weaning failures and ventilator-associated pneumonia, the length of stay in the ICU or hospital, the total duration of mechanical ventilation and the duration of invasive ventilation. Although noninvasive weaning had no effect on the duration of mechanical ventilation related to weaning, it significantly reduced tracheostomy and reintubation rates. Excluding a single quasirandomized trial supported the statistically significant reductions in mortality and ventilator-associated pneumonia rates favouring noninvasive weaning. Subgroup analyses suggested that the benefits of noninvasive weaning to mortality were significantly greater in trials exclusively enrolling patients with COPD than in trials enrolling mixed populations.

Most of the studies included in our review either exclusively or predominantly involved patients with COPD.[25,26,30–39] Our updated review adds 4 new trials to the evidence base, including 2 large trials,[25,26] 1 of which exclusively enrolled patients with COPD,[26] and 1 which predominantly enrolled patients with COPD.[25] Patients with chronic airflow limitation may be ideally suited to noninvasive ventilation given its ability to offset respiratory muscle fatigue and tachypnea, augment tidal volume and reduce intrinsic positive end-expiratory pressure. Subgroup analyses for mortality suggested noninvasive weaning conferred significantly greater benefits in patients with COPD. However, inferences from subgroup analyses may be limited by the inclusion of patients with COPD in mixed population studies and the small number of trials comparing the alternative weaning strategies in patients with other causes of respiratory failure. Whether other causes of respiratory failure are as amenable as COPD to noninvasive weaning remains to be determined.

Subgroup and study	Noninvasive: No. of events	Noninvasive: No. of patients	Invasive: No. of events	Invasive: No. of patients	RR (95% CI)
COPD					
Chen et al. 2001[31]	0	12	7	12	0.07 (0.00 to 1.05)
Nava et al. 1998[36]	0	25	7	25	0.07 (0.00 to 1.11)
Prasad et al. 2009[35]	1	15	5	15	0.20 (0.03 to 1.51)
Rabie Agmy et al. 2004[30]	0	19	4	18	0.11 (0.01 to 1.83)
Rabie Agmy et al. 2012[26]	3	134	30	130	0.10 (0.03 to 0.31)
Wang et al. 2004[32]	1	14	8	14	0.13 (0.02 to 0.87)
CRGNMV 2005[37]	3	47	12	43	0.23 (0.07 to 0.76)
Zheng et al. 2005[33]	1	17	4	16	0.24 (0.03 to 1.89)
Zou et al. 2006[34]	7	38	15	38	0.47 (0.21 to 1.01)
Subtotal		321		311	0.22 (0.13 to 0.37)
Total events	16		92		
I^2 = 3%					
Mixed					
Ferrer et al. 2003[39]	5	21	13	22	0.40 (0.17 to 0.93)
Girault et al. 1999[38]	1	17	1	16	0.94 (0.06 to 13.82)
Girault et al. 2011[25]	9	69	10	69	0.90 (0.39 to 2.08)
Tawfeek et al. 2012[27]	1	21	8	21	0.13 (0.02 to 0.91)
Trevisan et al. 2008[40]	1	28	17	37	0.08 (0.01 to 0.55)
Subtotal		156		165	0.38 (0.15 to 0.93)
Total events	17		49		
I^2 = 52%					
Total		477		476	0.25 (0.15 to 0.43)
Total events	33		141		
I^2 = 38%					

Test for subgroup differences $p = 0.31$, $I^2 = 1.2\%$

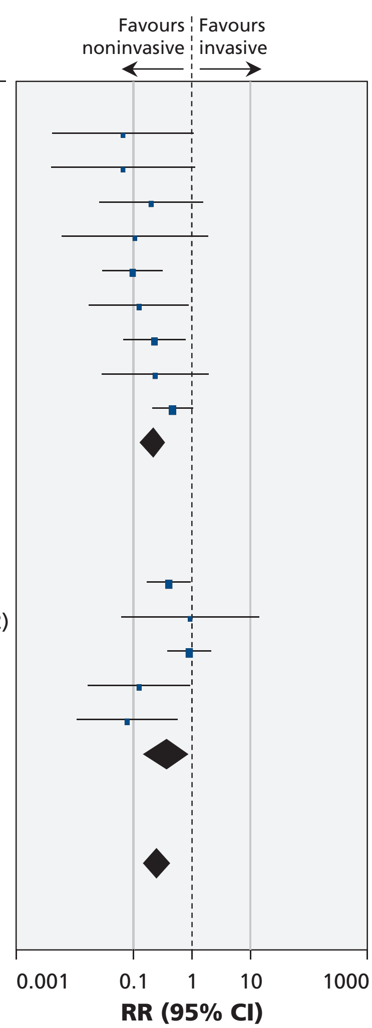

Figure 4: Effect of noninvasive weaning on ventilator associated pneumonia. CI = confidence interval, COPD = chronic obstructive pulmonary disease, CRGNMV = Collaborating Research Group for Noninvasive Mechanical Ventilation, RR = risk ratio.

Overall, most of the trials in this review were of moderate quality, with 3 trials evaluated to be at low risk of bias and 2 trials considered to be at high risk of bias. The methods used to identify weaning candidates varied among trials, but occurred before randomization and are unlikely to have biased the reported duration of ventilation. Conversely, unequal or inconsistent use of weaning protocols and the frequency with which periods of spontaneous breathing (noninvasive strategy) or spontaneous breathing trials (invasive strategy) were permitted after randomization varied among the included trials. Nonstandardization of weaning protocols in unblinded trials may bias estimates of the duration of ventilation. The administration of sedation may affect the duration of ventilation,[41] and only 1 trial[29] in our review used a sedation protocol.

Compared with our previous systematic review,[16] our updated review contains 4 new trials (2 of which are large), nearly doubles the number of included patients (994 v. 530), especially those with COPD, has narrower confidence intervals around point estimates of effect and shows that noninvasive weaning reduces weaning failure and reintubation rates overall, as well as mortality in the subgroup of patients with COPD. A recent systematic review included 16 trials evaluating bilevel noninvasive ventilation and continuous positive airway pressure to wean patients on invasive ventilation, prevent respiratory failure in postoperative patients ready for extubation, or treat postextubation respiratory failure.[15] Considering the population, the conclusions of that review were similar to those of ours, which included 16 trials focused on noninvasive ventilation (excluding continuous positive airway pressure) to wean patients on invasive ventilation.

Strengths and limitations

Our review was strengthened by an extensive search for relevant trials. We screened citations and abstracted data independently and in duplicate, and attempted to contact lead investigators to clarify study methods and outcomes reporting. Pooling results in a meta-analysis presupposes that the studies are sufficiently similar with respect to populations, interventions, outcome definitions and quality that one could expect a comparable underlying treatment effect. Anticipating heterogeneity across studies in pooling selected outcomes, we planned sensitivity and subgroup analyses. Furthermore, we used random-effects models, which generally give more conservative (wider) confidence intervals and consider both between-study and within-study variation. Finally, we reported our findings in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[42] In summary estimates, we found that noninvasive weaning significantly reduced mortality, length of stay in the ICU and hospital and the total duration of mechanical ventilation. These trends are consistent with, and possibly due to, reduced rates of ventilator-associated pneumonia. However, direct access to respiratory secretions among invasively weaned patients may have resulted in enhanced detection of pneumonia. The disparate mortality (range 11.1% to 60.0%)[29,30,35] and ventilator-associated pneumonia rates (6.3% to 59.1%) in the control group,[38,39] the potential for detection bias in assessing ventilator-associated pneumonia, and the total numbers of deaths (173) and cases of ventilator-associated pneumonia (174), which are both below several hundred,[43,44] may cause our effect estimates to be inflated and thereby limit the strengths of the inferences that can be drawn. Although estimates of the impact of heterogeneity associated with mortality, ventilator associated pneumonia and reintubation were moderate, those associated with most continuous outcomes were considerable; the estimates of impact of heterogeneity were unimportant for arrhythmia and tracheostomy rates. Recognizing that COPD may explain some of the heterogeneity we saw (Table 2 and Figure 2), we conducted additional post hoc secondary analyses for all study outcomes, comparing trials enrolling patients with COPD with those enrolling mixed patient populations (Appendix 5, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130974/-/DC1). Finally, in attempts to optimize the time to successful removal of invasive ventilation, clinicians are challenged by a trade-off between the risks associated with failed extubation and the complications associated with prolonged invasive ventilation.[45] Clinicians may be reluctant to use noninvasive weaning owing to the need to surrender a protected airway, inexperience, concerns regarding the partial support provided by noninvasive ventilation, and the increased risk for ventilator-associated pneumonia if reintubation is required.[45]

Conclusion

Summary estimates from 16 trials suggest that noninvasive weaning reduces mortality and pneumonia without increasing the risk of weaning failure or reintubation. Moreover, in a subgroup analysis, noninvasive weaning significantly reduced mortality in studies involving patients with COPD compared with studies involving mixed populations. Our results provide the rationale to conduct a large RCT, stratified by COPD status, comparing the alternative weaning strategies. In the meantime, clinicians and centres experienced in using noninvasive ventilation, who are currently using or considering using noninvasive ventilation for weaning patients with COPD may be reassured by our results.

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Acknowledgement: Karen Burns holds a Clinician Scientist (Phase 2) Award from the Canadian Institutes of Health Research.