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REVIEW ARTICLES

Complications of non-invasive ventilation techniques: a comprehensive qualitative review of randomized trials

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Editor's key points

- The authors provide a comprehensive review of all possible complications associated with non-invasive ventilation.
- Serious complications such as pneumonia, barotrauma, and haemodynamic compromise are discussed.
- Many less serious complications have also been described.
- Importantly, knowledge of these complications should encourage careful selection of the patients, equipment, and monitoring techniques.

Summary. Non-invasive ventilation (NIV) has become a common treatment for acute and chronic respiratory failure. In comparison with conventional invasive mechanical ventilation, NIV has the advantages of reducing patient discomfort, procedural complications, and mortality. However, NIV is associated with frequent uncomfortable or even life-threatening adverse effects, and patients should be thoroughly screened beforehand to reduce potential severe complications. We performed a detailed review of the relevant medical literature for NIV complications. All major NIV complications are potentially life-threatening and can occur in any patient, but are strongly correlated with the degree of pulmonary and cardiovascular involvement. Minor complications can be related to specific structural features of NIV interfaces or to variable airflow patterns. This extensive review of the literature shows that careful selection of patients and interfaces, proper setting of ventilator modalities, and close monitoring of patients from the start can greatly reduce NIV complications.

Keywords: complications; non-invasive ventilation; respiratory; ventilation

Over the last two decades, non-invasive ventilation (NIV) has become the standard of care in treating acute respiratory failure (ARF).[1–8] Several randomized controlled trials (RCTs) have shown that NIV improves dyspnoea and gas exchange and reduces the incidence of tracheal intubation. Compared with invasive mechanical ventilation (IMV), NIV reduces the length of intensive care unit (ICU) and hospital stay, morbidity, and mortality in patients with acute and chronic respiratory failure.[9–71] As NIV efficacy varies depending on the severity and type of respiratory pathology, patient selection must be based on failure predictors to reduce the risk of dangerous NIV failures.

Although NIV is well tolerated by most patients, it is not entirely free from serious adverse side-effects and complications. The safety of NIV can be enhanced by a greater awareness of complication predictive factors and afterward by prompt recognition and treatment of untoward occurrences.[1–8] To our knowledge, no review has been published on possible risks

and side-effects associated with NIV. Our objective was to comprehensively review the published literature on the pathophysiology and the management of complications associated with NIV. Major complications are those that are potentially life-threatening or lead to increased morbidity. Minor complications are defined as mild or transient medical problems related to features specific to NIV, such as interfaces or gas flow.

Methods

Search method

RCTs and observational and case report studies describing complications were considered for the qualitative review. Inclusion criteria for report selection for quantitative meta-analysis were: (i) complete, published RCT on NIV *vs* either oxygen delivery by the mask without ventilatory support or IMV, written in English; (ii) patients studied were all adults (i.e. ≥18 yr old); and (iii) studies were performed

in a clinical, and not experimental, setting. Exclusion criteria were irrelevance or paediatric studies, lack of data or full text for meta-analysis, or lack of complication report for qualitative description.

Two authors (M.C., U.F.) independently evaluated title, abstract, and, when available, the full manuscripts of all eligible studies and performed data extraction using a data collection form. Discrepancies were examined by the two investigators. If an agreement could not be reached between two investigators, the decision was made by a third investigator (C.O.).

We searched for publications on 'NIV' in the PubMed, Embase, Web of Science, and Cochrane Library electronic databases (from January 1990 to August 2012) and retrieved a total of 2823 reports. Reports were screened for relevance and for methodological soundness (Fig. 1). In order to improve search accuracy, we ran another search using the words 'noninvasive ventilation' combined with the terms 'skin lesion, noise, leaks, airway lesions, gas exchange alteration, pulmonary complications, haemodynamic effects, intolerance, discomfort, mechanical complications' using the 'AND' function. Finally, we searched the reference lists of previously published systematic reviews for any missing articles.

Statistical analyses

To determine the relative risk (RR) of an event (i.e. NIV failure or NIV-related complication), RCT data were assessed for RR with 95% confidence interval (95% CI) and P-value using MedCalc version 12.3 (MedCalc Software, Mariakerke, Belgium).

Selected papers were also subgrouped depending upon the primary underlying acute respiratory failure (ARF) reason for NIV administration [e.g. chronic obstructive pulmonary disease (COPD), acute cardiac pulmonary oedema (ACPO), and hypoxic ARF, hypoxic–hypercapnic ARF, postoperative ARF, post-extubation ARF, and weaning]. For meta-analyses investigating failure and pneumonia rates, only studies that directly compared NIV with standard medical therapy (i.e. oxygen delivered through a mask without ventilator support) were included. For meta-analyses of weaning studies, only studies that directly compared NIV with the conventional weaning approach (i.e. support ventilation provided through a tracheal tube) were included. No meta-analyses were performed to study haemodynamic or barotrauma effects of NIV, as there were insufficient data available in the literature.

For meta-analyses, data including incidence of complications, NIV interfaces and NIV technique, and sample sizes were extracted from trials and imported into the statistical software program Comprehensive Meta Analysis Version 2.0 for Windows (Biostat Inc., Englewood, NJ, USA). The data imported were dichotomous data (number of events) and sample size for each study of different ARF subgroups. The program showed the odds ratio (and 95% CI), z-value, P-value, and the relative weight assigned for each study. We visually assessed statistical heterogeneity by examining the forest plots and quantified heterogeneity using the I^2 statistic. An I^2 value of >50% was considered to indicate substantial heterogeneity. In all cases, P-values of <0.05 were considered indicative of statistical significance between groups.

Results

Paper selection

Of 2823 reports on NIV initially identified in the literature, 1967 records were excluded because they were not relevant to the review; a further 702 reports were excluded because they were short (i.e. abstract or letter), or not reporting on complication, or reporting on paediatric subjects. One hundred and fifty-four articles were selected and used in the qualitative review. Sixty-two RCTs including a total of 5870 patients were included for subsequent meta-analyses (Table 1). A schematic of our study selection protocol is presented in Figure 1.

Tables 2–4 detail the relative incidences of diverse NIV failure causes determined from our literature search and of major and minor complications related to NIV. Suggestions for clinical interventions to prevent and deal with complications are included as well.

NIV failure

After assessing the RCTs (NIV *vs* standard medical care), the overall NIV failure occurred in 16.3% (360/2198) of patients and failure for all causes had a small but significant RR of 0.88 (95% CI: 0.85–0.91; P<0.0001, not shown) (Table 2). Our meta-analysis categorized NIV failure causes according to underlying disease states (Fig. 2). Although NIV was associated with markedly lower mean failure ORs *vs* standard therapy in COPD (RR 0.71, CI: 0.71–0.87, P<0.0001), hypoxic ARF (RR 0.86, CI: 0.79–0.93, P=0.0004), hypoxic–hypercapnic ARF (RR 0.84, CI: 0.75–0.94, P=0.0025), and postoperative ARF (RR 0.92, CI: 0.88–0.96, P=0.0009), the statistical significance of these differences was not maintained after completion of and meta-analysis (Fig. 2).

Pneumonia

Overall NIV-associated pneumonia occurred in 5.7% (67/1172) of patients (not shown). Our meta-analysis of pneumonia incidence in NIV *vs* standard medical care showed no clear statistical association between NIV treatment and pneumonia in diverse medical conditions (Fig. 3). Nonetheless, pneumonia incidence comparing NIV *vs* standard medical care for all causes had a small but significant RR of 0.92 (95% CI: 0.89–0.94; P<0.0001, not shown). In particular, NIV was associated with markedly lower mean pneumonia ORs *vs* standard therapy for failure in hypoxic ARF (RR 0.89, CI: 0.82–0.95, P=0.0025) and postoperative ARF (RR 0.94, CI: 0.90–0.98, P=0.011), which may display significance in the future when additional studies are available for meta-analysis. In contrast, when NIV was compared with tracheal intubation for ventilator support weaning, NIV showed a significant risk reduction in pneumonia incidence (RR 0.79; 95% CI 0.71–0.88, P<0.0001), by meta-analysis of five relevant RCTs (Fig. 3). This suggests that NIV may be superior to typical approaches for weaning patients off ventilator support.

Fig 1 Schematic of study selection protocol.
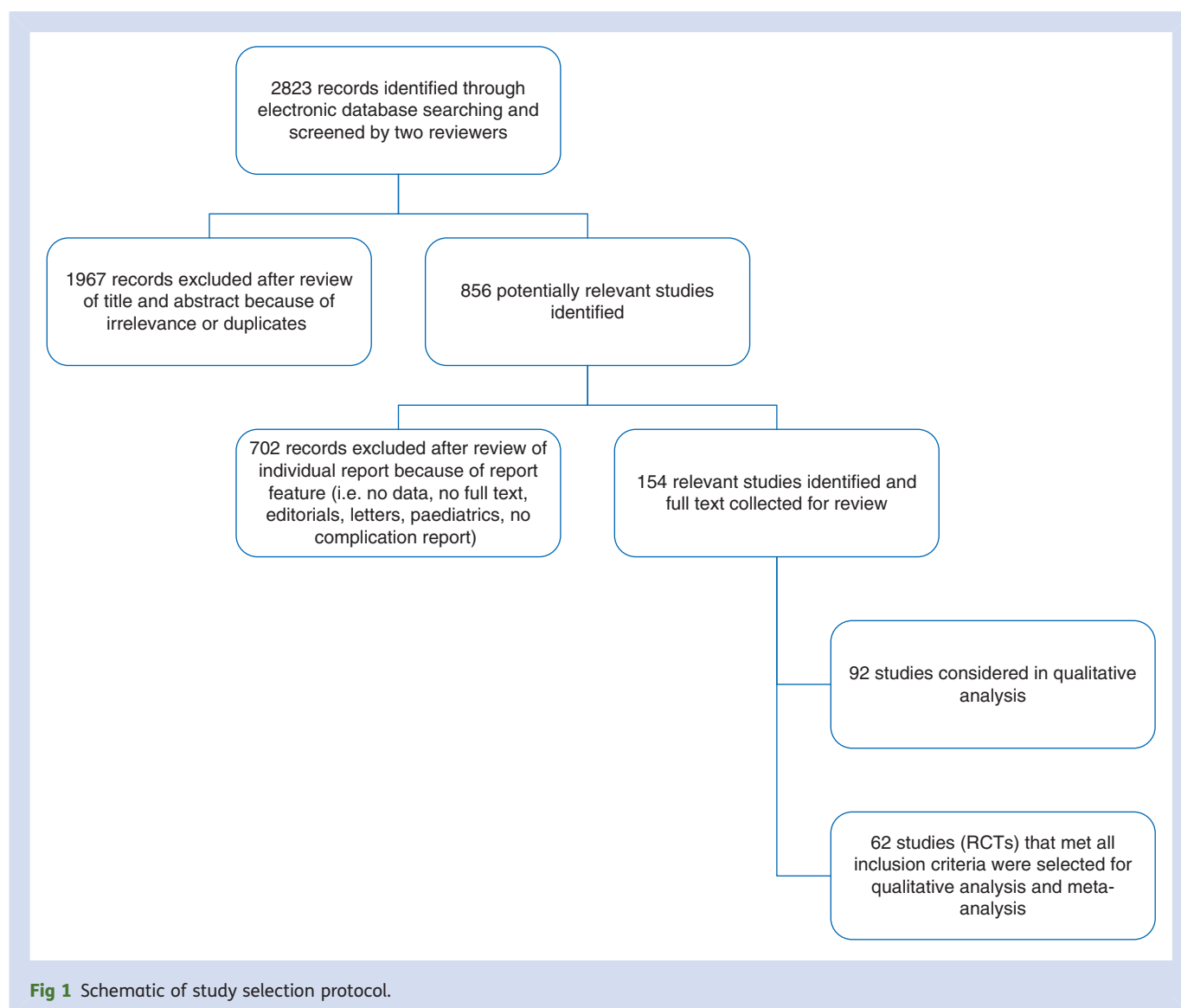
Other complications

All other complications ranged from 0% to 100% (Table 3). The literature did not provide sufficient data to conduct a meta-analysis on haemodynamic complications during NIV (Table 2).

Compared with standard medical care, NIV had a small but significant RR for intolerance (RR 0.91; 95% CI: 0.88–0.93; $P < 0.0001$), nasal lesions (RR 0.87; 95% CI: 0.84–0.90; $P < 0.0001$), nasal/oral dryness/congestion (RR 0.93; 95% CI: 0.89–0.97; $P = 0.0025$), and gastric insufflation (RR 0.96; 95% CI: 0.94–0.98; $P = 0.0008$).

Discussion

NIV failure

The number of patients treatable with NIV is large and likely to increase in the near future because of positive evidence from ongoing investigations. However, the inability to relieve dyspnoea and improve gas exchange still remains the most important evidence of NIV failure, especially in the least investigated conditions (Table 1). NIV failure depends on several factors such as delayed NIV treatment, inappropriate ventilation pressures, low experience of the clinical team, and, most importantly, the patient's clinical condition (i.e. two or more organ failures). Strong experimental evidence supports[1–8] the NIV use to avoid intubation in patients with ARF from COPD exacerbations,[10 11 13–15 72] acute cardiogenic pulmonary oedema,[19–30] or immunosuppression.[36 46 73] NIV also facilitates extubation in COPD patients who had required initial intubation.[9 59 61 63 69] Although supporting evidence is less abundant,[1–8] NIV can also be considered in patients with asthma exacerbations,[40 74 75] pneumonia,[76–78] acute lung injury or acute respiratory distress syndrome,[33–54 79–81] post-operative respiratory failure,[55–57 82] and acute hypercapnic respiratory failure complicating obesity hypoventilation.[83] In patients with hypoxaemic ARF, NIV trial is justified if patients are carefully selected according to available guidelines and known risk factors and predictors for NIV failure by highly experienced teams.[5 7 8 57 61 77–83]

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Table 1 RCTs of NIV. *NIV *vs* comparator (NIV/comparator); †failure: percentage of failure of ventilatory approach for major causes (hypoxia, haemodynamic instability or unstable cardiac arrhythmia, cardiac or respiratory arrest, upper airway obstruction, inability to cooperate/protect the airway, inability to clear respiratory secretions). ICU, intensive care unit; ED, emergency department; HDU, high dependency unit; RICU, respiratory intermediate care unit; POICU, postoperative intermediate care unit; OP, operating theatre; TI, tracheal intubation; SC, standard medical care (oxygen therapy); H, helmet; FM, face mask; NL, nose lesions; FL, facial lesions, EL, eye lesions; GI, gastric insufflation; I, intolerance to device; C, claustrophobia; DVT, deep venous thrombosis; AL; air leaks; OD, oral dryness; NC, nasal congestion; PNX, pneumothorax; NR, non-reported; VAP, ventilator-acquired pneumonia; CFM, cephalic face mask; IMV; invasive mechanical ventilation; PSV; pressure support ventilation; PEEP, positive end-expiratory pressure; ACV, assist-control (volume-cycled) ventilation; SIMV, synchronized intermittent mandatory ventilation; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive pressure; CPAP, continuous positive airway pressure

Study	Site	Interface*	Ventilation mode*	Patients (n)*	Failure (%)*,†	Minor complications (%)
COPD						
Bott and colleagues[10]	Ward	Nasal mask	CPAP/SC	30/30	10/30	NR
Brochard and colleagues[11]	ICU	Facial mask	PSV/SC	43/42	26/74	NL: 2
Barbé and colleagues[12]	Ward	Nasal mask	IPAP+EPAP/SC	14/10	29/NR	NR
Plant and colleagues[13]	ED	Facial-nasal mask	PSV+PEEP/SC	118/118	15/23	NR
Conti and colleagues[14]	ICU	Facial mask/TI	PSV/ACV+PEEP	23/26	52/NR	NR
Keenan and colleagues[15]	ICU	Facial mask	IPAP+EPAP/SC	25/27	8/**7**	I: 12
Kirakli and colleagues[16]	ICU	Facial mask	PSV/APCV+PEEP	17/17	24/18	I: 9
Carrera and colleagues[17]	ED	Facial mask	IPAP+EPAP/SC	37/38	14/34	NR
Maggiore and colleagues[18]	ICU	Facial mask	PSV+PEEP/PSV+PEEP	102/102	25/30	NL: 7; GI: 3; EL: 6
ACPO						
Bersten and colleagues[19]	ED-ICU	facial mask	CPAP/SC	19/20	0/35	NR
Mehta and colleagues[20]	ED-ICU	Nasal mask	IPAP+EPAP/CPAP	14/13	7/8	I: 8
Masip and colleagues[21]	ICU	Facial mask	PSV+PEEP/SC	19/18	5/33	GI: 5; I: 16
Levitt[22]	ED	Facial mask	IPAP+EPAP/SC	21/17	24/41	I: 19
Nava and colleagues[23]	ED	Facial mask	PSV+PEEP/SC	65/65	20/25	NL: 22; I: 6
Bellone and colleagues[24]	ED	Facial mask	PSV+PEEP/CPAP	24/22	8/5	NR
Crane and colleagues[25]	ED	Facial mask	IPAP+EPAP /SC	20/20	5/5	I: 10; NL: 5; GI: 5
Bellone and colleagues[26]	ED	Facial mask	PSV+PEEP/CPAP	18/18	11/6	NR
Moritz and colleagues[27]	ED	Facial mask	IPAP+EPAP/CPAP	60/69	4/2	NR
Ferrari and colleagues[28]	HDU	Facial mask	PSV+PEEP/CPAP	27/25	4/0	NR
Gray and colleagues[29]	ED	Facial mask	CPAP/SC	346/367	2/3	NR
Rusterholtz and colleagues[30]	ICU	Facial mask	PAV+PEEP/CPAP	17/19	41/31	NR
Ferrari and colleagues[31]	ED	Facial mask	PSV+PEEP/CPAP	40/40	8/0	NR
Nouira and colleagues [32]	ED	Facial mask	PSV+PEEP/CPAP	99/101	7/10	NR
Hypoxic ARF						
Wysocki and colleagues[33]	ICU	Facial mask	PSV+PEEP/SC	21/20	62/70	NR
Antonelli and colleagues[34]	ICU	Facial mask/TI	PSV+PEEP/SC	32/32	31/47	NL: 5
Delclaux and colleagues[35]	ICU	Facial mask	CPAP/SC	62/61	34/39	I: 14; NL: 3; GI: 2
Hilbert and colleagues[36]	ICU	Facial mask	PSV+PEEP/SC	26/26	46/77	NL: 23
Ferrer and colleagues[37]	ICU	Facial mask	PSV+PEEP/SC	51/54	25/52	NL: 25; GI: 2; EL: 6
Cosentini and colleagues[38]	HDU	Helmet	CPAP/SC	20/27	0/0	I: 5
Fartoukh and colleagues[39]	ED-ward	Facial mask	PSV+PEEP-IPAP+EPAP/SC	35/36	6/NR	NR
Gupta and colleagues[40]	ICU	Facial mask	PSV+PEEP/SC	28/25	7/16	NR
Wermke and colleagues[41]	Ward	Facial mask	PSV+PEEP/SC	43/44	14/25	NR
Hypoxic–hypercapnic ARF						
Kramer and colleagues[42]	ICU	Nasal mask	IPAP+EPAP/SC	16/15	31/73	NL: 13; AL: 13; I: 13
Wood and colleagues[43]	ED	Nasal mask	IPAP+EPAP/SC	11/16	31/68	PNX: 6
Celikel and colleagues[44]	ICU	Facial mask	PSV+PEEP/SC	15/15	7/40	NL: 46; GI: 6
Confalonieri and colleagues[45]	ICU	Nasal mask	PSV+PEEP/SC	28/28	21/61	GI: 4
Antonelli and colleagues[46]	ICU	Facial mask	PSV+PEEP/SC	20/20	20/70	NL: 5

Continued

Table 1 *Continued*

Study	Site	Interface*	Ventilation mode*	Patients (n)*	Failure (%)*,†	Minor complications (%)
Martin and colleagues[47]	ICU	Facial mask	IPAP+EPAP/SC	32/29	28/59	NR
Gay and colleagues[48]	ICU	Facial mask	PSV+PEEP/PAV+PEEP	23/21	4/10	NL: 26; C: 11
Kwok and colleagues[49]	ICU	Nasal/facial mask	IPAP+EPAP/ IPAP+EPAP	35/35	23/23	I: 34(NM) - 11 (FM)
Fernández-Vivas and colleagues[50]	ICU	Facial mask	PSV+PEEP/ACV+PEEP	59/58	37/34	NL: 26; GI: 6 EL: 9; I: 13
Honrubia and colleagues[51]	ICU	Facial mask	PSV+PEEP/ ACV+PEEP	31/33	58/100	NL: 13
Cuvelier and colleagues[52]	RICU	Full-facial mask	IPAP+EPAP/ IPAP+EPAP	17/17	6/0	CFM: 6; GI: 6; EL: 6
Girault and colleagues[53]	ICU	Facial/nasal mask	PSV+PEEP/PSV+PEEP	46/44	20/14	AL: 68 (NM)
Nava and colleagues[54]	RICU	Facial mask	PSV+PEEP/SC	42/44	24/27	NR
Postoperative ARF						
Auriant and colleagues[55]	ICU	Nasal mask	IPAP+EPAP/SC	24/24	21/50	I: 13
Böhner and colleagues[56]	POICU	Nasal mask	CPAP/SC	99/105	1/5	NL: 4; I: 9
Squadrone and colleagues[57]	ICU	Helmet	CPAP/SC	105/104	1/10	NR
Post-extubation						
Jiang and colleagues[58]	ICU	Facial mask	IPAP+EPAP/SC	47/46	28/15	NR
Keenan and colleagues[59]	ICU	Facial mask	IPAP+EPAP/SC	39/42	72/69	NR
Esteban and colleagues[60]	ICU	Facial mask	PSV+PEEP/SC	114/104	48/48	I: 3
Nava and colleagues[61]	ICU	Facial mask	IPAP+EPAP/SC	48/49	8/24	I: 8; NL: 29; EL: 4; NC: 4;OD: 2
Kindgen-Milles and colleagues[62]	ICU	Nasal mask	CPAP/SC	25/25	4/16	NR
Ferrer and colleagues[63]	ICU	Facial mask	IPAP+EPAP/SC	79/83	11/22	NL: 6; GI: 1
Ferrer and colleagues[64]	ICU	Facial mask	IPAP+EPAP/SC	54/54	11/19	NR
Zarbock and colleagues[65]	POICU	Nasal mask	CPAP/SC	232/236	1/3	NR
Khilnani and colleagues[66]	ICU	Facial mask	PSV+PEEP/SC	20/20	15/25	?
Weaning						
Nava and colleagues[67]	ICU	Facial mask/TI	PSV+PEEP/PSV+PEEP	25/25	12/32	NL: 56; GI: 2
Girault and colleagues[68]	ICU	Facial mask	PSV+PEEP/PSV+PEEP	16/17	24/25	NR
Ferrer and colleagues[69]	ICU	Facial mask	PSV+PEEP/PSV+PEEP	21/22	14/27	NL: 29; GI: 5
Trevisan and colleagues[70]	ICU	Facial mask	PSV+PEEP/ PSV+PEEP	21/22	21/NR	NL: 4
Girault and colleagues[71]	ICU	Facial mask	PSV+PEEP/SC	68/70	32/29	GI: 7; I: 7

The degree of lung involvement represents a key factor in NIV success or failure and it cannot be estimated easily.[76 79] In hypoxaemic ARF, NIV failure is predicted by advanced age, high acuity illness on admission (i.e. Simplified Acute Physiology Score II, SAPS-II, of >34), acute respiratory distress syndrome, community-acquired pneumonia with or without sepsis, and multi-organ system failure.[8 10 11 28 35 76–79 81] In hypercapnic ARF patients, failure is predicted by unimproved or worsened pH or respiratory rate, high-acuity illness at admission (i.e. SAPS-II >34), and lack of cooperation.[8 76 79] Some laboratory indices are more sensitive than clinical findings. Specifically, an unimproved or worsened $Pa_{O_2}/F_{I_{O_2}}$ ratio during a 1 h NIV accurately predicts NIV failure.[76 79] Compared with the $Pa_{O_2}/F_{I_{O_2}}$ ratio, however, the oxygenation index provides a superior estimate of lung function involvement and is a better predictor of NIV failure.[76]

Patient selection and monitoring are crucial to reduce NIV failure. NIV should not be used in patients suffering from claustrophobia, in respiratory arrest, or who are unable to tolerate the NIV device because of agitation or uncooperativeness.[1 3 5 6 8] NIV is contraindicated in patients who are unable to protect their airway due to a swallowing impairment or excessive secretions not sufficiently managed by clearance techniques, and after recent upper airway surgery.[1 3 5 6 8] Such patients need prompt IMV that, when postponed, is associated with increased morbidity and mortality.[1 3 5 6 8] All patients started on NIV should be monitored closely for signs of NIV failure until stabilized.[4–8]

Major NIV complications

Pneumonia

Depending on the comparator control population, NIV may modify the risk of nosocomial-acquired pneumonia. In single studies and in meta-analysis reviews, NIV reduces by three to five times the risk of pneumonia associated with

Table 2 Failure incidence and major complications of NIV. COPD, chronic obstructive pulmonary disease; ACPO, acute cardiogenic pulmonary oedema; ARF, acute respiratory failure; PS, pressure support; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure

Complication	Incidence (%)	Remedies
Failure (hypoxaemia)		
– COPD exacerbations	8–30	– Careful patient selection according to available guidelines, clinical judgement, and known risk factors and predictors for NIV failure
– ACPO	5–31	– Choose the correct interface and size
– Hypoxaemic ARF	7–52	– Give high-flow oxygen
– Hypercapnic–hypoxaemic ARF	15–62	– Optimize ventilatory support (i.e. increase pressure support gradually to get expiratory tidal volume 6 ml kg^{-1} or higher, titrate F_{IO_2} and PEEP level, aiming for $Sa_{O_2} > 90$% and
– Post-extubation ARF	1–72	consider the risk of air leaks, patient–ventilator dyssynchrony and discomfort)
– Weaning	16–25	
Aspiration pneumonia	<5	
		– Careful patient selection
		– Place the patient in the sitting position
		– Optimize ventilatory support (i.e. avoid PS>20 cm H$_2$O)
		– Wait at least half an hour after a meal
		– Gastric drainage when appropriate
Barotrauma	Rare	
		– Careful patient selection
		– Choose correct interface and size
		– Optimize ventilatory support (i.e. avoid PIP>25 cm H$_2$O)
Hypotension	Infrequent	
		– Careful patient selection (i.e. avoid medically unstable patient, hypotensive shock, uncontrolled cardiac ischaemia or arrhythmia, uncontrolled bleeding)
		– Consider adequate hydration and therapy, especially in septic patients
		– Optimize ventilatory support (i.e. avoid or reduce PEEP level)

IMV, especially in immunosuppressed patients and those with comorbidities (reported RR 0.31, 95% CI: 0.16–0.57, $P=0.0002$).[8 11 18 34 46 57 67 69 84–87] The benefit is strong not only for patients with hypercapnic ARF from COPD or acute cardiogenic pulmonary oedema, but also for those with postoperative hypoxaemia (2% vs 10% of patients, reported RR 0.19, 95% CI 0.04–0.88, $P=0.02$).[57 84 85]

In uncontrolled studies, NIV proved superior to standard medical therapy in preventing pneumonia (reported RR 0.56, 95% CI: 0.31–1.02, $P=0.06$).[85 86] In a recent survey of 6869 pneumonia cases from 400 German ICUs, the mean pneumonia incidences were 1.58 and 5.44 cases per 1000 ventilator days for NIV and IMV, respectively, and 0.58 cases associated with no ventilation, which suggests that NIV increases pneumonia risk.[86] However, there were no differences in the proportion of secondary sepsis and death between NIV and standard therapy.[85 86] In contrast, previous investigations reported a lower incidence of pneumonia with NIV than with no ventilation. All these studies are hampered by several shortcomings. First, NIV-associated pneumonia is uncommon and potentially under-reported.[86] Secondly, studies designed to determine whether NIV per se alters nosocomial pneumonia risk are few and retrospective. Thirdly, NIV reduces intubation rate and mortality, but it is not known whether patients who needed intubation or died had pneumonia.

Although the issue of nosocomial pneumonia from NIV remains unsettled, NIV requires caution regarding aspiration risk. Pneumonia is a possible event during NIV and results secondary to inhalation of foreign materials (i.e. condensed fluid in the ventilator circuit) or aspiration of gastric contents and secretions.[85–87] Although unreported in RCTs,[9–71] aspiration pneumonia has been described in as many as 5% of NIV patients.[3 85–87] The risk of aspiration pneumonia is minimized by excluding patients with compromised upper airway function or with difficulty in clearing secretions, by permitting at-risk patients nothing by the mouth until they are stabilized, and by placing the patient in the sitting or semi-sitting position during NIV.[85–87] Caution should be taken in patients with excessive gastric distension, ileus, nausea or vomiting, or in those who are deemed to be at high risk for gastric aspiration (i.e. gastrooesophageal reflux disease).[87] A nasogastric tube can be inserted, but it can interfere with mask fitting, promote air leaking, and add to discomfort.[5] Finally, physicians should be wary of sedating patients during NIV.[87]

Barotrauma

Barotrauma is a well-recognized complication of positive pressure ventilation.[88] The risk of barotrauma is very low during NIV and much lower than during IMV.[3 87] Barotrauma has been described in the presence of COPD, acute lung

injury secondary to pneumonia, interstitial lung diseases, cystic fibrosis, and neuromuscular disorders.[40 88 89]

Barotrauma risk can be minimized by adopting the following approaches: using pressure-controlled ventilation, especially in patients with low pulmonary compliance; keeping the peak inspiratory pressure as low as possible (i.e. <30 cm H_2O); optimizing the inspiratory and expiratory times in order to allow sufficient expiratory time to avoid auto-PEEP and breath stacking; applying a PEEP not exceeding auto-PEEP; and avoiding patient–ventilator desynchronization (Table 4).[88 89] When attempting to balance adequate ventilation with peak inspiratory pressure, some patients may develop mild hypercapnia, which is acceptable as long as the patient remains asymptomatic.[89]

Haemodynamic effects

Artificial ventilation can have negative haemodynamic effects because by increasing intrathoracic pressure, it reduces venous return (preload) and left and right ventricle filling.[90–93] Continuous positive airway pressure (CPAP) decreases cardiac output (CO) and stroke volume (SV) in a pressure-dependent fashion, and increases systemic vascular resistance without changing heart rate and arterial pressure (AP) both in healthy subjects and in patients at risk for respiratory distress, and during NIV via a mask or helmet.[90–96] In stable COPD patients, pressure-support ventilation (PSV) (PS of 10–20 cm H_2O over PEEP of 5 cm H_2O) decreases CO without changing arterial AP or heart rate.[97] In COPD patients with severe hypercapnic ARF, PSV (i.e. PS of 12 cm H_2O over PEEP 3 cm H_2O) through a full face mask decreases CO by 10–13%.[98] NIV has more evident haemodynamic effects in patients with severe disease who are hypotensive or have a low circulating blood volume (i.e. fluid depletion), and in patients with an underlying cardiac disease without adequate pharmacological therapy.[3 99] PSV (i.e. PS of 5 cm H_2O over PEEP 4 cm H_2O) reduces cardiac index by >15% in COPD patients with severe ARF and fluid depletion.[99] In the presence of acute lung injury, NIV has negligible effects on haemodynamics.[94]

In patients with ARF after lung or liver transplant, neither CPAP (i.e. 5 cm H_2O) nor PSV (i.e. PS of 15 cm H_2O over PEEP 5 cm H_2O) altered the CO, heart rate, or mean AP.[100] In patients requiring post-extubation NIV, neither a face mask nor a helmet altered haemodynamics.[100 101] In the presence of acute impairment of left ventricle performance, NIV may have beneficial effects.[102–104] CPAP lowers left ventricular transmural pressure and afterload and increases CO, providing additional rationale for NIV use in treating such patients.[6 8 104] In patients with acute decompensation of congestive heart failure, nasal CPAP (5–15 cm H_2O) increases CO and SV by ~15% and the effects persist after CPAP discontinuation.[102] This has been interpreted as improved cardiac performance by CPAP.[102 103] For the same reason, in patients with acute cardiogenic pulmonary oedema, CPAP and PSV (i.e. PS of 5 or 10 cm H_2O over PEEP of 5 cm H_2O) may be or not associated with altered heart rate, AP, CO, and

SV.[102 103 105 106] High CPAP caused small decreases of CO (i.e. <10%) of doubtful clinical significance.[103] In patients with chronic heart disease and pulmonary capillary wedge pressures <12 mm Hg, CO and SV decreased by 24% and 22%, respectively, during nasal CPAP at 10 cm H_2O, and by 26% and 24% during nasal bi-level positive airway pressures of 10/15 cm H_2O.[106] In patients with pulmonary capillary wedge pressures >12 mm Hg, there were no changes in haemodynamic parameters.[106] In general, NIV seems to have significant effects on haemodynamics of patients with ARF. Special precautions should be taken in patients with fluid depletion and in those with poor left ventricular function or cardiac disease without adequate pharmacological therapy.[3] In patients with chronic right ventricular dysfunction and/or reduced LV compliance, with or without lung hyperinflation, both PEEP application and the cautious delivery of conservative tidal volumes can prevent negative circulatory effects (Table 4).[104]

Minor NIV complications

Interface-related complications

Arm oedema and deep venous thrombosis Oedema is the result of uncompensated fluid filtration from blood vessels to the tissue in the upper extremity that may be aggravated by lymphatic drainage failure as during helmet NIV (Table 3).[72 107] The helmet is secured by two armpit braces to a pair of hooks on the plastic ring that joins the helmet to a soft collar.[72] Prolonged compression from the armpit braces may produce venous and lymphatic stasis with consequent oedema.[72] Such occurrence is more frequent in patients with severe malnutrition and cachexia and may promote deep venous thrombosis in the axillary vein that requires anticoagulant therapy.[72] Proper brace fixation is essential.[72] These side-effects might be prevented by substituting armpit braces with elastic bands that can be fixed to the bed.

Carbon dioxide rebreathing Carbon dioxide (CO_2) rebreathing may impair CO_2 elimination and load the ventilatory muscles.[108–114] Rebreathing may be related to the interface used for NIV, ventilator circuit, and the mode and respiratory pattern of NIV delivery.[109]

The interface for NIV and ventilator circuit represent an additional dead space which increases the chances of CO_2 rebreathing in proportion to dead space volume.[108 114] The dead space of facial and nasal masks is small compared with the tidal volume, and the amount of CO_2 that is rebreathed is also small.[110] Unlike masks, helmets predispose to CO_2 rebreathing because its internal gas volume is larger than the tidal volume.[72 110 111] Nevertheless, this beneficial effect decreases quasi-linearly as tidal volume decreases.[112] Decreasing helmet size will not necessarily prevent CO_2 rebreathing.[110] When CPAP is delivered through a helmet with a valveless continuous flow system, CO_2 rebreathing is minimized by a high fresh gas flow.[110 113] CO_2 rebreathing has been documented with some common home ventilators that have a single gas delivery circuit and

Table 3 Problems related to interface–ventilator interaction during NIV and remedies. *With helmet NIV only. †The incidence of skin abrasion or necrosis may increase to 100% after 48 h of NIV with the mask. CO_2, carbon dioxide; CPAP, continuous positive airway pressure; PS, pressure support; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; NAVA, neurally adjusted ventilatory assist

Problem	Incidence (%)	Remedies
Arm oedema*	<5	
		– Careful patient selection
		– Check helmet armpits, use elastic bands
		– Optimize ventilatory support (i.e. reduce pressures slightly)
		– Change interface
CO_2 rebreathing	50–100	
		– Careful patient selection
		– Choose correct interface and size
		– Optimize ventilatory support (i.e. reduce RR, ensure an adequate inspiratory tidal volume, increase the expiratory time, add PEEP$\geq$4 cm H_2O)
		– Reduce high end-tidal CO_2 (i.e. reduction in caloric intake)
		– Use a two-line ventilatory circuit
		– Use interface with exhalation ports located within the mask
		– Insert foam rubber to reduce dead space
Claustrophobia	5–20	
		– Select carefully the patient
		– Choose correct interface and size
		– Use of manual mask application (i.e. placing the interface gently over face, holding it in place and starting ventilation; then tighten straps to avoid major air leaks)
		– Start a prudent ventilatory support (i.e. starting with CPAP and adding the lowest PS needed to improve patient comfort)
		– Optimize ventilatory support (i.e. reduce pressures slightly)
		– Reassure patient
		– Change device (i.e. consider the helmet instead of the face mask)
		– Consider mild sedation
Discomfort	30–50	
		– Careful patient selection
		– Choose correct interface and size
		– Check mask fit, readjust straps (masks) or helmet armpits (helmet)
		– Change strap system or device
		– Optimize ventilatory support (i.e. reduce pressures slightly, decrease leaks)
		– Reassure patient
		– Consider mild sedation
Mechanical	Infrequent	
		– Check equipment
		– Active alarm system
Nasal skin lesions†	2–50	
		– Choose correct interface and size
		– Use interfaces with a smaller mask area and a larger mask cushion
		– Consider water instead of air to fill the cushion of a facemask
		– Check mask fit, readjust straps (masks)
		– Consider forehead spacer, artificial skin, Granuflex® dressing
		– Change device (i.e. consider full face mask or helmet)
		– Optimize ventilatory support (i.e. reduce pressures slightly)
Noise	50–100	
		– Choose correct interface and size
		– Change device (i.e. consider the face mask instead of the helmet)
		– Use heat and moisture, earplugs, sound traps

Continued

Table 3 Continued

Problem	Incidence (%)	Remedies
Patient–ventilator dyssynchrony	13–100	– Careful patient selection
		– Choose correct interface and size
		– Optimize ventilatory support (i.e. increase PS, add PEEP, increase inspiratory flow trigger, and use low respiratory rate for the helmet)
		– Check factors for patient–ventilator dyssynchrony (i.e. air leaks, water in circuit, noise)
		– Consider a reduction in PS to a tidal volume of about 6 ml kg^{-1}
		– Consider NAVA

do not contain a true exhalation valve. Using a two-line circuit with a non-rebreather valve, or masks with exhalation ports located within the mask instead of in the ventilator circuit, are expected to minimize the CO_2 rebreathing during NIV.[109] Other factors that may enhance CO_2 rebreathing are the end-tidal CO_2 concentration, respiratory rate, and PEEP level.[109 110] Among these, high end-tidal CO_2 concentration correlates with an increased possibility that the CO_2 fraction for inspiratory tidal volume will exceed 0.10% and this is likely to occur in patients with increased CO_2 production (i.e. infections and high caloric intake), and/or during helmet NIV.[109 111] Lowering the respiratory rate, ensuring an adequate inspiratory tidal volume, adding PEEP, and increasing the expiratory time have been advocated as general measures to reduce CO_2 rebreathing (Table 4).[110]

Claustrophobia Claustrophobia may present as minor discomfort or, worse, as a frightening sense of restriction and suffocation. Claustrophobia involves not only the impossibility to begin, but also to continue NIV with a variable incidence that ranges from 5% to 20%.[1–3 16 20 37 48 50 72 80 87] Nasal masks are less likely to cause claustrophobia than face masks.[5 8 27 115 116] Although some authors consider claustrophobia as a long-term adverse experience during helmet NIV, helmet use is actually believed to minimize this event.[8 105 116 117] The proper choice and application of the device is crucial to ameliorate claustrophobia (Table 4).[1–3 8 87 118 119]

Discomfort Although NIV is generally perceived as more comfortable for patients than IMV, intolerance may affect as many as 30–50% of patients, and despite the best efforts of skilled caregivers, discomfort remains responsible for 12–33% of NIV failure.[3 12 14 20 29 38 42–44 49 51 52 61 73 87 120]

Discomfort is related to the device and the ventilation modality adopted for NIV.[1–3 8 87] Among different models of NIV masks, tolerance was poorest for the mouthpiece followed by the nasal and oronasal masks.[121] All attachment systems were considered variably uncomfortable against the skin, and tolerance may decrease by tightening the straps in an attempt to reduce air leaks and improve patient–ventilator synchrony.[116 121] It may require a change to a different strap system or mask in order to reduce the discomfort.[8 87 121]

Helmets are better tolerated than masks, resulting in longer use and lower NIV failure rates.[72 76 80 87 116 118 121–123] However, other authors found that comfort was similar with the two interfaces or even worse with the helmet.[96 111 124] A short NIV duration may explain lack of differences in comfort between NIV with the mask and helmet in the acute setting.[96]

On average, patients are more comfortable with PSV than volume-controlled ventilation; therefore, PSV should be the preferred mode for NIV in the acute setting.[125] During PSV, the comfort levels follow a U-shaped trend when level of assistance is modified, and the extreme levels of PS (both lowest and highest) are associated with the worst comfort.[126] So, as for IMV, choosing an optimal PS is important for patient degree of comfort during NIV.[126 127] With a helmet, it is advisable to increase both the PS level and PEEP and to use a higher pressurization rate than with a facial mask.[96]

In uncontrolled studies, patient discomfort diminished without worsening respiratory function with remifentanil-based sedation and target-controlled propofol infusion during NIV.[128 129] However, sedation during NIV will remain controversial and an unsettled issue until larger controlled investigations is carried out.

Facial skin lesions Nasal skin lesions (i.e. erythema, ulcers) at the site of mask contact increase with longer NIV durations.[3 8] Nasal lesions account for a large portion of mask NIV complications, occurring in 5–30%[18 23 25 34 36 37 42 44 46 48 50 51 61 63 69 72] to 50%[44 67] of patients after a few hours and in, virtually, 100% of patients after 48 h of mask NIV.[130] The development of skin abrasions or necrosis is one factor that can limit the tolerance and duration of mask NIV.[1–3 8 87 130] During NIV, lesions develop more frequently on the bridge of the nose.[115 130] Progressive tightening of the harness, increasing the air volume in the mask cushions, and increasing inspiratory pressure are factors that promote nasal pressure lesions.[130] Strategies to decrease the incidence of nasal skin lesions during NIV should be carefully considered from the beginning of therapy.[3 8 87 130 131]

BJA

Table 4 Problems related to air pressure and flow during NIV and remedies. NM, nasal mask; FM, facial mask

Problem	Incidence (%)	Remedies
Aerophagia	Common	
		– Reassure patient
		– Consider simethicone
Air leaks		
(1) Minor air leaks	80–100	
(2) Major air leaks		– Careful patient selection
– Mouthpiece	68	– Choose correct interface and size
– Nasal mask	34	– Prefer ventilator with air-leak compensation
– Oronasal mask	31	– Encourage mouth closure with NM
– Integral face mask	18	– Check interface fit
– Helmet	18–31	– Consider change device
		– Optimize ventilatory support (i.e. reduce pressures slightly)
Airways dryness	10–20	
		– Choose correct interface and size
		– Add humidifiers and emollients
		– Consider adequate hydration
		– Optimize ventilatory support (i.e. reduce pressures slightly)
Facial skin erythema	20–34	
		– Choose correct interface and size
		– Check mask fit, readjust straps
		– Optimize ventilatory support (i.e. reduce pressures slightly)
		– Apply artificial skin
		– Ask for dermatologic consultation
Nasal congestion	20–50	
		– Choose correct interface and size
		– Consider topical and systemic decongestants (i.e. saline solution, emollients, steroids, and antihistaminergics)
		– Optimize ventilatory support (i.e. reduce pressures slightly)
		– If NM, consider switching to FM or helmet
Nasal or oral dryness	10–20	
		– Choose correct interface and size
		– Add humidifiers, nasal saline/emollients
		– Optimize ventilatory support (i.e. decrease leaks, reduce pressures slightly)
Nose/sinus/ear pain	10–30	
		– Choose correct interface and size
		– Check mask fit, readjust straps
		– Optimize ventilatory support (i.e. reduce pressures slightly)
Gastric insufflation	10–50	
		– Choose correct interface and size
		– Optimize ventilatory support (i.e. reduce pressures slightly)
		– Gastric drainage when appropriate
		– Consider simethicone
Orthodontic problems (prolonged use of mouthpiece)	Infrequent	
		– Remodel mouthpiece
		– Consult orthodontist
Vomiting	Infrequent	
		– Optimize ventilatory support (i.e. reduce pressures slightly)
		– Consider antiemetics
		– Gastric drainage when appropriate
		– Quick-release of straps and remove device if occurs

Noise During NIV, device noise may exceed usual ICU background noise and may potentially increase patient discomfort, cause sleep disruption, and affect ear function (i.e. tinnitus, temporary auditory threshold shift, or permanent hearing loss).[132 133] Recent studies have reported that sleep disruption in the ICU is multifactorial, and that noise is responsible for only a limited proportion of arousals and awakenings.[132 134] Noise level is influenced by the interface used, being significantly greater during helmet NIV than during mask NIV.[132 133] The intensity of noise inside the helmet during NIV may exceed 100 dB and is mostly caused by the turbulent gas flow through the respiratory circuit. The intensity of noise during mask NIV, caused primarily by the ventilator, does not exceed 70 dB and differs from the background noise that is measured bedside in the ICU.[132] The systems provided with a flow generator using the Venturi effect to deliver CPAP are associated with greater measured noise levels compared with noise levels from mechanical ventilators, and helmet CPAP is noisier than mask CPAP.[132 133] Noise exposure during helmet NIV may be attenuated by some devices. Heat and moisture exchanger (HME) filters decrease the noise perceived by subjects.[132] Adding sound traps to the inspiratory branch of the respiratory circuit may potentially limit noise inside the helmet without major inconvenience.[132] Earplugs may be effective against sleep disruption, but may also make contact with the environment more difficult.[132]

Patient–ventilator dyssynchrony During NIV, triggering and cycling-off of ventilatory assistance should be, ideally, synchronized with the patient's inspiratory efforts.[135] During actual NIV, there is an inspiratory delay between the beginning of the inspiratory effort and the start of the positive inspiratory pressure boost, and an expiratory delay between the time at which inspiratory flow reached 25% of its peak inspiratory value and the end of the positive inspiratory pressure boost are expected.[111 136] In a multicentre study, auto- and double-triggering, ineffective breaths, and premature and late cycling were observed in 12–23% of ARF patients receiving mask NIV.[137] When measured with a global asynchrony index, patient–ventilator dyssynchrony (PVD) was observed in 24–43% of ARF patients.[137 138]

Factors related to interface, patient, and ventilatory modality influence the patient–ventilator interaction during NIV.[111 136 139] PVD is more evident with a mouthpiece than with a nasal or an oronasal mask.[136] In comparison with masks, the low elasticity and high inner volume of helmets may explain the longer inspiratory and expiratory delays and worse patient–ventilator interaction.[96 111] Random noise, water in the circuit, or cardiogenic oscillations may result in auto-triggering, whereas low respiratory drive, weak inspiratory muscles, or dynamic hyperinflation resulting in intrinsic PEEP may cause ineffective breaths.[137 138] Premature cycling may be observed with increased inspiratory times in the case of a short respiratory cycle (restrictive

respiratory disease) and delayed cycling with short inspiratory times in the case of a long respiratory cycle (obstructive respiratory disease).[137 138] Although air leakage is a major contributing factor for PVD during mask NIV, PS level and tidal volume may also play an important role.[137 139] High PS levels can delay pneumatic expiratory cycling, extending the ventilator breath into neural expiration. Low PS levels may activate the expiratory cycling early, so that inspiratory muscle contraction continues into the mechanical expiratory phase, thus leading to delayed ventilator triggering and wasted trigger efforts (non-triggered breaths).[135 137]

During NIV, careful patient and display monitoring help to identify PVD and optimize ventilator settings, thereby reducing patient discomfort and morbidity.[111 135 136 138 139] Optimizing ventilatory support (i.e. increasing PS, adding PEEP, increasing inspiratory flow trigger, and using low respiratory rates for the helmet) and checking factors for PVD (i.e. air leaks, water in circuit, noise) may limit the PVD. Neurally adjusted ventilatory assist reduces PVD by reducing the triggering and cycling delays, especially at higher levels of assistance and, at the same time, preserves spontaneous breathing and blood gases.[135]

Air pressure and flow-related complications

Air leaks Air leakage is virtually universal during NIV (Table 4). Air leaks depend on sealing features of interfaces being larger with small facial mask than with larger masks and helmets.[3 72 96 114 116 121] Large air leaks decrease the F_{IO_2} and arterial oxygen saturation, and increase ventilator autotriggering, PVD, and rebreathing of exhaled gas, all of which increase chances of NIV failure. Hence, air leaks should be monitored closely and taken care of promptly.[96 140 141]

Air leaks are negligible when a proper device for NIV is chosen and fitted.[96 140 141] A tighter fitting of the interface may alone improve leaks and ventilation but should be done cautiously because it increases the risk of skin discomfort and damage.[3 72 96 114] Pressure-controlled ventilation causes less air leaks than volume-controlled ventilation because it delivers a similar tidal volume at a lower peak inspiratory pressure, but could also cause mouth and throat dryness, conjunctivitis, or sleep disturbances.[141] A reduction in inspiratory pressure or tidal volume may also reduce air leaks.[3 8]

Nasal or oral dryness and nasal congestion During NIV, nasal/oral dryness affects 10–20% of patients and nasal congestion 20–50% of patients, particularly when a nasal mask or nasal CPAP is used.[1–3 8 87 142] Nasal or oral dryness is usually indicative of air leaking through the mouth with consequent loss of the nasal mucosa's capacity to heat and to humidify inspired air. Nasal mucosa progressively dries and releases inflammation mediators that increase nasal congestion and resistance, thus reducing tidal volume and patient comfort.[142 143] Strategies to decrease the airways dryness and congestion during NIV

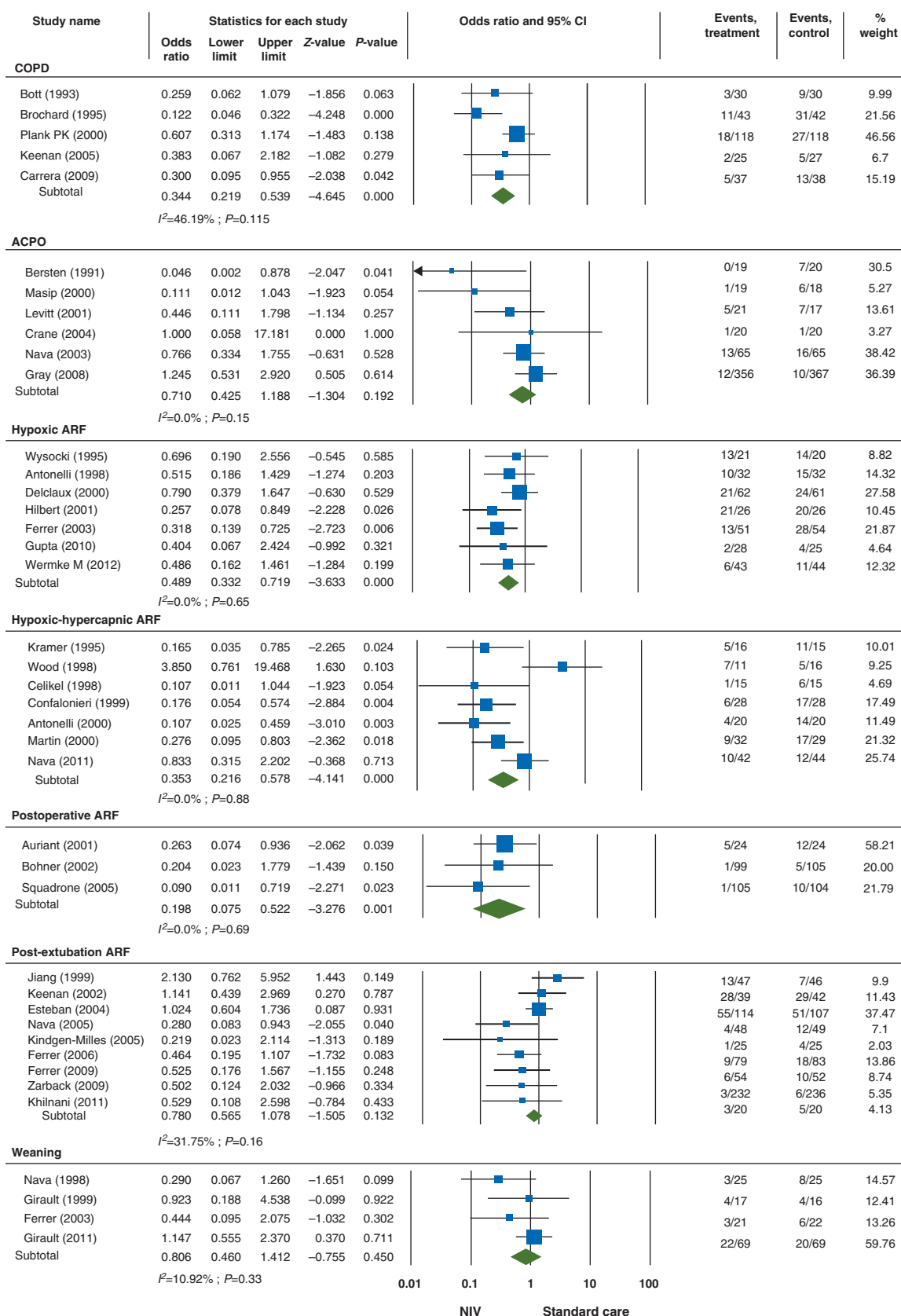| Study name	Statistics for each study					Odds ratio and 95% CI	Events, treatment	Events, control	% weight
	Odds ratio	Lower limit	Upper limit	Z-value	P-value				
COPD									
Bott (1993)	0.259	0.062	1.079	−1.856	0.063		3/30	9/30	9.99
Brochard (1995)	0.122	0.046	0.322	−4.248	0.000		11/43	31/42	21.56
Plank PK (2000)	0.607	0.313	1.174	−1.483	0.138		18/118	27/118	46.56
Keenan (2005)	0.383	0.067	2.182	−1.082	0.279		2/25	5/27	6.7
Carrera (2009)	0.300	0.095	0.955	−2.038	0.042		5/37	13/38	15.19
Subtotal	0.344	0.219	0.539	−4.645	0.000				
	I^2=46.19% ; P=0.115								
ACPO									
Bersten (1991)	0.046	0.002	0.878	−2.047	0.041		0/19	7/20	30.5
Masip (2000)	0.111	0.012	1.043	−1.923	0.054		1/19	6/18	5.27
Levitt (2001)	0.446	0.111	1.798	−1.134	0.257		5/21	7/17	13.61
Crane (2004)	1.000	0.058	17.181	0.000	1.000		1/20	1/20	3.27
Nava (2003)	0.766	0.334	1.755	−0.631	0.528		13/65	16/65	38.42
Gray (2008)	1.245	0.531	2.920	0.505	0.614		12/356	10/367	36.39
Subtotal	0.710	0.425	1.188	−1.304	0.192				
	I^2=0.0% ; P=0.15								
Hypoxic ARF									
Wysocki (1995)	0.696	0.190	2.556	−0.545	0.585		13/21	14/20	8.82
Antonelli (1998)	0.515	0.186	1.429	−1.274	0.203		10/32	15/32	14.32
Delclaux (2000)	0.790	0.379	1.647	−0.630	0.529		21/62	24/61	27.58
Hilbert (2001)	0.257	0.078	0.849	−2.228	0.026		21/26	20/26	10.45
Ferrer (2003)	0.318	0.139	0.725	−2.723	0.006		13/51	28/54	21.87
Gupta (2010)	0.404	0.067	2.424	−0.992	0.321		2/28	4/25	4.64
Wermke M (2012)	0.486	0.162	1.461	−1.284	0.199		6/43	11/44	12.32
Subtotal	0.489	0.332	0.719	−3.633	0.000				
	I^2=0.0% ; P=0.65								
Hypoxic-hypercapnic ARF									
Kramer (1995)	0.165	0.035	0.785	−2.265	0.024		5/16	11/15	10.01
Wood (1998)	3.850	0.761	19.468	1.630	0.103		7/11	5/16	9.25
Celikel (1998)	0.107	0.011	1.044	−1.923	0.054		1/15	6/15	4.69
Confalonieri (1999)	0.176	0.054	0.574	−2.884	0.004		6/28	17/28	17.49
Antonelli (2000)	0.107	0.025	0.459	−3.010	0.003		4/20	14/20	11.49
Martin (2000)	0.276	0.095	0.803	−2.362	0.018		9/32	17/29	21.32
Nava (2011)	0.833	0.315	2.202	−0.368	0.713		10/42	12/44	25.74
Subtotal	0.353	0.216	0.578	−4.141	0.000				
	I^2=0.0% ; P=0.88								
Postoperative ARF									
Auriant (2001)	0.263	0.074	0.936	−2.062	0.039		5/24	12/24	58.21
Bohner (2002)	0.204	0.023	1.779	−1.439	0.150		1/99	5/105	20.00
Squadrone (2005)	0.090	0.011	0.719	−2.271	0.023		1/105	10/104	21.79
Subtotal	0.198	0.075	0.522	−3.276	0.001				
	I^2=0.0% ; P=0.69								
Post-extubation ARF									
Jiang (1999)	2.130	0.762	5.952	1.443	0.149		13/47	7/46	9.9
Keenan (2002)	1.141	0.439	2.969	0.270	0.787		28/39	29/42	11.43
Esteban (2004)	1.024	0.604	1.736	0.087	0.931		55/114	51/107	37.47
Nava (2005)	0.280	0.083	0.943	−2.055	0.040		4/48	12/49	7.1
Kindgen-Milles (2005)	0.219	0.023	2.114	−1.313	0.189		1/25	4/25	2.03
Ferrer (2006)	0.464	0.195	1.107	−1.732	0.083		9/79	18/83	13.86
Ferrer (2009)	0.525	0.176	1.567	−1.155	0.248		6/54	10/52	8.74
Zarback (2009)	0.502	0.124	2.032	−0.966	0.334		3/232	6/236	5.35
Khilnani (2011)	0.529	0.108	2.598	−0.784	0.433		3/20	5/20	4.13
Subtotal	0.780	0.565	1.078	−1.505	0.132				
	I^2=31.75% ; P=0.16								
Weaning									
Nava (1998)	0.290	0.067	1.260	−1.651	0.099		3/25	8/25	14.57
Girault (1999)	0.923	0.188	4.538	−0.099	0.922		4/17	4/16	12.41
Ferrer (2003)	0.444	0.095	2.075	−1.032	0.302		3/21	6/22	13.26
Girault (2011)	1.147	0.555	2.370	0.370	0.711		22/69	20/69	59.76
Subtotal	0.806	0.460	1.412	−0.755	0.450				
	I^2=10.92% ; P=0.33								

0.01   0.1   1   10   100

NIV   Standard care

Fig 2 Failure rates with NIV vs standard medical therapy in ARF. The figure shows the meta-analysis for (top to bottom) COPD, ACPO, hypoxic ARF, hypoxic–hypercapnic ARF, postoperative ARF, post-extubation ARF, and weaning.
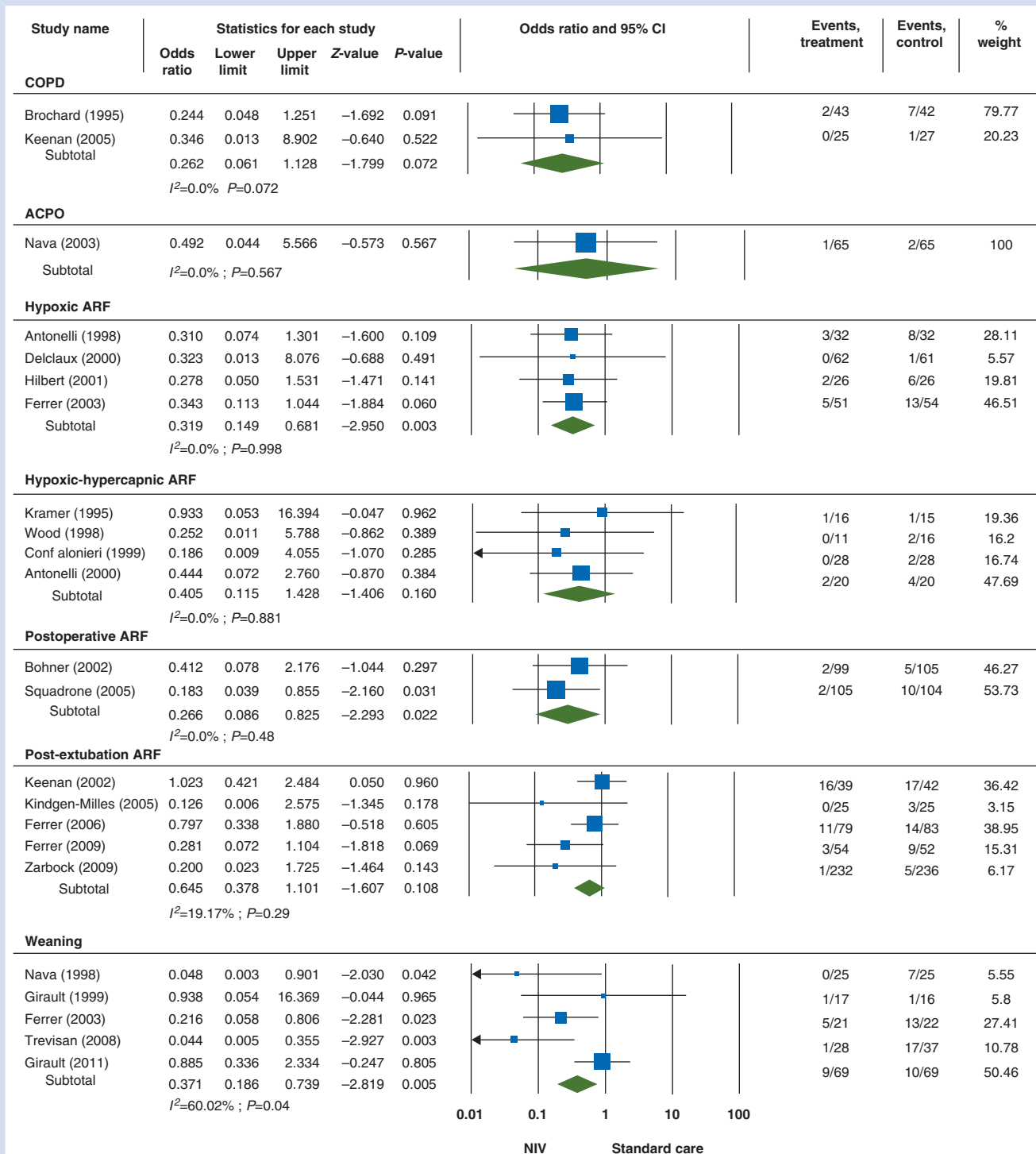
Study name	Statistics for each study					Odds ratio and 95% CI	Events, treatment	Events, control	% weight
	Odds ratio	Lower limit	Upper limit	Z-value	P-value				
COPD									
Brochard (1995)	0.244	0.048	1.251	−1.692	0.091		2/43	7/42	79.77
Keenan (2005)	0.346	0.013	8.902	−0.640	0.522		0/25	1/27	20.23
Subtotal	0.262	0.061	1.128	−1.799	0.072				
	I^2=0.0% P=0.072								
ACPO									
Nava (2003)	0.492	0.044	5.566	−0.573	0.567		1/65	2/65	100
Subtotal									
	I^2=0.0% ; P=0.567								
Hypoxic ARF									
Antonelli (1998)	0.310	0.074	1.301	−1.600	0.109		3/32	8/32	28.11
Delclaux (2000)	0.323	0.013	8.076	−0.688	0.491		0/62	1/61	5.57
Hilbert (2001)	0.278	0.050	1.531	−1.471	0.141		2/26	6/26	19.81
Ferrer (2003)	0.343	0.113	1.044	−1.884	0.060		5/51	13/54	46.51
Subtotal	0.319	0.149	0.681	−2.950	0.003				
	I^2=0.0% ; P=0.998								
Hypoxic-hypercapnic ARF									
Kramer (1995)	0.933	0.053	16.394	−0.047	0.962		1/16	1/15	19.36
Wood (1998)	0.252	0.011	5.788	−0.862	0.389		0/11	2/16	16.2
Conf alonieri (1999)	0.186	0.009	4.055	−1.070	0.285		0/28	2/28	16.74
Antonelli (2000)	0.444	0.072	2.760	−0.870	0.384		2/20	4/20	47.69
Subtotal	0.405	0.115	1.428	−1.406	0.160				
	I^2=0.0% ; P=0.881								
Postoperative ARF									
Bohner (2002)	0.412	0.078	2.176	−1.044	0.297		2/99	5/105	46.27
Squadrone (2005)	0.183	0.039	0.855	−2.160	0.031		2/105	10/104	53.73
Subtotal	0.266	0.086	0.825	−2.293	0.022				
	I^2=0.0% ; P=0.48								
Post-extubation ARF									
Keenan (2002)	1.023	0.421	2.484	0.050	0.960		16/39	17/42	36.42
Kindgen-Milles (2005)	0.126	0.006	2.575	−1.345	0.178		0/25	3/25	3.15
Ferrer (2006)	0.797	0.338	1.880	−0.518	0.605		11/79	14/83	38.95
Ferrer (2009)	0.281	0.072	1.104	−1.818	0.069		3/54	9/52	15.31
Zarbock (2009)	0.200	0.023	1.725	−1.464	0.143		1/232	5/236	6.17
Subtotal	0.645	0.378	1.101	−1.607	0.108				
	I^2=19.17% ; P=0.29								
Weaning									
Nava (1998)	0.048	0.003	0.901	−2.030	0.042		0/25	7/25	5.55
Girault (1999)	0.938	0.054	16.369	−0.044	0.965		1/17	1/16	5.8
Ferrer (2003)	0.216	0.058	0.806	−2.281	0.023		5/21	13/22	27.41
Trevisan (2008)	0.044	0.005	0.355	−2.927	0.003		1/28	17/37	10.78
Girault (2011)	0.885	0.336	2.334	−0.247	0.805		9/69	10/69	50.46
Subtotal	0.371	0.186	0.739	−2.819	0.005				
	I^2=60.02% ; P=0.04								

0.01   0.1   1   10   100

NIV   Standard care

Fig 3 Pneumonia incidence with NIV *vs* standard medical therapy in ARF. The figure shows the meta-analysis for (top to bottom) COPD, ACPO, hypoxic ARF, hypoxic–hypercapnic ARF, postoperative ARF, post-extubation ARF, and weaning.

should be carefully considered from the beginning of NIV.[3] [8] [87] [142] [143]

Airways dryness   During NIV, cool and dry gases alter the tracheobronchial mucosa. By drying secretions and desquamating mucosal epithelium, NIV may cause mucous plugging and atelectasis.[143] Inspissated secretions predispose to difficult tracheal intubation in the case of NIV failure and may precipitate life-threatening airway obstruction.[144] [145]

Without humidification, gas humidity is very low when an ICU ventilator is used (5 mg H_2O litre^{-1}) and humidification

of inspired gases during NIV should target absolute humidity level from 10 mg to above 15 mg H_2O litre^{-1} (with temperatures ranging from 25 to 30°C).[143] However, despite the benefit of gas humidification in terms of comfort and tolerance during long-term NIV in COPD patients, controversy continues on whether supplemental humidification is routinely required during NIV in the acute-care setting.[143] The main types of humidification devices used, heated humidifiers and HMEs, are used for both short-term and long-term humidification during NIV.[143 146] Although numerous clinical evaluations indicate that HME performances are close to those of heated humidifiers during IMV, HME has the potential to increase minute ventilation, mouth occlusion pressure at 0.1 s, Pa_{CO_2}, and work of breathing during PSV in comparison with heated humidifiers.[146 147] This is due to the substantial dead space that HME adds to the ventilatory circuit because of their large internal volume and may be avoided with small dead space HME.[148] During helmet NIV, the high internal gas volume could serve as a 'mixing chamber' between the heated humidified expired gas and the dry medical gas entering the helmet.[149] This could raise the heat and humidity of the medical gas, thus avoiding the need for a heated humidifier.[149] Patients with ARF and healthy individuals exhibited similar abilities to heat and to humidify medical gases and the use of the heated humidifier does not affect the level of patient comfort.[149]

Gastric insufflation   Aerophagia occurs in most NIV patients and gastric insufflation in 5%[21 25 45 50 52 53 57 62 67 69] to 30–40% of patients.[87] During NIV, the ventilation volume distributes between lungs and stomach depending on respiratory system resistance and lower oesophageal sphincter pressure (∼20–25 cm H_2O in adults) which, in turn, varies with head position, inflation flow rate, inspiratory time, and tidal volume.[150] Large tidal volumes (800–1200 ml), high airway resistance, low respiratory system compliance, and short inspiratory time all increase airway pressure and air entering the stomach.[150] Smaller tidal volumes (≈500 ml) are safe and effective as long as oxygen supplementation is used.[150] When gastric insufflation occurs during NIV, gastric distension compresses the lungs, thereby decreasing lung compliance and demanding higher airway ventilation pressure.[150 151] The latter is also associated with increased risk of gastric distension, thus generating a vicious cycle.[150 151] The aberrant respiratory pattern may be exacerbated by bronchoconstriction and bronchial hyperreactivity induced by gastric distension.[151] Although rarely intolerable, gastric insufflation facilitates vomiting and inspiration of gastric contents and can cause serious complications (i.e. pulmonary aspiration, abdominal compartment and hypertension syndromes, stomach rupture, and, exceptionally, death).[3 151]

Theoretically, airway pressures higher than 20–25 cm H_2O should be avoided. Moreover, considering recent evidence of its efficacy in severe chronic hypercapnic COPD, high pressure NIV should also be carried out in an almost sitting position approximately half an hour after a meal and with routine gastric decompression care.[3 151]

In conclusion, to optimize patient outcome, NIV should be applied by a trained and experienced team, with careful patient selection according to available guidelines and good clinical judgement, taking constantly into account the risk factors for NIV failure. Once begun, patients should be closely monitored in an ICU or step-down unit until adequately stabilized, paying attention not only to vital signs and gas exchange, but also to tolerance, comfort, air leaks, and patient–ventilator interaction. The proper choice of device, an adequate management of ventilatory support, a skilled team, and accurate clinical and instrumental monitoring are crucial to minimize the risk of complications during NIV.[152 153]

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