Non-Invasive Mechanical Ventilation in Critically Ill Trauma Patients: A Systematic Review

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There is limited literature on non-invasive mechanical ventilation (NIMV) in patients with polytrauma-related acute respiratory failure (ARF). Despite an increasing worldwide application, there is still scarce evidence of significant NIMV benefits in this specific setting, and no clear recommendations are provided. We performed a systematic review, and a search of clinical databases including MEDLINE and EMBASE was conducted from the beginning of 1990 until today. Although the benefits in reducing the intubation rate, morbidity and mortality are unclear, NIMV may be useful and does not appear to be associated with harm when applied in properly selected patients with moderate ARF at an earlier stage of injury by experienced teams and in appropriate settings under strict monitoring. In the presence of these criteria, NIMV is worth attempting, but only if endotracheal intubation is promptly available because non-responders to NIMV are burdened by an increased mortality when intubation is delayed.

Keywords: Non-invasive mechanical ventilation, continuous positive airway pressure, acute lung injury, acute respiratory distress syndrome, acute respiratory failure, transfusion-associated circulatory overload

Introduction

Trauma patients are a heterogeneous patient population with different respiratory needs. The intensity and modality of respiratory and ventilatory supports mainly depend on the severity of respiratory dysfunction, the degree of gas exchange impairment, associated injuries and the feasibility of non-invasive mechanical ventilation (NIMV) as the first-line approach.

The usefulness of NIMV (either non-invasive positive pressure ventilation [NPPV] or continuous positive airway pressure [CPAP]) in the respiratory management of trauma patients has still not been sufficiently investigated on a large scale. According to the British Thoracic Society guidelines from 2002 (1), the indications and efficacy of NIMV in trauma-induced respiratory insufficiency were inconsistent and merely received a low-grade recommendation. In the last 20 years, several reports have demonstrated that NIMV may be effective in trauma patients as a means of preventing or treating...
impeading or evident respiratory failure. However, despite increasing worldwide application, there are still no specific recommendations on the NIMV use in such a setting.

Factors that may account for the scarce evidence of the significant benefit of NIMV in trauma patients include the lack of uniformity, standardisation and design of various NIMV trials, the wide range of different traumatic events after which it was attempted and the low number of patients with significant hypoxemia included in the trials. Different conclusions likely emerge because of different objectives and comparisons of the investigations. For example, some trials compared NIMV with conventional ventilation, some compared it with high-flow nasal oxygen, and some assessed its ability to improve gas exchange, prevent tracheal intubation or reduce mortality (2-5).

When evaluating the benefits of NIMV, the aetiology of acute respiratory failure (ARF) may become an important determinant of the final outcome, which likely explains the variable outcomes of NIMV application in various diseases and severities of lung injury.

Given the lack of a clear consensus on the use of NIMV in patients with trauma-related ARF, we performed a systematic review on clinical experience, recommendations, technical aspects and final results of its use in this setting.

Methods

Study design and literature search

By selecting several major key topics, our aim was to investigate the indications for NIMV in polytrauma as well as its foremost effects.

We included data only from studies that enrolled adults (aged >18 years) who developed ARF as a consequence of blunt or penetrating trauma and who were admitted to the emergency department, trauma service or intensive care unit (ICU) and treated with NIMV.

Randomised and non-randomised controlled trials, as well as observational studies including cohort, case-control and case series, were searched from previously published systematic reviews and meta-analyses. The list of studies was updated by a number of clinical databases, including MEDLINE and EMBASE, from January 1990 until the day when the search strategy was developed to maximise the sensitivity of article identification, and it was not restricted by language. The selected keywords were non-invasive mechanical ventilation, CPAP and polytrauma, which were cross-referenced with flail chest, pulmonary contusion, chest injury, blunt chest trauma, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO). Because this was a retrospective review, ethical approval was deemed not necessary for data collection.

Results

ARF in trauma

Two major mechanisms are responsible for ARF following trauma: (a) the direct involvement of the thoracic cage or lung parenchyma, such as in the case of multiple rib fractures, pulmonary contusions, pneumothorax and injury to airway structures, major vessels, heart and pericardium, diaphragm and other structures of the mediastinum and (b) the leakage of oedema fluid into the lung and inflammatory cellular infiltrates associated with altered surfactant composition and diffusion abnormalities. The latter mechanism is the typical feature of lung involvement from non-thoracic trauma associated with shock, disseminated intravascular coagulation, sepsis syndrome, large transfusion of blood products and acute pancreatitis. Both pathogenic events may converge on a common pathophysiological pathway and cause differing degrees of ARDS severity.

In spontaneously breathing patients, the trauma-induced alteration of the chest wall mechanics decreases the tidal volume interfering with the cough reflex, predisposing to the retention of secretions, atelectasis and pneumonia. An associated pulmonary contusion can dramatically contribute to intrapulmonary shunt and the worsening of gas exchange.

Non-invasive ventilation in flail chest

There has been an increasing use of NIMV in patients with ARF to avoid endotracheal intubation (ETI) and its complications (5).

Chest injury and its relevant complications are responsible for as much as 25% of blunt trauma mortality. Flail chest occurs in almost 20% of patients hospitalised for blunt chest trauma, and the overall mortality may be as high as 35% (6, 7).

Flail chest is defined as fractures of more than three consecutive ribs at two separate sites. When adjacent ribs are fractured, that segment of the thorax becomes disconnected from the remaining of the rib cage, resulting in a paradoxical movement of the involved part. During inspiration, the flail segment moves inwards, pulled by the negative intra-thoracic pressure, whereas during expiration, it moves outwards due to the positive intra-thoracic pressure, causing a variable degree of disarrangement in ventilation and gas exchange (7). This is particularly evident in patients with flail chest who present with hypoxemic ARF and are at high risk for respiratory impairment (8). The causes of respiratory failure in these patients include shunt (secondary to lung contusion), ventilation-perfusion mismatch, atelectasis, pneumothorax or haemothorax. After an appropriate pain management, the goal should be to avoid ETI (9). The application of positive pressure to the airways, either by NPPV or CPAP, may reduce the need to intubate such patients.

Tzelepis et al. (10) investigated the physiological role of CPAP in the treatment of flail chest-related respiratory failure by as-
sessing chest wall distortion in patients with flail chest on var-
ious ventilatory modes. The results of their study showed that
there was less chest wall distortion during a high-flow CPAP
than during intermittent mandatory ventilation. Moreover,
CPAP produced the least overall distortion, which was like-
ly related to the effect of positive pleural pressure and the
minimal ventilator-imposed load of this system. Therefore,
CPAP may provide enough pneumatic force to stabilise the
flail segments, thereby providing a true “internal pneumatic
stabilisation” (11).

Mechanical ventilatory support is not always mandatory for
the treatment of flail chest (12); its need depends on the se-
verity of ARF and existing co-morbidities, such as pulmo-
nary contusion and post-traumatic ALI. In 1975, Trinkle et
al. (13) showed that flail chest-associated ARF was mainly
due to the underlying pulmonary contusion, rather than para-
adoxical respiration due to the flail chest itself. There is a lack
of scientific evidence for the treatment of flail chest; recent
guidelines (14) made no level 1 recommendations for the
management of flail chest and pulmonary contusion.

In a prospective study, patients with flail chest had a higher
rate of mechanical ventilation use, greater incidence of respi-
atory complications and longer length of hospital stay than
those with rib fractures only, despite similar clinical severity,
and rates of lung contusion and extrathoracic injury (15).

Only two randomised controlled trials (RCTs) have com-
pared NIMV with ETI in patients with flail chest or multiple
rib fractures, and only one has evaluated NPPV as opposed
to oxygen therapy to prevent ETI. The first RCT comparing
CPAP with ETI was published in 1990 by Bolliger and Van
Eeden (16). In 69 patients with more than three rib frac-
tures and hypoxemia, CPAP with regional analgesia was com-
pared with ETI, NPPV with positive expired pressure
(PEEP) and systemic analgesia. The CPAP group had a short-
er duration of treatment and length of ICU stay and a lower
rate of complications (28% vs. 73%). The main difference
in complications was the incidence of infections, primarily
pneumonia, which occurred in 14% as opposed to 48%.

In another RCT, Gunduz et al. (17) compared CPAP with
ETI and NPPV in patients with flail chest. In the CPAP
group, pain control was achieved with morphine sulphate
patient-controlled analgesia. In the NPPV group, propofol
plus fentanyl were infused continuously. \( \text{PaO}_2 \) was higher in
the NPPV group in the first 2 days, but no differences were
observed over the following days. There were no differences
in the mean ICU or hospital length of stay. Differences were
observed in the incidence of nosocomial infections (47.6%
in the NPPV group vs. 18.2% in the CPAP group) and mor-
tality directly or indirectly linked to infection (seven vs. two
patients).

In a retrospective study by Tanaka et al. (11), CPAP was ap-
plied in patients with flail chest trauma. These patients were
compared with historical controls who were primarily treated
with mechanical ventilation. The patients treated with CPAP
had a lower rate of pulmonary complications (atelectasis 47%
vs. 95%; pneumonia 27% vs. 70%) than the historical controls.

Hernandez et al. (18) performed an RCT to assess if NPPV,
as compared to high-flow nasal oxygen, could reduce the in-
tubation rate in patients with severe chest trauma-related hy-
poxemia. They also enrolled patients with flail chest (seven of
50 patients). The primary end-point was the intubation rate,
which was higher in the control group, even for the seven
patients had flail chest.

**NIMV in non-flail chest trauma**

Gregoretti et al. (19) evaluated 22 trauma patients who were
weaned from invasive mechanical ventilation and switched
to NIMV at similar levels of both inspiratory and expiratory
pressures. They found that all patients tolerated NIMV and
had a similar improvement in gas exchange and respiratory
pattern, but nine (40.9%) patients required re-intubation. In
this study, gas exchange improved earlier with invasive me-
chanical ventilation.

In 2005, a prospective observational study was conducted to
evaluate the safety and efficacy of NIV in patients with ARF
due to blunt thoracic trauma (20). Twenty-two patients were
enrolled and treated with NIMV combined with regional an-
eaesthesia. Gas exchange and heart and respiratory rates im-
proved 1 h after starting NIMV. Eighteen of the 22 patients
avoided ETI and four required intubation, of whom one de-
veloped septic shock and died.

Table 1 summarises some studies that investigated NIMV in
patients with chest trauma and fail chest.

Vidhani et al. (21) conducted a retrospective review of 75
adults with blunt traumatic pulmonary contusions and found
that patients with significant pulmonary contusion, as indi-
cated by \( \text{PaO}_2/\text{FiO}_2<300 \), were safely managed with NPPV.

The trial by Hernandez et al. (18) was prematurely inter-
rupted because the intubation rate was much higher in con-
trols than in patients who underwent NIMV (40% vs. 12%,
p<0.02). Furthermore, the length of hospital stay was shorter
in patients who underwent NIMV (14 vs. 21 days p<0.001),
but no differences were observed in survival or other second-
ary end-points.

In a study by Antonelli et al. (22), NIMV significantly re-
duced the intubation rate in patients with severe thoracic
trauma compared with the rate in the control group (12% vs.
18%). The benefit of NIMV was attributed to the inclusion
of patients within 48 h after trauma, high prevalence of lung
contusions as the major underlying cause of hypoxia and ex-
tended length of NIMV use. The authors concluded that in
patients with severe thoracic trauma-related hypoxia, an early
and continuous application of NIMV is effective in reducing
the need for intubation.
NIMV in trauma-induced ARF and ARDS

Although the use of NIMV strategies has not gained universal approval in this setting because of the increased transpulmonary pressure and the uncontrolled overdistention of the alveoli, the commonly advocated advantages include the preservation of airway defence mechanisms, the decreased need for sedation and improvements in gas exchange.

One of the first randomised trials investigating the use of CPAP in trauma patients was conducted by Hurst et al. (23). Patients presenting with hypoxemia despite supplemental oxygen administration, and normo- or hypocarbia were treated with CPAP via a facemask. In 32 of 33 patients with isolated chest trauma, the therapeutic end-point of PaO\textsubscript{2}/FiO\textsubscript{2} > 300 mm Hg was achieved. ETI was required in only two patients for reasons other than an elevation in PaCO\textsubscript{2}.

Although the number of studies in this field is limited, CPAP alone, compared with NPPV, does not appear to decrease respiratory fatigue or dyspnoea or have substantial effects on oxygenation. In various reports, the addition of pressure support (PS) to PEEP was more effective than CPAP alone in unloading the inspiratory muscles, reducing neuromuscular drive and alleviating dyspnoea (24-26).

In the paper by Antonelli et al. (27), four of 32 patients who were assigned to NPPV had respiratory distress due to trauma-induced pulmonary contusion or atelectasis. This treatment was associated with a rapid and significant improvement in the PaO\textsubscript{2}-to-FiO\textsubscript{2} ratio, and ETI was avoided in all

<table>
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<th>Study</th>
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<td>Tanaka et al. (2001, case series)</td>
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<td>CPAP vs. spontaneous breathing</td>
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<tr>
<td>Bolliger and Van Eeden (1990, RCT)</td>
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<td>Duration of treatment, CPAP vs. MV (4.5±2.3 vs. 7.3±3.7 days, p=0.0003)</td>
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<td>Gunduz et al. (2005, RCT)</td>
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<td>Hernandez et al. (2010, RCT)</td>
<td>50</td>
<td>Lung contusions/ quadrant, thoracolumbar vertebral trauma, flail chest</td>
<td>NPPV vs. high-flow nasal oxygen</td>
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<td>Nosocomial infection: 8% vs. 12% Pneumothorax: 24% vs. 12% Mortality: 4% vs. 4%</td>
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RCT: randomized controlled trial; CPAP: continuous positive airway pressure; MV: mechanical ventilation; NPPV: non-invasive positive pressure ventilation; NIMV: non-invasive mechanical ventilation; PaO\textsubscript{2}: partial pressure of oxygen
four patients and no mortality occurred. In contrast, one of the four patients assigned to the conventional mechanical ventilation group died.

In a retrospective clinical study, Beltrame et al. (28) evaluated NPPV treatment in 46 patients with trauma-related ARF. Thirty-three (72%) patients were successfully weaned to spontaneous breathing. The effectiveness of NPPV was demonstrated by an improvement in the PaO₂-to-FiO₂ ratio, an increase in the tidal volume and a decrease in the respiratory rate. The failure group included nine patients with hypercapnia and four with hypoxemic respiratory failure; all required invasive mechanical ventilation.

In the study by Antonelli et al. (22), 88 patients were admitted to the ICU with trauma-related ARDS. Sixty-one (69%) of the 88 patients avoided intubation following NIMV, whereas 27 (31%) required invasive mechanical ventilation. In the subgroup of patients with pulmonary contusions and multiple trauma, only 18% required intubation.

In 2003, Ferrer et al. (29) compared the efficacy of NPPV to that of Venturi oxygen mask in avoiding intubation and improving the survival in patients with severe hypoxemic ARF. Six patients with thoracic trauma were enrolled in the NIMV group and 12 were enrolled in the control group. No ICU mortality was observed in the NIMV group, whereas three deaths were observed in the control group. Despite the small sample size, the authors observed a non-significant reduction of the intubation rate in patients in the NIMV group.

In a study by Xirouchaki et al. (20), several patients had bilateral lung injuries and were more likely to require intubation and prolonged mechanical ventilation. Within 24 h after starting NPPV, four patients required ETI.

According to the current available evidence, the practical results of NIMV techniques for ALI/ARDS are conflicting.

Despite initial favourable observations of Antonelli et al. (27), more recent trials (30, 31), although not the ones that enrolled trauma patients, have shown that the failure rate of NIMV in ALI/ARDS appears to exceed 50%.

Moreover, a recent meta-analysis (32) has highlighted that the number of RCTs reporting on NIMV in patients with ARDS is very limited and that the results of these studies suggest that these patients were unlikely to have important added outcome benefits from NIMV. The overall intubation rate in the NIMV group was 48%, and the overall mortality rate was 35%. However, patient selection widely differed among the studies, and none of these studies included trauma-associated ARDS, thus making the generalisation of the review’s results problematic.

The controversial role of NIMV as a definitive treatment of chest trauma-induced respiratory distress has also been highlighted in the systematic review published by Duggal et al. (33). They concluded that while NIMV may prevent intubation and decrease complications and ICU length of stay in selected patients with chest trauma and without respiratory failure, either no data or low-/moderate-quality data attest to its benefit in patients with severe hypoxemia and ARDS.

**NIMV in Massive TRALI**

Trauma patients suffering from multiple injuries and haemorrhagic shock necessarily undergo the transfusion of large amounts of blood, plasma and platelets. Almost no data are available on the effectiveness of non-invasive approaches in the management of ALI associated with massive transfusion. Most pertinent studies have emphasised the potential of NIMV in supporting ventilatory fatigue, alleviating dyspnoea and improving oxygenation, but no RCTs have been published that compared its efficacy and clinical outcomes with those of other treatments.

TRALI is characterised by a severe acute reaction, occurring during or within 6 h of transfusion and with no other apparent cause, which may cause pulmonary infiltrates, hypoxemia and respiratory distress. According to the “two hit” pathogenetic mechanism of TRALI, a first event such as sepsis or trauma potentially induces pulmonary endothelial activation, release of cytokines and “neutrophil priming.” The subsequent exposure to lipids, cytokines or antibodies associated with massive transfusion would then activate adherent neutrophils and release inflammatory mediators, leading to lung injury (34, 35).

TRALI and ARDS share a common pathophysiologic pathway and clinical definition except that TRALI is temporally and mechanistically related to the transfusion of blood or blood components. In both diseases, the increased pulmonary capillary permeability results in the movement of plasma into the alveolar space, thereby causing pulmonary oedema (36).

In some individuals, such as the elderly or patients with borderline cardiac function, trauma-associated massive transfusion may be responsible for another complication-TACO—which might cause hypoxemia and respiratory distress by itself. Although it can be difficult to differentiate the signs and symptoms of TRALI from those of the other forms of ARDS, patients affected by TACO usually manifest ARF associated with signs of circulatory overload, such as jugular venous distension and elevated pulmonary artery occlusion pressure, sometimes even before the initiation of a transfusion. The B-type natriuretic peptide level has been identified as a valid laboratory adjunct in the differentiation of TRALI from TACO (37).

The treatment of TRALI is identical to that of ARDS; for mild disease, supplemental oxygen and supportive care may be sufficient; for the most serious cases, either NIMV or invasive mechanical ventilation may be necessary, depending on the patient’s clinical condition and the severity of respiratory
insufficiency; and for less severe cases, a trial of NIMV could be warranted. Van Stein and associates (38) retrospectively evaluated 49 patients with TRALI and found that 11 (29%) were already on mechanical ventilation during transfusion, 21 (55%) required mechanical ventilation after the onset of TRALI, two (5%) underwent successful NIMV treatment and the remainder required only supplemental oxygen.

Discussion

Previous statements from the International Consensus Conference (39) have confirmed that in selected patients, the early institution of NIMV may reverse the acute episode and obviate the need for ETI; however, the switch to invasive ventilation has been reported in a high number of patients. After several years of NIMV application, there are still insufficient RCTs that support the use of NIMV in trauma patients. The available reports have mainly investigated its benefits or harm in small subgroups, with almost no comparisons with controls. A recent summary of clinical practice guidelines’ statements (5) made no recommendation on the use of NIMV in chest trauma without respiratory distress because of the lack of RCTs and no recommendation on its use in patients with chest trauma and respiratory distress. The same guidelines specifically recommended that CPAP should not be used.

However, in a recently published meta-analysis (40), the authors suggested that NIMV is useful in the management of patients with ARF due to chest trauma because it is associated with a significant reduction in the intubation rate, in the incidence of overall complications and infections, in the length of ICU stay and in mortality.

As emphasised by Hernandez et al. (18), when NPPV is applied early, the beneficial results can be ascribed to the ease of the recruitment of contused lung regions. By increasing the intra-thoracic pressure, NIMV increases the functional residual capacity, improves oxygenation, reduces the work of breathing and does not significantly alter the haemodynamics.

Given the disappointing results of various trials and meta-analyses, the selection of appropriate patients is crucial for optimising NIMV success rates and resource utilisation; otherwise, the extensive application of NIMV in patients with trauma-associated ARF may be challenging.

Although it has become a part of routine care for several patients with ARF, implementing NIMV for some patients may simply prolong the time to the inevitable intubation. Therefore, close monitoring is mandatory because delaying the time to intubation often leads to further respiratory instability. Non-responders to NIMV are burdened by an increased mortality risk when intubation is delayed (30, 32).

As a result, the role of NIMV in managing moderate respiratory insufficiency associated with trauma or TRALI may become important if applied in properly selected patients at an earlier stage of their lung injury by trained and experienced teams, with optimal choice of devices and in appropriate settings.

Conclusion

1. NIMV for the management of trauma patients may avoid risks associated with ETI-related infections. However, scientific evidence for an appropriate treatment of flail chest is lacking. A recent publication that reviewed management guidelines found no level 1 recommendations for flail chest (14). Level 2 recommendations comprise fluid resuscitation, pain management, avoidance of steroids and ventilatory management. An NIMV trial should be considered in alert and compliant patients with marginal respiratory status (level 3 recommendation), and the discontinuation of mechanical ventilation at the earliest possible time is advisable (40).

2. The optimal non-invasive approach is based on an understanding of the pathophysiology of individual patients with traumatic lung damage and the severity of gas exchange impairment. The main ventilatory goals are to improve oxygenation, unload respiratory muscles and relieve dyspnoea. PEEP added to PS has been shown to potentially recruit and stabilise previously collapsed lung tissue, and gradually adjusting the PS may help relieve dyspnoea.

3. Patients with flail chest-related respiratory failure should be treated early with NPPV and should not be prophylactically intubated. Further investigations are needed to assess which technique (CPAP or NPPV) is the best for the treatment of these patients.

4. Even if not supported by clear evidence, NPPV seems to be more effective than CPAP alone in maximising lung function until the reversal of the precipitating cause. Although the benefits in terms of reducing the intubation rate, morbidity and mortality are unclear, NIMV does not appear associated with harm when applied in properly selected patients in an adequate environment and under strict monitoring. In the presence of reliable selection criteria, it is worth attempting (41).

5. NIMV for patients with moderate trauma-related ARF should be considered as the first-choice treatment in the absence of contraindications; however, it should be implemented only where patients are closely monitored and ETI is promptly available.

6. In the specific setting of lung dysfunction due to chest trauma, the likelihood of success increases if proper measures of adequate pain control are adopted.
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