NIV in the Treatment of Acute Respiratory Failure: The Magnificent Five

11

In the full flood of evidence-based medicine, whose contents we often do not actually agree with, it is now relative easy to organize a grading of the evidence on the indications for NIV, which we have listed according to the scheme proposed by the Oxford Centre for Evidence-based Medicine (Fig. 11.1).

According to this classification, there are the "magnificent five" indications for the use of NIV: exacerbation of COPD, acute pulmonary edema, pneumonia in immunocompromised patients, weaning the COPD patient from invasive ventilation and, finally, prevention of post-extubation respiratory failure in patients at risk.

The other clinical applications, although important and worthy of further study, have not yet been conferred the level of scientific evidence for which NIV is to be considered the gold standard management for those applications. This does not mean that NIV for these applications cannot be validated scientifically and—why not—tested in our clinical practice, but greater caution is required. We will deal with each one of the five confirmed indications separately.

11.1 Exacerbation of COPD

After the first uncontrolled, nonrandomized studies back at the end of the 1980s, during which the promising advantages of NIV already began to be seen, in the period between 1993 and 1998 there were five important randomized, controlled trials comparing the efficacy of NIV combined with standard medical therapy compared to standard medical therapy alone in the treatment of exacerbations of COPD. Four of these studies demonstrated the superiority of NIV, which was successful in more than 90 % of cases, compared to medical therapy alone, which had a maximum success rate of 70 % in the study by Bott and much lower rates in the other studies (Bott et al. 1993).

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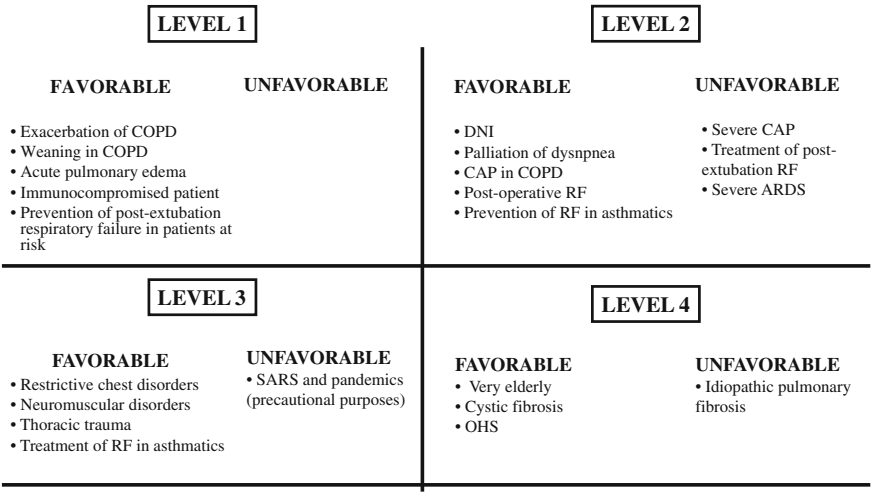

Fig. 11.1 Levels of scientific evidence: *LEVEL 1* systemic reviews based on randomized control trials with small confidence intervals; *LEVEL 2* reviews of single cohort studies, cohort studies or poorer quality randomized controlled trials; *LEVEL 3* reviews of case-controlled studies or individual case-controlled studies, *LEVEL 4* observational studies or case-controlled cohort studies of lesser quality

Only the study by Barbé et al. produced data that were discordant with these: in their study, the percentage success rates of NIV and medical therapy were 70 and 100 %, respectively (Barbé et al. 1996). This study, which was performed on patients with mild disease was mild, showed that NIV should be reserved to relatively compromised patients and should not, therefore, be used when medical treatment has a reasonable possibility of success and the NIV could be poorly tolerated by the patient.

This concept was clearly reaffirmed in a subsequent systematic review of the literature by Keenan, who showed that the efficacy of NIV is maximal in severe exacerbations of COPD (Keenan et al. 2003). Nevertheless, it is important to consider in what context the ventilator therapy is applied. For example, a multicenter randomized study by Plant et al. published in The Lancet and carried out in so-called "respiratory wards" showed that NIV was superior to medical therapy; however, a subsequent analysis showed that this effect too was explained by the high success rate among patients with a pH between 7.34 and 7.30 (Plant et al. 2000). The most severely ill patients did not have particularly satisfactory outcomes, and these were comparable to those obtained with traditional therapy.

As we said in the chapter, "When to start (or not) ventilation treatment" it is not only the timing of NIV, but also its place of use, that is fundamental in determining whether the therapy will be a failure or success. In other words, although the various reviews suggest that the success rate of NIV during an exacerbation of COPD is high also among patients with a pH < 7.30, we must bear in mind that

many of the studies considered were carried out in protected environments (*i.e.* intensive or subintensive care units) and that these results should not be generalized to classical respiratory or general medicine wards without considering the staff, structure, monitoring, and ventilators available in such wards. In conclusion, compared to medical treatment alone, in patients with an exacerbation of COPD, NIV improves survival, reduces the need for intubation, lowers the rate of complications and shortens the time spent in intensive care and in hospital.

All the studies on the efficacy of NIV considered so far compared this method with standard medical therapy, in part because the purpose of NIV was usually prevention of endotracheal intubation and not as an alternative to it. The only two clinical studies in which the two methods of ventilation, invasive and non invasive, are compared were performed in Italy and Croatia.

In a study by Conti and colleagues in 2002 (Conti et al. 2002), a group of patients were admitted to the intensive care unit because of acute hypercapnic respiratory failure resulting from an exacerbation of COPD (mean pH, 7.21) after failure of standard medical treatment in the emergency department, so with an elective indication for ventilatory support. The patients were randomized to treatment with invasive or non invasive ventilation. The outcome of the two groups was comparable; they had the same improvement in blood gases, duration of ventilation, time spent in hospital, and number of complications. About 50 % of the NIV group avoided intubation. A follow-up carried out 1 year later revealed that the patients in the NIV group had required fewer hospital admissions and prescriptions of home oxygen therapy. This study confirmed that patients with more severe blood-gas disturbances should be treated in the intensive care unit, in order that they can be intubated immediately if the NIV fails. In the Croatian study, the duration of mechanical ventilation was overall 78 h shorter in the NIV group, and the time spent in the intensive care unit was also reduced. Ventilator-associated pneumonia occurred in 6 % and 37 % of the NIV group and intubated group, respectively.

In another case-controlled study, Squadrone and colleagues (Squadrone et al. 2004) recruited patients with hypercapnic respiratory failure due to an acute exacerbation of COPD or pneumonia with a mean pH of 7.18. The NIV failed in 60 % of the patients who were then intubated. The mortality, duration of mechanical ventilation, and length of hospital stay were similar in the two groups of patients, but the patients treated with NIV had fewer complications.

NIV is, therefore, undoubtedly the first-line treatment for exacerbations of COPD, provided that the patient does not have any of the classical contraindications to the method. This should now be standard practice in our wards; although it unfortunately sometimes still occurs, it is no longer acceptable to deny these patients ventilation treatment *a priori* with the excuse of age, number of past exacerbations or, worse still, the impossibility of finding a bed.

11.2 Acute Pulmonary Edema

The treatment of acute, cardiogenic pulmonary edema with NIV deserves a section apart. From a physiological point of view, the application of a positive pressure has beneficial effects on both respiration and hemodynamics.

In particular, continuous positive pressure such as CPAP increases residual functional capacity, thereby improving lung compliance and, consequently, oxygenation. The decreased respiratory work load resulting from the administration of CPAP, particularly the reduction in deflections of pleural pressure, leads to a decrease in transmural pressure of the left ventricle which, in turn, reduces the preload, thereby improving hemodynamics, which are severely compromised during acute pulmonary edema. Is there any sense adding inspiratory support (i.e., Pressure Support) to the CPAP? From a physiological point of view, the combination of the two pressures could have a rationale when the patient not only has hypoxia but also hypercapnia, which, it should be recalled, is the sign of ventilatory pump impairment. In these conditions, inspiratory support could further reduce the load against which the respiratory muscles contract, thus avoiding respiratory distress and the potential onset of fatigue.

From a clinical point of view, numerous meta-analyses have shown that CPAP combined with medical therapy is more effective than oxygen therapy associated with medical therapy in reducing the need for intubation and, above all, in improving survival. Medical therapy should not, however, be suspended because the reason for any form of CPAP or other ventilatory support is to "gain time" until the nitrates and any diuretics prescribed can act.

CPAP delivered via a helmet is currently the first-line treatment of acute pulmonary edema in most emergency departments, intensive care units and cardiology, nephrology, internal medicine, respiratory, etc. wards, while some teams even use it in the earliest stages of care in the community, in the patient's home and during transport in the ambulance.

As mentioned above, some patients with acute pulmonary edema develop a mixed acidosis in which the respiratory component appears predominant, both because of concomitant COPD and incipient fatigue of the respiratory muscles with alveolar hypoventilation and consequent hypercapnia. For this reason, ventilation with a combination of CPAP + Pressure Support (bilevel ventilation) has been and is still widely used as an alternative to CPAP. In fact, following the first negative data indicating a higher incidence of myocardial infarction in a study by Mehta et al., which was found to have some not irrelevant biases, the results of other randomized, controlled clinical trials on the use of bilevel ventilation were published. Some of these showed benefit only for hypercapnic patients, while in others the bilevel ventilation was equally effective independently of the initial carbon dioxide levels. Various meta-analyses demonstrated that, compared to oxygen therapy alone, bilevel ventilation is able to reduce the need for intubation but not survival, and that it does not increase the risk of myocardial complications,

thus confirming its safety. The same studies did not reveal significant differences in various outcomes when comparing CPAP with bilevel NIV.

For the sake of correctness, we must also mention a multicenter study from England that produced partially negative results on the use of NIV in acute pulmonary edema. Both CPAP and bilevel ventilation were found to be more effective than oxygen therapy in accelerating the process of healing, but the intubation rate was not statistically significantly different between the three groups. The study raised great interest, mainly because it was published in the most important medical journal in the world, the *New England Journal of Medicine*, even though it was vitiated by many problems (e.g., very low number of intubations, <3 %; the fact that some centers were not familiar with the method of ventilation; the very advanced age of the patients) which, in our opinion, limited the scientific validity of the results.

It is a pity that this study was then used to support the choices of those who do not like NIV. However, we console ourselves with the fact that our cardiology colleagues have already included both CPAP and bilevel ventilation in their guidelines on the management of acute pulmonary edema as first-line therapy together, of course, with medical treatment. Indeed, the most recent meta-analysis, which includes the above mentioned study, confirmed the effectiveness of both NIV and CPAP in reducing the need for intubation vs standard treatment.

In conclusion, we believe that CPAP can be considered the standard treatment for acute pulmonary edema, while the bilevel mode of ventilation is to be preferred in cases characterized by marked respiratory acidosis and concomitant COPD.

11.3 Pneumonia in Immunocompromised Patients

NIV is considered the treatment of choice during episodes of acute respiratory failure in immunocompromised patients with pneumonia because of the capacity of this form of ventilation to reduce infectious complications. The presence of a focus of bronchopneumonia is relatively common in immunocompromised patients (e.g., AIDS patients, patients after chemotherapy, solid organ transplantation, or bone marrow transplantation) and, if associated with acute respiratory failure, often leads to the patient's death. The reported mortality rate of these patients when intubated and, therefore, ventilated invasively is greater than 90 %. In the 1990s, the first observational studies and case reports suggested that NIV could be a valid alternative to intubation, at the same as improving clinical outcomes. At the height of the AIDS emergency, Confalonieri and colleagues demonstrated, in a case-controlled study, that patients with *Pneumocystis carinii* pneumonia treated with NIV had a lower in-hospital mortality rate than intubated patients and also a lower rate of pneumothorax (Confalonieri et al. 2002).

Some years later, Hilbert et al., in a classical randomized study whose results were published in the *New England Journal of Medicine*, showed that early use of NIV in immunocompromised patients with lung infiltrates significantly improved

gas exchange and, in particular, infectious complications, reduced the use of intubation and lowered the mortality rate compared to the same outcomes in the patients treated with standard therapy with oxygen (Hilbert et al. 2001). In detail, while the mortality rate in the NIV group was high (50 %), it was clearly lower than that in the group treated traditionally (81 %). In the wake of this study, numerous other studies confirmed the results, such that NIV, also by CPAP with a helmet, is currently common practice even outside intensive care units, for example in hematology and oncology units.

When discussing respiratory complications in immunocompromised patients, we must not forget subjects who have received a solid organ transplant. Antonelli and colleagues randomized such patients to receive NIV or standard medical therapy and oxygen (Antonelli et al. 2000). The PaO_2/FiO_2 ratio improved in 70 % of the former group and in only 25 % in the latter group, such that the use of intubation and the number of fatal complications were lower in the NIV group. The mean time spent in intensive care and the mortality rate in intensive care both decreased significantly, although in-hospital mortality did not. Given the difficulties in undertaking a study of this sort and possible medico-legal problems (particularly in the USA), this work has never been replicated since.

In conclusion, the data from this very particular population suggest that NIV should be used early to prevent intubation rather than to replace it in immunocompromised patients with acute respiratory failure.

11.4 Weaning from Invasive Ventilation in COPD

Although NIV is associated, as we have seen, with a high percentage of success in the management of exacerbations of COPD, some subjects must nevertheless be intubated for various reasons, such as a severely depressed sensorium, respiratory arrest, impossibility of removing secretions, and hemodynamic instability. If all goes well, the recourse to intubation rapidly resolves the problem that made NIV impossible to use. For example, a reduction in the $PaCO_2$ should improve the level of consciousness, just as energetic bronchial lavage, possibly associated with antibiotic treatment, could reduce the bulk of secretion and enable a new trial with NIV. Based on this physiological rationale, some uncontrolled studies suggested NIV as a method for shortening the period of intubation. In 1998, in the first randomized, controlled study, we treated one group of patients with traditional weaning through Pressure Support with the tube *in situ* and another group to early extubation (after 2–3 days) and application of NIV as a "bridge" to weaning (Nava et al. 1998). This is only possible if the patient has favorable clinical criteria, such as a reasonable degree of collaboration, sufficient capacity to expectorate, not severely altered gas exchange and a minimal ability to breathe autonomously. The method we used drastically shortened the weaning time and also had a positive effect on hospital stay and number of infectious complications, such as pneumonia, thus improving the 3-month survival rate.

Two subsequent randomized, controlled studies in France and in Brazil confirmed the concept presented above, which was also validated in another study carried out in patients who failed repeated trials of "traditional" weaning, showing that NIV, applied early after extubation, can reduce the duration of total ventilation, infectious pulmonary complications, and the time spent in an intensive care unit.

Burns et al. in a meta-analysis and systematic review identified 12 randomized controlled trials involving 530 participants, mostly with chronic obstructive pulmonary disease. Compared with invasive weaning, non invasive weaning was associated with significantly reduced mortality (relative risk 0.55, 95 % confidence interval 0.38–0.79), ventilator associated pneumonia (0.29, 95 % confidence interval 0.19–0.45),, length of stay in intensive care unit (weighted mean difference −6.27 days, −8.77 to −3.78) and hospital (−7.19 days, −10.80 to −3.58), total duration of ventilation, and duration of invasive ventilation. Non invasive weaning had no effect on weaning failures or weaning time.

More recently Girault et al. completed a randomized controlled trial in a large number of patients with chronic hypercapnic respiratory failure intubated for acute respiratory failure in 17 centers in France. Patients were randomized into three groups either to continue invasive mechanical ventilation with conventional weaning, to receive oxygen therapy after extubation, or to start NIV. Reintubation rates were 30, 37, and 32 % for the invasive weaning, oxygen-therapy and NIV groups, respectively. Weaning failure rates, including post-extubation acute respiratory failure, were 54, 71, and 33 %, respectively and this was statistically significant in favor of NIV. Rescue NIV success rates for the invasive and oxygen-therapy groups were 45 and 58 %, respectively. Apart from a longer weaning time in the NIV group than in the invasive group (2.5 vs. 1.5 days; $p = 0.033$), no significant outcome difference was observed between groups. It was therefore concluded that NIV decreases the duration of intubation and may improve the weaning results in difficult-to-wean patients with hypercapnic respiratory failure, by reducing the risk of post-extubation acute respiratory failure.

In order to convince even the most skeptical person that NIV is ventilation to all effects and not a poor relative of invasive ventilation, we conducted physiological evaluations of about 10 patients just before they were extubated and immediately after extubation when they were ventilated non invasively with the same parameters. The gas exchange and the work load of the respiratory muscles were exactly the same with the two methods of ventilation and definitely more advantageous than spontaneous breathing. This unequivocally shows that, in the stable patient, the switch from intubation to NIV merely means a change in the interface of the ventilation, but not its physiological effects. Although it cannot be used in all disorders or in all clinical settings, since it needs careful and continuous monitoring by medical and paramedical staff, we strongly believe that this method of weaning can be advantageous for some well-selected patients, above all those with COPD or chronic hypercapnia.

11.5 Prevention of Post-Extubation Respiratory Failure in High-Risk Subjects

Post-extubation respiratory failure is certainly a much more common occurrence than often thought; indeed, more than 15 % of subjects develop this complication in the 24–48 h after a weaning trial considered satisfactory. The more alarming fact is that about 40–50 % of these patients die once re-intubated. The efforts of researchers are, therefore, focused on the earliest possible treatment of patients who show initial signs of respiratory distress after being extubated. Unfortunately, as we shall see in the next chapter, waiting until the patient becomes symptomatic in some way could be too late.

Numerous epidemiological studies have identified the main causes of re-intubation, which can be summarized as the presence of comorbid conditions (in particular, chronic respiratory and cardiac disorders), upper airway problems, difficulty in expectoration, chronic hypercapnia, advanced age, and a fairly high severity score at the time of extubation. Taking into account these characteristics, three randomized controlled studies evaluated whether early application of NIV as pure prevention of possible post-extubation respiratory failure is actually able to reduce recourse to re-intubation.

The data from the first two studies were almost identical. Both studies showed that NIV administered sequentially for a few hours a day in the first 2 or 3 days after extubation in subjects who were at risk, but completely asymptomatic, significantly reduced the percentage of cases of re-intubation compared to that in patients simply kept under observation as usual practice. The studies differed only with regards to the effect on mortality, which was statistically significant in the Spanish study, whereas it just failed to be so in ours. An improvement in survival was demonstrated in a subgroup of patients who were hypercapnic at the time of extubation, confirming the fact that NIV seems to be particularly useful in the presence of high values of $PaCO_2$. This concept was recently validated in the third randomized, controlled trial carried out by the same Spanish group. All these studies excluded, *a priori*, patients with a high body weight in order to avoid factors that could confound the results. Some North American colleagues joked that since most of their patients are overweight, this indication for NIV does not have a future in the USA. Just to contradict them, a few months later it was a precisely an American study which demonstrated that preventive administration of NIV after extubation is associated, also in obese subjects, with a lower rate of re-intubation and improved survival compared with traditional behavior.

In conclusion, using NIV as a strategy to avoid the development of post-extubation respiratory failure is associated with a lower percentage of new requirement of mechanical invasive ventilation and, possibly, with improved survival.

Suggested Reading

Exacerbation of COPD

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