
NIV in the Treatment of Acute Respiratory Failure: Controversial Indications

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13.1 Pneumonia

A case of pneumonia that requires ventilation, whether invasively or non invasively, is always a serious event associated with a high mortality rate, particularly in the elderly, even though it is often considered by the media as an infection that is “easy” to resolve.

Why is this a controversial indication for NIV? Because there are observational studies that are absolutely against the use of NIV and a couple of randomized controlled trial in favor, in theory, but not necessarily in all cases of pneumonia or in all patients.

The difficulty in taking a position on this indication derives from the fact that it is not easy to compare the studies which, besides anything else, used the NIV in patients with differing severity of disease, based on the $\text{PaO}_2/\text{FiO}_2$ ratio. Once again it is important to talk about the timing of application. Nobody would consider intubating a patient with a $\text{PaO}_2/\text{FiO}_2$ between 250 and 300, although it is precisely in this category of patient that NIV could act best as prevention to avoid a subsequent worsening. This concept is supported by Cosentini et al. (2010) who used this philosophy in the treatment of patients with pneumonia, ventilating the patients with CPAP through a helmet in the Accident and Emergency department. CPAP delivered by helmet rapidly improved oxygenation in patients with community-acquired pneumonia suffering from a moderate hypoxemic acute respiratory failure. This trial represents a proof-of-concept evaluation of the potential usefulness of CPAP in patients with community-acquired pneumonia.

The data are much less encouraging when NIV is used as a true alternative to intubation. On this subject we advise you to read the article by Domenighetti, a Ticinese friend who, breaking out of the typical framework of evidence-based medicine, has launched a very important clinical message: for equivalent levels of hypoxia, patients with acute pulmonary edema have a clearly better outcome than those with pneumonia, despite the initial improvement in blood-gases (Domenighetti et al. 2002).

In other words, the $\text{PaO}_2/\text{FiO}_2$ ratio is important, but it is also an umbrella under which we group different disorders with different pathophysiological backgrounds and times of onset; it is not, therefore, surprising that we also observe completely different responses to NIV. Of course, this not only applies to acute pulmonary edema and pneumonias, but to all those disorders that lead to hypoxia.

The randomized controlled trial to which we referred early is that by Confalonieri and colleagues, who compared NIV versus standard medical therapy + oxygen (Confalonieri et al. 1999). Overall, the results were in favor of NIV, in that significantly fewer of the patients in the group treated this way required intubation. However, a post hoc analysis showed that this was entirely due to the subgroup of patients with COPD and hypercapnia on admission. A high PaCO_2 is, therefore, the *leit-motif* for obtaining favorable results.

In conclusion, the advice is to use NIV as early as possible in patients with pneumonia, remembering that it is the hypercapnic patient who is the ideal candidate and that applying NIV could lead to disappointing results not only for you but above all for your patients.

13.2 Acute Respiratory Distress Syndrome

The mortality rate of patients with acute respiratory distress syndrome (ARDS) is very high and even now it still reaches 30–40 %. We are, therefore, talking about a disorder that should always be treated in an intensive care unit except, perhaps, for the earliest stages but in any case in a protected environment. We should also say that, for reasons of safety, any trial with NIV should only be performed in the absence of multiorgan failure and in patients who are hemodynamically stable, without sepsis and never with a $\text{PaO}_2/\text{FiO}_2$ below 150.

For example, a randomized study by Ferrer et al., carried out in patients with hypoxic respiratory failure, demonstrated the efficacy of NIV versus standard therapy in reducing recourse to intubation but, at the same time, showed that the patients with the highest risk of failure were precisely those with ARDS (Ferrer et al. 2003). A review of the literature leads us to be very prudent concerning the use of NIV. One study always reported as a “positive” one was published in the *New England Journal of Medicine* by Antonelli and colleagues, who demonstrated that an improvement in oxygenation 1 h after starting treatment could be obtained by using either traditional intubation or NIV, with the latter being associated with a significant reduction in severe complications (Antonelli et al. 1998). The study by Antonelli is certainly robust and well designed and has, therefore, become one of the most frequently cited works in the literature; nevertheless, due care should be taken before generalizing its results. First of all, the study is often referred to as having been carried out in patients with ARDS, whereas only about 25 % of the population studied had this syndrome; furthermore, the study was performed in a single center in a hospital in which the team was particularly experienced in and enthusiastic about NIV, limiting the certainty that the results could be reproduced in every intensive care unit. A Chinese

study (Zhan et al. 2012) is probably the first randomized controlled trial comparing NIV versus high-concentration oxygen in patients with mild ARDS, according to the new Berlin definition (i.e., those patients with a $\text{PaO}_2/\text{FiO}_2$ ratio $> 200 < 300$). A total of 21 patients were assigned to NIV and 19 to the control group. The proportion of patients requiring intubation was lower in the former group, and there was also a tendency to reduced mortality in this group.

However, a series of observational studies carried out in ‘real life’ situations dampened the optimism somewhat, highlighting the difficulty in treating a patient with averagely severe ARDS with NIV. A multicenter study carried out in three intensive care units with great experience in NIV is particularly interesting: this study demonstrated that, after having excluded a series of patients with hemodynamic instability, those requiring protection of the airways, and patients with severe sensorial disorders or multiorgan failure, it was possible to use NIV in about 65 % of the patient admitted to hospital. Of these cases just under a half had to be intubated subsequently because of a poor response to NIV. These patients were characterized by being male, being older, and having a higher SAPS II score (i. e. >34) and more marked hypoxia on admission (i. e. $\text{PaO}_2/\text{FiO}_2 < 175$). The development of sepsis after starting NIV was associated with a low success rate. So, if we calculate the percentage of patients in whom we can use NIV successfully in real life conditions, this is <20 %, eroding the enthusiasm of even the most optimistic individuals.

In conclusion, it is probably reasonable to use NIV for an initial, short trial period in a patient with ARDS who is hemodynamically stable and has moderate hypoxia ($\text{PaO}_2/\text{FiO}_2 > 180$), but you must be ready to intubate the patient quickly.

13.3 Treatment of Post-extubation Respiratory Failure

We are really sorry to define this indication as “controversial” since we are convinced that at least in a limited number of patients NIV has a role and a rationale. Post-extubation respiratory failure is associated with a very high mortality rate and so its treatment with non invasive strategies could, in theory, reduce at least the possible infectious complications due to intubation, which are major causes of death.

We said previously that early identification of patients at risk and preventive use of NIV for a few days is associated with a better clinical outcome, but it is not always possible to “allow” this approach for reasons of time, staff, availability of beds, and appropriate instruments. So, we often find ourselves in the intensive care unit with a patient who is progressively developing first respiratory distress and then frank respiratory failure hours after being extubated.

However, two randomized controlled trials have “demolished” the use of NIV. A multicenter, international study by Esteban et al. demonstrated that, compared to the more conservative medical therapy, in this setting NIV is associated with a higher mortality rate, probably because too long a time passes between the

development of the respiratory distress and the intubation (Esteban et al. 2004). However, once again, a series of problems related to the study should be pointed out, starting with the limited experience that most of the centers involved had with NIV and finishing with the strange results obtained in the control group in which NIV could be used as rescue therapy. The success rate of NIV was greater than 50 % in this subgroup of patients, who were theoretically more severely ill, since they had already failed a trial of medical therapy, than in the group in whom NIV was used immediately.

In contrast, the other single-center study by Keenan et al. did not show any statistically significant differences in the main outcomes (i.e., re-intubation, mortality, duration of hospital admission) between patients managed with medical therapy or NIV. However, this study excluded, *a priori*, a group of patients who would theoretically have benefited most from NIV, that is, hypercapnic patients with COPD (Keenan et al. 2002). In fact, the preceding study carried out in France had shown that, compared to the effect of traditional treatment in a control group, NIV significantly reduced recourse to re-intubation precisely in the patients with post-extubation hypercapnic respiratory failure.

In conclusion, although the data from the two largest randomized controlled trials were negative, we do not feel that we can totally condemn the use of NIV in the treatment of post-extubation respiratory distress; indeed, we feel we can recommend its cautious use in patients with COPD who are hypercapnic.

13.4 Severe Acute Respiratory Syndrome and Other Pandemics

We should say immediately that the Canadian medical authorities have vetoed the use of NIV in severe acute respiratory syndrome (SARS) and the American authorities are considering this indication with considerable skepticism. We all hope that the alarm created by these pandemics is unjustified and the day of the apocalypse will never come, but let us consider that it will. Someone is going to have to explain to us where all the hundreds, if not thousands, of patients will be treated. The number of beds in intensive therapy units would clearly be insufficient, as would the availability of the more technologically advanced ventilators; furthermore, intubation is usually performed after sedation and neuromuscular blockade, which can only be done by specialists. We will, therefore, be asked to make dramatic choices between who does or does not “deserve” treatment. Perhaps, after all, we should think about alternative strategies, such as NIV, for the people who are still not very seriously ill and who could even be treated outside intensive care units.

This is not a completely unrealistic hypothesis because it is actually supported by some observational studies carried out in China during the outbreak of SARS. These studies demonstrated the efficacy, but above all the safety and feasibility, of NIV in this situation. In particular, one of these studies showed that of more than

100 healthcare workers who had been involved in using NIV, none had developed the disease or become positive for the coronavirus. Of course, all this was obtained by taking the right precautions such as admitting the patients to negative pressure rooms, and supplying the workers with special protective overalls and helmets. We should point out that not using these safety measures could put both the staff and patients at a real risk of infection since aerosol particles are sprayed for almost a meter during the phase of expiration of NIV.

This has, however, been recently challenged by Simonds et al. who showed how NIV is a droplet-generating procedure, producing droplets $>10\text{ }\mu\text{m}$, so that they are not likely to remain airborne. A few observational studies have described the outcomes of ventilated patients during the recent H1N1 pandemics, in which only a minimal part of the subjects received NIV. Most of the large multicenter studies reported moderate ($\sim 50\%$) rates of NIV failure while other single center investigations have recently described a better outcome, suggesting that individual training and experience with NIV may be determinants of success in this high-risk condition.

In conclusion, we believe that NIV could be a valid alternative to intubation during a pandemic, particularly if used outside an intensive care unit. Obviously, we hope that our belief never needs to be put to the test.

Suggested Reading

Pneumonia

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