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EDITORIAL

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Non-invasive pressure support ventilation in acute hypoxemic respiratory failure: common strategy for different pathologies?

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"Tu ne quaesieris (scire nefas) quem mihi, quen tibi finem di dederint (Q. Horati Flacci 65 B.C.-8 B.C. Carminum Liber Primus IX.)

It is better that you do not ask any question about the meaning that the Gods gave to your life, since you do not deserve to understand.

The era of Horace has long passed and it is now about time that we have to face, and in particular to understand, why things in medicine do not always go the way we would like them to. The application of non-invasive mechanical ventilation to treat episodes of acute respiratory failure has raised considerable enthusiasm in recent years. In the age of evidence-based medicine the use of non-invasive positive pressure ventilation (NPPV) as first choice treatment in hypercapnic respiratory failure is widely supported by the literature [1] and in some cases seemingly mandatory to avoid endotracheal intubation. In this respect, the International Consensus Conference on Non-Invasive Mechanical Ventilation in Acute Respiratory Failure [2] concluded that "the addition of NPPV to standard medical therapy of patients with hypercapnic respiratory failure may prevent intubation, reduce the rate of complications and mortality". On the other hand its application in hypoxemic respiratory failure is controversial so that the same Consensus Conference [2] stated that "larger, controlled studies are required to determine the potential benefit of adding NPPV to standard medical treatment in the avoidance of endotracheal intubation".

In 1995 Wysocki et al. [3] observed, for the first time, that patients with "pure" hypoxemic or hypercapnic acute respiratory failure had different responses to non-invasive pressure support ventilation (NPSV). He found that a selected group of non-COPD patients had no benefit, when compared to medical therapy, from application of this technique, with the exception of a subgroup of patients with a $PaCO_2$ higher than 45 mmHg.

The definition and severity of an episode of hypoxemic respiratory failure still relies on the PaO_2/FIO_2 ratio, thus including a variety of conditions of different etiologies and causes under the same umbrella. Most of the studies performed in "pure" hypoxemic respiratory failure were focused particularly on a single pathology such as cardiogenic pulmonary edema [4], ARDS, ALI [5] or community-acquired pneumonia [6, 7], so that a generalized recommendation on the use of NPPV for an episode of hypoxemic respiratory failure was difficult to make. When applied routinely for the treatment of hypoxemic respiratory failure due to acute lung injury of various causes, continuous positive airway pressure (CPAP) neither reduced the need for intubation nor improved outcomes compared to oxygen therapy [8]. However compared to CPAP, NPSV is most commonly used in ICU [9].

At least three randomized and controlled studies have employed NPSV in the ICU to treat patients with hypoxemic respiratory failure, irrespective of their underlying primary disease, basing the inclusion criteria mainly on the PaO_2/FIO_2 ratio. In two of these investigations [10, 11] the control group received standard medical therapy plus oxygen, so that NPSV was shown to be more effective than the usual treatment in avoiding endotracheal intubation, while the third one [12] still remains the only study directly comparing invasive with non-invasive ventilatory treatment. In this last study, Antonelli et al.

showed that application of the two different ventilatory techniques in hypoxemic respiratory failure resulted in similar short-term improvements in arterial blood gases, while NPSV was associated with fewer serious complications and a shorter stay in the ICU stay when compared with conventional mechanical ventilation. Unfortunately, despite the two groups of patients being apparently homogeneously composed, the small sample size did not allow the authors to perform a subgroup analysis according to the underlying diseases, so that it is possible that their results may have been influenced by a subgroup having a particularly better response to NPSV.

As a matter of fact, experience gained from other studies suggested, even though it was not clearly demonstrated, that, for a similar PaO_2/FIO_2 ratio, the efficacy of NPSV, and therefore the patient's outcome, depends predominantly on the underlying pathology. Confalonieri et al. [6] showed that, in selected patients with acute respiratory failure caused by severe community-acquired pneumonia, NPSV could significantly reduce the need for intubation when compared with medical treatment. But the subgroup analysis compels us to temper any excessive optimism since this clearly showed that only hypercapnic patients really benefited from the treatment, while in non-hypercapnic patients the rate of failure did not differ from that of the standard treatment. This was confirmed by Jolliet et al. [7] who, in an uncontrolled study performed in non-COPD patients with community-acquired pneumonia, showed an ever higher rate of NPSV failure than in the Italian study (66% versus 38%). The average PaO_2/FIO_2 ratio, lower than that in Confalonieri's study, could explain the difference in part.

Pulmonary edema has also been proposed as a cause of acute respiratory failure which could respond favorably to application of CPAP or NPSV. A meta-analysis by Pang et al. [4] showed that CPAP may reduce the rate of intubation compared to medical therapy while, in a more recent randomized controlled study, Masip et al. [13] showed that NPSV was superior to conventional treatment in avoiding intubation. But, again, data from the latter study showed that, apart from the faster improvement in gas exchanges, which was a feature common to all the patients treated by NPSV, the subgroup of patients who really benefited in terms of a reduction in the need for intubation had hypercapnic respiratory failure [14]. However, if we compare the results obtained in the subgroup of patients with "pure" hypoxemic cardiogenic pulmonary edema reported in Masip's study [13] (5% intubation rate) with those obtained for patients with a similar degree of hypoxemia during severe pneumonia reported by Confalonieri [6] or Jolliet [7], the difference in intubation rate in the patients with these two pathologies is striking.

To our knowledge, the study by Domenighetti et al.[15], published in this issue of the journal, is the first attempt to study whether similar degrees of hypoxemia (PaO_2/FIO_2 ratio) with two different causes have different outcomes.

We know that hypercapnic respiratory failure is a direct consequence of alveolar hypoventilation, whatever the cause, leading to the impairment of the respiratory pump. In this condition, application of an artificial muscle, i.e. the ventilator, takes on the work of breathing entirely or in part, giving time for bronchodilator therapy to decrease airway obstruction and hyperinflation. On the other hand, hypoxemic respiratory failure can be the "end point" of several pathologies, each acting through different physiopathological mechanisms (shunt, ventilation/perfusion mismatch, impairment of alveolar-capillary diffusion). Providing adequate oxygenation is, therefore, the life-saving procedure. The addition of CPAP may be helpful in many ways, depending on the underlying pathologies, because it can increase functional residual capacity, improve respiratory mechanics and therefore oxygenation and, in certain instances such as cardiogenic pulmonary edema, decrease the left ventricular afterload.

On the other hand, in most of these conditions, the inspiratory aid (i.e. NPSV) given by the ventilator may, theoretically, not be needed if hypercapnia, as a direct sign of respiratory pump failure, is not present. Once satisfactory oxygenation is reached, through one or more of the above mentioned mechanisms, the major determinant of the outcome remains the response to medical therapy. In this respect the main role of ventilation is to buy time for this therapy to start having an effect. Interestingly, Domenighetti et al. [15] have shown that, despite initial improvements being similar in terms of PaO_2/FIO_2 in the first hour of treatment, the outcome of patients affected by pneumonia was much worse than that of patients with cardiogenic pulmonary edema. Pneumonia has a relatively slow onset and time is also needed for conventional therapy to show its effects, conversely the onset of cardiogenic pulmonary edema is very rapid, but its resolution is similarly quick if the appropriate medical therapy works. Providing good oxygenation and ventilatory assistance, through an oxygen mask, NPSV or invasive ventilation, may therefore not be enough in terms of outcome when an inflammatory disease of any nature is healing too slowly. In the era of evidence-based medicine it is, therefore, rather surprising that the randomized, controlled trials on the use of NPSV in hypoxemic respiratory failure were performed on different case-mixes, taking into account only the PaO_2/FIO_2 ratio, which probably represents only the tip of very different icebergs.

Most of us still have a tendency to consider only data from randomized, controlled studies as being "true" and scientifically worthy, although this belief has been recently questioned [16, 17]. Indeed, observational studies such as the one by Domenighetti et al. [15] must be viewed positively, despite their intrinsic limitations, be-

cause they may offer us the possibility of considering the fact that, in medicine, the same clinical sign, i.e. hypoxemia (an epiphenomenon of different pathologies), does not necessarily benefit from the same treatment strategy (i.e. non-invasive mechanical ventilation). In this respect, studies aimed at assessing the physiological response to NPSV in acute respiratory failure due to different clinical conditions are more than welcome to help us to understand the rationale of what we are doing.

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