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Is the noninvasive ventilatory mode of importance during cardiogenic pulmonary edema?

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Despite its high incidence [1, 2] and a high mortality rate after a first episode (20–40%) [3, 4], cardiogenic pulmonary edema (CPE) treatment has changed very little during the past 35 years, the only real novelties coming from the proposal for nitrate boluses and the introduction of noninvasive ventilation (NIV). NIV is now routinely used during the emergency care of patients with acute CPE, with the aim of rapidly improving acute respiratory distress symptoms and reducing the need for endotracheal intubation [5]. Several meta-analyses and consensus have positioned the early use of NIV during CPE [6–10], at least in the case of persistent respiratory distress after an adequate medical treatment failure. In such indications, NIV is presumed to reduce by half the intubation and early mortality rates, and was also suggested to be associated with decreased ICU length of stay and hospital costs.

CPE is the clinical consequence of increased extra-vascular lung water, itself responsible for reduced lung volumes, compliance, and increased airway resistances by interstitial bronchial edema [11–14]. In response to such physiologic changes, inspiratory muscle load is elevated that in turn generates significant pleural pressure depression. These large pleural pressure swings are responsible for hemodynamic modifications, via an increase of left ventricular afterload and myocardial transmural pressure [15, 16]. A concomitant impairment in cardiac index in the case of systolic heart failure is likely to decrease oxygen delivery to tissues, particularly within respiratory muscles, thus creating a vicious circle.

Acute hypercapnia is frequently observed in the clinical field [17, 18], especially in elderly patients [3], by the combination of respiratory exhaustion and underlying bronchopulmonary diseases. Therefore, at least from a physiological point of view, the best NIV mode should aim to improve clinical signs of respiratory distress, to decrease the inspiratory muscles' workload, and to improve hemodynamics.

Continuous positive airway pressure (CPAP) is not a new therapeutic issue! By the early twentieth century evidence showed that the application of a positive pulmonary pressure to a patient experiencing acute cardiac failure allowed hemodynamic and respiratory mechanics improvements, while improving clinical signs of respiratory distress [19–21]. The effectiveness of CPAP plus medical treatment was compared with that of medical treatment alone by Bersten et al. [17] in a randomized study of 39 hypoxemic patients with respiratory exhaustion (mean $\text{PaCO}_2 \sim 60$ mmHg). Those authors observed a more rapid improvement of oxygenation under CPAP, associated with a rapid PaCO_2 decrease, as compared to control. No patient required the use of endotracheal intubation in the CPAP arm, whereas 35% of patients in the control group were intubated within 3 h of enrollment. Similar clinical and biological benefits, associated with a drastic decrease of the 48-h mortality rate, were

observed in an emergency room multicenter study of elderly patients with severe alveolar hypoventilation [3]. These results were observed and confirmed in various other clinical studies [7–10].

Noninvasive positive pressure ventilation (NIPPSV) can be considered the addition of an inspiratory support to CPAP. Several physiological studies have evidenced in various pathological situations (sub-acute COPD exacerbations, hypoxemic respiratory distress, stabilized CPE) that while CPAP alone was able to reduce the work of breathing (WOB), this effect was greater under NIPPSV [22–24]. NIPPSV also proved superior to CPAP in terms of dyspnea relief [23].

In a first randomized controlled trial comparing CPAP with NIPPSV for CPE, Mehta et al. [25] pointed out a greater improvement of most clinical, biological parameters, and dyspnea reduction under NIPPSV, whereas only the respiratory rate and oxygenation were improved under CPAP. This study induced several interrogations due to its premature termination given the high rate of myocardial infarction in the NIPPSV arm. The fact that these myocardial infarcts preceded inclusion or were the direct result of the ventilator mode was questioned. In a subsequent randomized study, Bellone et al. [26], however, concluded that CPAP and NIPPSV were equivalent in terms of clinical parameters improvement, but also in terms of myocardial infarction rate or troponin plasma levels increase. In all subsequent clinical comparisons, both CPAP and NIPPSV proved superior to medical therapy alone in terms of reducing the intubation rate [27, 28], without any adverse event rate or outcome differences.

A recent randomized trial comparing CPAP, NIPPSV, and standard oxygen therapy in 1,069 patients with acute cardiogenic pulmonary edema raised an important controversy while it demonstrated no mortality benefit from emergent NIV [29]. However, as clearly stated by the authors within their discussion, NIV (whatever its mode of application) allowed rapid improvements in patients' symptomatology and oxygenation parameters at the early phase of treatment, which by itself may be sufficient to justify such a treatment.

In this issue of intensive care medicine, Nourira and colleagues [30] reported the results of another prospective, multicenter, randomized trial comparing the use of NIPPSV versus CPAP during the emergency care of CPE. The study was very well performed and the patients were

carefully screened and selected. The primary outcome of the study is really accurate, whereas the authors chose to combine both hospital death and the need for tracheal intubation in composite criteria. Secondary outcomes are also of importance, including the resolution time, myocardial infarction rate, and the hospital length of stay. Mortality rate was rather low in both groups ($\leq 5\%$), and the combined outcome parameter was similar between NIPPSV and CPAP. No difference in terms of myocardial infarction rate was observed within groups, thus confirming all previous data. NIPPSV was clearly associated with a shorter resolution time (-50 ± 19 min).

Taking into account previous literature and the new data provided by Nourira et al. [30], what conclusions can be drawn from a clinical point of view? First, the use of NIV during acute respiratory distress is still an issue of importance. Even if outcome parameters improvement is not as important as it was during an initial period when nitrate boluses were not the standard of care [3, 17], such respiratory distress and dyspnea lessening should be all clinicians' first goal. Second, even if one considers that the final outcome parameters (mortality, length of stay) are equivalent while using either CPAP or NIPPSV, the shorter resolution time with NIPPSV associated with a more rapid PaCO_2 decrease should favor its use when such a ventilatory mode is available.

However, the choice of ventilatory mode should also be based on factors such as the operation setting (pre-hospital, emergency, intensive care), the staff experience, and the devices' ergonomics. In an ICU setting, NIPPSV would probably be the best choice; the use of lightweight, cheap, and simple CPAP devices during the pre-hospital care could be considered a better one, especially due to volumetry constraint and to the low efficiency of pressure support modes from several emergency and transport ventilators. Within an emergency department that has modern ICU ventilators and experienced staff that are able to use them on a routine basis for intubated patients, the use of simple CPAP devices might not be as interesting as it will in another emergency unit environment with less experience on the topic. We should consider that on a routine basis, beside real differences in terms of physiological improvements between CPAP and NIPPSV, the choice of one ventilatory mode over another is based primarily on the physicians' expertise and the operation setting.

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