The use of non-invasive ventilation in the treatment of acute cardiogenic pulmonary edema

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Abstract. – The patient with acute heart failure may present with acute cardiogenic pulmonary edema (ACPE), a condition accompanied by severe respiratory distress, with crackles over the lung and orthopnea, and an O₂ saturation usually < 90% on room air, prior to treatment.

Non-invasive ventilation is the delivery of assisted ventilation without the need for endotracheal intubation and an invasive artificial airway.

Two techniques are used for ventilatory support: continuous positive airway pressure (CPAP) and non-invasive positive-pressure ventilation (NPPV).

There is a strong consensus that one of these two techniques should be used before endotracheal intubation and mechanical ventilation because non-invasive techniques dramatically reduce the need for mechanical ventilation via endotracheal intubation and its complications.

The aim of this review is to evaluate and resume the evidence for the use of non-invasive positive pressure ventilation in the treatment of acute cardiogenic pulmonary edema according recent literature in order to guide physicians in using CPAP and NPPV in patients affected by ACPE in clinical practice.

Recent literature showed that CPAP and NPPV both significantly decrease the need for endotracheal intubation, and CPAP significantly decreases mortality when compared to standard medical treatment. These techniques resulted safe and there is no evidence of increased risk of acute myocardial infarction (AMI) with either of them.

Although both CPAP and NPPV present similar efficacy, CPAP has been shown to be cheaper and easier to implement in clinical practice and it could be considered the preferred intervention in patients with ACPE especially in the Emergency Department setting.

Key Words: Continuous positive airway pressure, Non-invasive positive pressure ventilation, Acute cardiogenic pulmonary edema, Pulmonary edema.

Introduction

Heart failure is the most frequent cause of hospitalisation in persons over 65 years of age¹ with a hospital mortality of 4% that increases to 36%²,³ in severe cases needing mechanical ventilation. The patient with acute heart failure (AHF) may present with acute cardiogenic pulmonary edema (ACPE) which is a form of hypoxemic acute respiratory failure.

Standard therapy for patients with acute respiratory failure that is unresponsive to conservative medical therapy often requires endotracheal intubation and mechanical ventilation. However, endotracheal intubation (ETI) is associated with a considerable risk of morbidity, including upper airway trauma, nosocomial pneumonia, and sinusitis and also this procedure may prolong intensive Care Unit and Hospital stays, as additional time may be necessary for weaning from ventilation and the treatment of complications⁴.

The potential benefit of continuous positive airway pressure (CPAP) using a face mask in patients with acute respiratory failure was recognized decades ago⁵.

In more recent years, non-invasive positive-pressure ventilation (NPPV), for example the combination of pressure support (PS) and posi-
tive end-expiratory pressure (PEEP) delivered via face mask or nasal mask has been used increasingly to avoid endotracheal intubation and its attendant complications in patients with acute respiratory failure.

The term hypoxic respiratory failure refers to a subgroup of patients whose acute respiratory failure is characterized by severe hypoxemia (PaO2/fraction of inspired oxygen (FiO2) ratio ≤ 200), severe respiratory distress (respiratory rate > 35 breaths/min), and a non-chronic obstructive pulmonary disease (COPD) diagnosis, including pneumonia, acute respiratory distress syndrome (ARDS), trauma, or cardiogenic pulmonary edema.

Cardiogenic pulmonary edema, along with chronic obstructive pulmonary disease (COPD) exacerbation, is one of the two most common diagnoses among recipients of non-invasive positive-pressure techniques in the acute setting. The evidence supporting the use of positive-pressure therapy in patients with pulmonary edema, however, is stronger for the use of CPAP than for NPPV (in which air pressure is increased during inspiration).

The aim of this review is to evaluate and resume the evidence for the use of non-invasive positive pressure ventilation in the treatment of acute cardiogenic pulmonary edema according recent literature in order to guide physicians in using CPAP and NPPV in patients affected by ACPE in clinical practice.

All English language articles related to non-invasive positive pressure ventilation were searched in MEDLINE database from 1966 to 2006. The keywords included “non-invasive positive pressure ventilation” or “non-invasive ventilation” or “continuous positive airway pressure” AND “pulmonary edema” or “pulmonary oedema”. The selection criteria included all prospective and retrospective studies, all clinical and basic reviews and basic science papers involving non-invasive ventilation in the treatment of ACPE.

Physiopathology of Cardiogenic Pulmonary Edema

Acute heart failure (AHF) is defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function and it may occur with or without previous cardiac disease. AHF can present itself as acute de novo (new onset of acute heart failure in a patient without previously known cardiac dysfunction) or acute decompensation of chronic heart failure (CHF).

The patient with AHF may present with one of several distinct clinical conditions like pulmonary edema, hypertensive acute heart failure, cardiogenic shock, high output failure, and right heart failure.

Pulmonary edema (verified by chest X-ray) is accompanied by severe respiratory distress, with crackles over the lung and orthopnea, with O2 saturation usually < 90% on room air prior to treatment.

In the normal lung, fluid and protein leakage is thought to occur primarily through small gaps between capillary endothelial cells. Fluid and solutes that are filtered from the circulation into the alveolar interstitial space normally do not enter the alveoli because of the very tight junctions of the alveolar epithelium. Rather, once the filtered fluid enters the alveolar interstitial space, it moves proximally into the peribronchovascular space. Under normal conditions the lymphatic circulation removes most of this filtered fluid from the interstitium and return it to the systemic circulation and movement of larger plasma proteins is restricted. The hydrostatic force for fluid filtration across the lung microcirculation is approximately equal to the hydrostatic pressure in the pulmonary capillaries which is partially offset by a protein osmotic pressure gradient.

A rapid increase in hydrostatic pressure in the pulmonary capillaries, leading to increased transvascular fluid filtration, is the hallmark of acute cardiogenic pulmonary edema. Increased hydrostatic pressure in the pulmonary capillaries is usually due to elevated pulmonary venous pressure from increased left ventricular end-diastolic pressure and left atrial pressure. Mild elevations of left atrial pressure (18 to 25 mmHg) cause edema in the perimicrovascular and peribronchovascular interstitial spaces. As left atrial pressure rises further (> 25 mmHg), edema fluid breaks through the lung epithelium, flooding the alveoli with protein-poor fluid.

The pathogenesis of acute cardiogenic pulmonary edema (ACPE) is related to a critical interaction between progressive decrease in left ventricular systolic function and acute increase in systemic vascular resistance, with the resultant migration of fluid from the intravascular compartment into the lung interstitium and alveoli.
This leads to a vicious cycle amplified by the following three important processes:

1. as pulmonary congestion increases, oxygen saturation decreases, resulting in decreased myocardial oxygen supply. This leads to ischaemia in regions with already borderline blood supply, further impairing cardiac performance;

2. hypoxemia and increased fluid content in the lungs induces pulmonary vasoconstriction increasing the right ventricular pressure. This compromises left ventricular function through the ventricular interdependence mechanism;

3. finally, circulatory insufficiency results in metabolic acidosis, which further jeopardises cardiac performance.

ACPE is characterised by an increase in extravascular lung water, which causes a decrease in respiratory system compliance, increased airway resistance, air trapping, arterial hypoxaemia, and decreased diffusing capacity. Retention of carbon dioxide, not previously associated with chronic obstructive pulmonary disease, is a common finding in patients presenting with ACPE and is associated with a poor prognosis. Hypercapnia is generally attributable to respiratory muscle fatigue as a result of increased work of breathing from both reduced lung compliance and increased airway resistance secondary to interstitial and bronchial edema.

Moreover, the respiratory muscles have to generate large negative swings in pleural pressure to start inspiratory flow and maintain adequate tidal volumes. This increase in negative intrathoracic pressure aggravates pulmonary edema by increasing both preload and afterload.

Another important point to consider while managing patients with ACPE is that respiratory distress and dyspnea are not directly related to hypoxaemia, and thus cannot be reversed with oxygen administration alone.

Non-Invasive Ventilation

Non-invasive positive pressure ventilation (NPPV) is the delivery of assisted mechanical ventilation without the need for an invasive artificial airway.

The guidelines on the diagnosis and treatment of acute heart failure of the European Society of Cardiology consider the strategy of ventilatory support without endotracheal intubation (non-invasive ventilation) in the treatment of those patients with AHF resistant to standard medical therapy.

Two techniques are used for ventilatory support: continuous positive airway pressure (CPAP) and non-invasive positive-pressure ventilation (NPPV), that is a method of providing mechanical ventilation to patients without the need for endotracheal intubation.

There is a strong consensus that one of these two techniques should be used before endotracheal intubation and mechanical ventilation because utilization of non-invasive techniques dramatically reduce the need for mechanical ventilation via endotracheal intubation and its complications.

Application of CPAP can cause pulmonary recruitment and is associated with an increase in the functional residual capacity. The improved pulmonary compliance, reduced transdiaphragmatic pressure swings, and decreased diaphragmatic activity can lead to a decrease in the overall work of breathing and therefore a decreased metabolic demand from the body.

NPPV is a more sophisticated technique that requires a ventilator. With this ventilation modality a certain volume of oxygen/air mix can be delivered to the patient from the ventilator at a preset pressure through either a nasal- or face-mask (inspiratory assistance). The addition of a positive end-expiratory pressure (PEEP) to the inspiratory assistance results in a bilevel positive airway pressure (also known as BiPAP).

The physiological benefits of this mode of ventilation are the same as for CPAP but also include the inspiratory assist. This would further increase the mean intrathoracic pressure and therefore potentially increase the benefits of CPAP, but can further reduce the work of breathing and therefore the overall metabolic and oxygen demand of patients with AHF.

Intrinsic positive end-expiratory positive pressure (PEEP) is commonly observed in patients with airflow limitation. PEEPi is overcome by isometric respiratory muscle contraction before airflow can begin and, for the patient receiving non-invasive ventilation, a triggered breath initiated. By offsetting intrinsic PEEP, expiratory positive airway pressure pressure (EPAP, or CPAP or PEEP) therefore helps triggering and, by reducing the inspiratory effort, it improves comfort.
CPAP

Continuous positive airway pressure (CPAP) refers to the non-invasive application of positive airway pressure using a face or nasal mask rather than in conjunction with invasive techniques. CPAP is not a true mode of mechanical ventilation, as all the ventilation occurs through the patient’s spontaneous efforts. The ventilator provides fresh gas to the breathing circuit with each inspiration and charges the circuit to a constant, operator-specified pressure that can range from 0 to 20 cm H$_2$O. The immediate goals in the treatment of ACPE are to improve systemic oxygen saturation by giving oxygen with a high flow facemask and to decrease preload and afterload of both the ventricles by a combination of morphine, diuretics, and nitrates.

As early as 1936, CPAP had been shown to be an effective therapy for patients with ACPE who were unresponsive to medical treatment. Acute cardiogenic pulmonary edema may be treated effectively with CPAP, which does not exert its primary effect on ventilation per se, but through its efficacy in counteracting the pathophysiologic pathways in cardiogenic pulmonary edema.

Delivery of positive end-expiratory pressure (PEEP) opens flooded or collapsed alveoli, thereby increasing functional residual capacity and improving gas exchange. There seem to be direct mechanical effects on the heart and great thoracic vessels attributed to CPAP, resulting in reduction of cardiac afterload and cardiac wall stress. CPAP also reduces the work of breathing, in part by overcoming upper airway resistance, which may be increased by soft-tissue edema seen in association with heart failure.

CPAP therapy in patients with cardiogenic pulmonary edema in the acute setting is associated with immediate and pronounced improvement in respiratory and haemodynamic variables.

Furthermore CPAP increases the respiratory and expiratory flow and pressure thereby increasing the tidal volume and unloading the inspiratory muscles. It decreases dead space ventilation and improves alveolar ventilation, re-expands flooded alveoli, and counteracts intrinsic PEEP, prevents microatelectasis and places the respiratory pressure volume characteristics in a more favourable position.

The effective filling and emptying of the heart is determined in part by the pressure difference between the inside of the heart and the intrathoracic pressure, known as the cardiac transmural pressure (P$_{TM}$). The amplitude of inspiratory swings is greater in patients with ACPE and leads to an increase in P$_{TM}$ in those patients.

The more positive the P$_{TM}$ is during diastole, the greater the filling of the heart (preload). The more positive the P$_{TM}$ is during systole, the higher the workload is for the heart (afterload).

During systole, CPAP-induced increase in intrathoracic pressure reduces the venous return, decreasing the right and left ventricular preload, thereby improving mechanics in an overloaded ventricle, whereas in diastole, CPAP increases pericardial pressure, reduces transmural pressure, and thus decreases afterload.

Although CPAP can decrease cardiac index in normal subjects, it increases cardiac index in patients with ACPE. CPAP also causes a significant decrease in the heart rate, resulting from increased lung inflation. Nevertheless, treatment with non-invasive ventilation in ACPE is beneficial only in those patients who have systolic dysfunction. In patients with diastolic dysfunction, who usually require a comparatively high filling pressure, the effects of positive pressure therapy compromises venous return, resulting in deterioration of haemodynamics.

In fact, the favourable hemodynamic effect of CPAP is most likely to occur when filling pressures are high and ventricular performance is poor. However, in patients with relatively low filling pressures and good ventricular performance, the hemodynamic effects of CPAP can be adverse, by diminishing venous return. Pending further studies, the most sensible recommendation is to use CPAP (10 cm H$_2$O) initially and to consider switching to NPPV if the patient is found to have substantial hypercapnia or unrelenting dyspnea. This recommendation is in line with the conclusion of meta-analyses that found insufficient evidence to support the use of NPPV in preference to CPAP to treat patients with acute pulmonary edema.

NPPV

Non-invasive positive-pressure ventilation (NPPV) is the delivery of assisted mechanical ventilation without the need for an invasive artificial airway.
In recent years, modalities of NPPV like the combination of pressure support ventilation (PSV) and positive end-expiratory pressure (PEEP), delivered via face mask or nasal mask, has been used increasingly in order to avoid endotracheal intubation and its complications in patients with acute respiratory failure. Pressure support ventilation (PSV) is a patient-triggered, flow-cycled and pressure-limited mode of ventilation. During PSV, the inspiratory phase is terminated when inspiratory airflow falls below a certain level. When PSV is used, patients receive ventilator assist only when the ventilator detects an inspiratory effort by the patient.

The success of NPPV is partly associated to the skill of the medical team in selecting appropriate patients. Physicians must take into consideration a lot of factors, including the patient’s diagnosis, the reversibility of the respiratory failure, patient’s clinical characteristics, risk of failure and the judgement depends largely on physician experience.

Some predictors of success of NPPV have been identified by several studies and they are listed in Table I.

Patients with better neurologic conditions and more cooperative, who are able to protect their airway, without severe acid-base or gas exchange derangements have more chances of success after NPPV application.

The neurologic status can be evaluated and described using the Kelly-Matthay scale which is based on a score ranging from 1 to 6 (Table II).

| Grade 1: | Alert, follows complex 3-step commands. |
| Grade 2: | Alert, follows simple commands. |
| Grade 3: | Lethargic, but arousable and follows simple commands. |
| Grade 4: | Stuporous: patient only intermittently follows simple commands even with vigorous attempts at arousal. |
| Grade 5: | Comatose, brainstem intact. |
| Grade 6: | Comatose with brainstem dysfunction. |


Some studies have shown that the initial response to NPPV after 1 hour of treatment (documented by improvements in pH, PaCO2 at arterial haemogasanalysis and level of consciousness) are associated with success of treatment.

These issues indicate the existence of a “window of opportunity” when initiating NPPV, which opens when patients become distressed enough to require ventilatory assistance, but closes if patients progress too far and become severely acidemic in spite of NPPV therapy.

Selection guidelines recommend first establishing the need for ventilatory assistance according to clinical and blood gas criteria, and then excluding patients in whom NPPV is contraindicated or who are likely to fail (Table III).

### Table I. Determinants of success for NPPV in the acute setting.

- Synchronous breathing
- Dentition intact
- Lower APACHE score
- Less air leaking
- Less secretions
- Good initial response to NPPV
  - Correction of pH
  - Reduction of pH
  - Reduction in respiratory rate
  - Reduction in PaCO2
- No pneumonia
  - pH > 7.10
  - PaCO2 < 92 mmHg
- Better neurologic score
- Better compliance


### Table II. The Kelly-Matthay scale.

### Table III. Selection criteria for NPPV in the acute setting.

- Appropriate diagnosis with potential reversibility
- Establish need for ventilatory assistance
- Moderate to severe respiratory distress
- Tachypnea
- Accessory muscle use or abdominal paradox
- Blood gas derangement
  - PH < 7.35, PaCO2 > 45 mmHg, or PaO2/FiO2 < 200
- Exclude patients with contraindications to NPPV
  - Respiratory arrest
  - Medically unstable
  - Unable to protect airway
  - Excessive secretions
  - Uncooperative or agitated
  - Unable to fit mask
  - Recent upper airway or gastrointestinal surgery

After patient selection, a successful application of NPPV in patients with ACPE requires the choice of an adequate interface, an optimal setting of the ventilator, continuous monitoring of vital signs and, above all, the conscientious attention of skilled physicians who must recognize the conditions for non-invasive positive pressure ventilation discontinuation and indication to endotracheal intubation (Table IV)\textsuperscript{18}.

**Interface**

Most commonly a nasal or oronasal interface is used to apply NPPV. The nasal mask is usually well tolerated because it causes less claustrophobia and discomfort than oronasal masks. It allows eating, drinking and expectorating and its dead space volume is about 105 ml.

The oronasal mask is sensed less comfortable by patients, but it lowers CO\textsubscript{2} more effectively than the nasal masks. A facial mask is preferable in patients affected by severe respiratory failure with severe hypoxemia, because dyspnoic patients breath through the mouth in order to bypass resistance of the nasal passages, and mouth opening during nasal mask ventilation results in air leakage and decreased effectiveness\textsuperscript{18,41}.

Masks are firmly secured with elastic straps to the head of patients and have transparent dome to allow visual monitoring of oral airway for the presence of secretions or vomiting. An ideal mask should be lightweight to aid in its application and have a soft, pliable, adjustable seal to reduce trauma and leaking\textsuperscript{42}.

**Ventilator Settings**

Ventilators employed in non-invasive ventilation range from intensive care unit (ICU) ventilators with full monitoring and alarm systems normally employed in the intubated patient, to light weight, free standing devices with limited alarm systems specifically designed for non-invasive respiratory support. If possible, a single model of ventilator should be used in any one clinical area for ease of training and familiarity of staff with the equipment\textsuperscript{20}.

The mask is connected to the ventilator like an endotracheal tube. To prevent drying of the nasal fossae and oropharinx, a humidifier should be connected but without a heater, because the upper airways, that naturally warm inspired gas, are not bypassed. As an alternative, a heat-moisture exchanger (HME) can be added to the ventilatory circuit in order to ensure natural humidification and heating, reducing the risk of bacterial colonization\textsuperscript{18}.

Pressometric modalities are preferred for most short-term applications, because they are sensed as more comfortable than volumetric modalities by patients.

Inspiratory pressures of > 20 cm H\textsubscript{2}O are discouraged in order to minimize adverse side effects such as sinus pain and gastric insufflation, especially if the opening pressure of upper oesophageal sphincter (25-30 cm H\textsubscript{2}O) is overcome\textsuperscript{43}.

The aim of treatment is to unload the breathing muscles and to alleviate respiratory distress while avoiding the excessive discomfort caused by air pressure and flow\textsuperscript{6}.

At starting treatment the mask is gently held on patient’s face until the patient is comfortable and in synchrony with the ventilator and FiO\textsubscript{2} must be titrated to achieve an oxygen saturation over 90%. After the mask is secured with head elastic straps, continuous positive airway pressure/positive end-expiratory pressure (CPAP/PEEP) is set at 3-5 cm H\textsubscript{2}O (up to 8-10 cm H\textsubscript{2}O in severe hypoxemic patients) and inspiratory pressure/pressure support (PS) is set at 10 cm H\textsubscript{2}O and can be increased to obtain the largest exhaled tidal volume (> 7 ml/kg), a respiratory rate below 25 breaths per minute and patient comfort (Table 5)\textsuperscript{18}. Nevertheless, endotracheal intubation must be rapidly available, when indicated\textsuperscript{18}. It is important to un-

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Table IV. Criteria for noninvasive positive pressure ventilation discontinuation and endotracheal intubation.

| Mask intolerance due to pain, discomfort or claustrophobia |
| Inability to improve gas exchange and/or dyspnoea |
| Haemodynamic instability or evidence of cardiac ischaemia or ventricular dysrythmnia |
| Need for urgent endotracheal intubation to manage secretions or protect the airways |
| Inability to improve mental status, within 30 minutes after the application of non-invasive positive pressure ventilation, in hypercapnic, lethargic chronic obstructive pulmonary disease patients or agitated hypoxemic patients |

understand that excessive pressure levels can cause excessive inflation, with consequent patient-ventilator asynchrony and activation of expiratory muscles during inspiration44.

A last problem that must be considered is patient-ventilator asynchrony which may still result from undetected inspiratory effort, a delay in response to the start of inspiration or in the detection of the end of inspiration, especially in presence of excessive air-leaks45.

Monitoring

The guidelines of the British Thoracic Society for the non-invasive ventilation in acute respiratory failure recommend careful monitoring of patients in which non-invasive positive pressure ventilation modalities are used. Monitoring of patients on non-invasive ventilation should include clinical evaluation combined with pulse oximetry and arterial blood gas analysis. When initiating ventilatory support it is important that the therapist observes the effect of treatment in enhancing chest wall movement, in fact the lack of an improvement may indicate that alveolar ventilation is not increasing and causes (like inappropriate ventilator settings, inadequate tidal volume or inflation pressure, and leaks around the mask) should be understood39.

Monitoring of heart and respiratory rate is essential to and can be useful to in determining the response to ventilatory support before other physiological measurements are made46.

Other clinical features to be considered are the coordination of respiratory effort with the ventilator, the accessory muscles recruitment and patients comfort. Improvement in breathlessness is usually appreciable within 1-2 hours46 and is usually associated with improvement in the neurologic state20,47.

The need for arterial blood gas analysis, according the guidelines of the British Thoracic Society for the non-invasive ventilation in acute respiratory failure, will be governed by the patient’s clinical progress, but should be measured in most patients after 1-2 hours of non-invasive ventilation and after 4-6 hours if the earlier sample showed little improvement. If there has been no improvement in PaCO2 and pH after this period, non-invasive ventilation should be discontinued and invasive ventilation considered. Oxygen saturation should be monitored continuously for at least 24 hours after commencing ventilatory treatment and supplementar oxygen administered to maintain saturations between 85% and 90%20,47.

Complications of NPPV

The complications of non-invasive positive pressure ventilation are usually minor and are related to the mask and airflow pressure48. The most frequent adverse effects are nasal bridge or mucosal pain, nasal bridge erythema or ulceration49 and can be minimized or avoided by minimizing strap tension, using forehead spacers, or routinely applying artificial skin to the area under pressure.

Other less common but noteworthy complications that are associated to NPPV include claustrophobia, nasal congestion, sinu/ear pain, mucosal dryness, eye irritation and gastric insufflation.

Exceptionally NPPV is associated with major complications like hypotension, aspiration and pneumothorax that may indicate the discontinuation of non-invasive ventilatory treatment6.

CPAP or NPPV: the Best Choice in Treatment of Patients with ACPE

Table V. Ventilator settings and monitoring in treatment of patients affected by acute cardiogenic pulmonary edema with CPAP or NPPV (PEEP + PS).

| CPAP (PEEP) | 3-5 cm H2O up to 8-10 cm H2O in severe hypoxemic patients |
| PS         | 10 cm H2O and can be increased to obtain the largest exhaled tidal volume (> 7 ml/kg), a respiratory rate below 25 breaths per minute and patient comfort |
| FiO2       | Must be titrated to achieve an oxygen saturation over 90% |
| Monitoring | Oxygen saturation, heart rate, respiratory rate, arterial pressure, electrocardiogram |

with SMT \textsuperscript{51-57} the results of those studies were recently evaluated by meta-analyses\textsuperscript{32-34,61}.

A recent systematic review and meta-analysis of randomised controlled trials focusing on the effect and safety of CPAP and NPPV in the treatment of ACPE was undertaken by Winck et al in 2006. The aim of this study was to systematically review the evidence in order to answer key clinical questions about the efficacy and safety of CPAP and NPPV in the treatment of patients with ACPE considering three different outcomes: the need for endotracheal intubation (ETI), inhospital all cause mortality and incidence of newly developed acute myocardial infarction (AMI). Secondary aims were to analyse the impact of hypercapnia on the efficacy of CPAP and NPPV and to test the hypothesis about the advantage of NPPV when using higher levels of pressure support ventilation\textsuperscript{34}.

According to the most recent meta-analysis of Winck et al CPAP therapy showed a statistically significant 22\% risk reduction in need for endotracheal intubation (95\% confidence interval (CI) –34\% to –10\%; \(p = 0.0003\)) and a 13\% risk reduction for mortality (95\% CI, –22\% to –5\%; \(p = 0.0003\)) when compared to SMT group.

The NPPV therapy showed a statistically significant 18\% risk reduction in need for endotracheal intubation (95\% confidence interval (CI) –32\% to –4\%; \(p = 0.0101\)) and a non-significant 7\% risk reduction for mortality (95\% CI, –14\% to 0\%; \(p = 0.060\)) when compared to the SMT group\textsuperscript{34}.

In the studies comparing NPPV with SMT the random effects pooled analysis of risk differences for AMI showed a small but non-significant risk increase for the NPPV group (\(p = 0.720\)) \textsuperscript{34,58,59,60}.

To test the clinical hypothesis about an advantage of NPPV over SMT when using higher levels of pressure support ventilation Winck et al performed a predefined subgroup analysis with stratification based on the level of pressure support ventilation (PSV \(\geq\) 10.0 cm H\(_2\)O versus PSV < 10.0 cm H\(_2\)O). In the subgroups of studies with higher levels of pressure support ventilation\textsuperscript{58,62}, a random effects pooled analysis showed a statistically non-significant risk reduction in need for endotracheal intubation (\(p = 0.430\)) and mortality (\(p = 0.190\)) favouring the NPPV group.

In the subgroup of studies with lower levels of pressure support ventilation\textsuperscript{59,60,63,64}, the random effects pooled analysis showed a statistically significant risk reduction in need for endotracheal intubation and a non-significant risk reduction for mortality\textsuperscript{34}.

In these two subgroup analyses no evidence was found supporting the clinical hypothesis about the advantage of NPPV over SMT when using higher levels of pressure support ventilation\textsuperscript{58,62,65}.

**CPAP Versus NPPV**

Results from studies directly comparing CPAP with NPPV\textsuperscript{62,64,66-69} showed a statistically non-significant need for endotracheal intubation risk reduction (95\%CI –4\% to 9\%; \(p = 0.041\)) and mortality reduction (95\%CI –6\% to 10\%; \(p = 0.640\)) in the NPPV group.

According to the recent meta-analyses by Winck et al, by Peter et al and by Masip et al in patients affected by acute cardiogenic pulmonary edema, CPAP and NPPV both significantly decrease need for endotracheal intubation risk, and CPAP alone significantly reduces mortality when compared to SMT\textsuperscript{32-34}.

Although both NPPV and CPAP appear to reduce need for ETI and mortality, NPPV does not yet show a significant reduction in mortality, probably due to the low power related to the limited number of patients in the studies analysed.

To explore the hypothesis proposed by some clinicians on the advantage of NPPV over CPAP in hypercapnic patients\textsuperscript{60}, Winck et al analysed the impact of patients’ baseline hypercapnia in the comparison between CPAP and NPPV. A subgroup analysis was performed with stratification based on mean baseline level of arterial carbon dioxide pressure (PaCO\(_2\) < 50 mmHg versus PaCO\(_2\) \(\geq\) 50 mmHg). In the group of studies with more hypercapnic patients at baseline, the random effects pooled analysis showed a statistically non-significant risk reduction in need for endotracheal intubation (\(p = 0.560\)) and mortality (\(p = 0.690\)) favouring the NPPV group. In the group of studies with less hypercapnic patients at baseline, the random effects pooled analysis showed a statistically non-significant risk reduction in need for endotracheal intubation (\(p = 0.430\)) and a non-significant risk increase for mortality (\(p = 0.820\)) for the NPPV group. According to the recent meta-analyses by Masip et al\textsuperscript{32} and that by Winck et al\textsuperscript{34} the suggested superiority of NPPV in hypercapnic acute cardiogenic pulmonary edema patients due to respiratory muscle unloading\textsuperscript{60} was not confirmed\textsuperscript{34}.  
Finally the results of a meta-analysis about non-invasive ventilation in Emergency Department (ED) patients with acute cardiogenic pulmonary edema by Collins et al suggest that a strategy of noninvasive ventilation plus standard medical therapy significantly reduces hospital mortality and need for endotracheal intubation when compared with standard medical therapy alone, even if, according to all available data, there is no evidence to suggest superiority of either continuous positive airway pressure or non-invasive positive pressure ventilation in that group of patients. The authors showed that early application of a strategy of non-invasive ventilation in the ED can decrease the relative risk of mortality by 39% and the necessity of endotracheal intubation by 57%. Definitive pharmacological therapy, such as vasodilators and diuretics, requires time for administration (preparing intravenous solutions), as well as time for therapeutic effect to occur.

Non-invasive ventilation in patients with cardiogenic pulmonary edema can be considered an immediate and effective temporizing measure meanwhile intravenous solutions are prepared and drugs’ effect occurs.

A last important issue that must be considered is the costs and difficulties involved in implementing non-invasive ventilation in clinical practice and the differences between CPAP and NPPV. Nowadays CPAP results more easily implemented in clinical practice and carries smaller associated costs when compared to NPPV and the cost-effectiveness of CPAP has already been demonstrated by Holt et al.

**Myocardial Infarction Rate**

In 1997, a randomised prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema by Mehta et al showed a higher myocardial infarction rate in the bilevel positive airway pressure group (71%) compared with both the CPAP group (31%) and historically matched controls (38%) and the authors had to stop their trial for that reason.

The authors suggested that the prolonged increase in intrathoracic pressure during inspiration may explain their results: in fact they delivered NPPV using a spontaneous timed mode with a ventilator that at the time of the study was not equipped with the now available sophisticated expiratory triggering system, so that air leaks, when present, may have unduly prolonged the inspiratory time (phenomenon described as a failure to cycle off). Furthermore, most of the patients reported chest pain at admission, so that it is likely that acute ischaemia preceded rather than followed the application of non-invasive positive-pressure ventilation.

In the multicenter randomised trial about non-invasive ventilation in cardiogenic pulmonary edema by Nava et al in 2003 the authors found the same incidence of myocardial infarction as that reported by Masip et al and by Takeda et al who described a satisfactory outcome in a group of patients with acute pulmonary edema secondary to myocardial infarction.

Furthermore a recent study, specifically addressing the myocardial infarction rate in acute pulmonary edema treated by non-invasive pressure support ventilation versus continuous positive airway pressure showed no differences between both techniques. The authors concluded that NPPV proved to be equally effective in improving vital signs and ventilation without increasing acute myocardial infarction rate in patients with non-ischaemic acute pulmonary edema in comparison to CPAP alone, but recommended caution when applying NPPV to patients with acute coronary syndromes complicated by cardiogenic pulmonary edema.

In studies comparing CPAP therapy with SMT evaluated in the recent meta-analysis of Winck et al no difference in AMI risk between the CPAP and SMT groups was showed. Results from studies directly comparing CPAP with NPPV concerning risk differences for AMI showed a non-significant risk reduction in the CPAP group respect to NPPV groups (95% CI, –18% to 8%; p = 0.430).

According to recent meta-analyses there is no evidence of increased risk of AMI with either CPAP or NPPV.

Although one study found a higher incidence of AMI with NPPV, subsequent studies have not confirmed this finding.

In the latest meta-analysis by Winck et al the authors stated that there was no significant difference in the risk of AMI between CPAP and NPPV when compared to SMT. Nevertheless careful and frequent monitoring of patients affected by cardiogenic pulmonary edema remain mandatory, especially in presence of AMI or acute coronary syndromes, but there is no evidence to contraindicate the use of NPPV.
Conclusions

Both CPAP and NPPV gained important roles in the treatment of several forms of hypoxemic acute respiratory failure like acute cardiogenic pulmonary edema. The evidence from recent literature showed that both CPAP and NPPV significantly decrease the need for endotracheal intubation, and CPAP significantly decreases mortality when compared to standard medical treatment. These techniques resulted safe and there is no evidence of increased risk of AMI with either of them.

Although both CPAP and NPPV present similar efficacy, CPAP has been shown to be cheaper and easier to implement in clinical practice. Furthermore, no evidence supporting the superiority of NPPV in hypercapnic patients with cardiogenic pulmonary edema was found.

For these reasons, CPAP should be considered the preferred intervention in patients with cardiogenic pulmonary edema, especially in the Emergency Department.

As a consequence of the previous considerations, physicians should incorporate the application of these techniques as a first line intervention in patients affected by cardiogenic pulmonary edema in the acute setting.

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