Management of acute hypercapnic respiratory failure

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Purpose of review
The objective of this article is to review the most recent literature regarding the management of acute hypercapnic respiratory failure (AHRF).

Recent findings
In the field of AHRF management, noninvasive ventilation (NIV) has become the standard method of providing primary mechanical ventilator support. Recently, extracorporeal carbon dioxide removal (ECCO2R) devices have been proposed as new therapeutic option.

Summary
NIV is an effective strategy in specific settings and in selected population with AHRF. To date, evidence on ECCO2R is based only on case reports and case-control trials. Although the preliminary results using ECCO2R to decrease the rate of NIV failure and to wean hypercapnic patients from invasive ventilation are remarkable; further randomized studies are needed to assess the effects of this technique on both short-term and long-term clinical outcomes.

Keywords
chronic obstructive pulmonary disease, extracorporeal carbon dioxide removal, hypercapnia, noninvasive ventilation

INTRODUCTION

Acute hypercapnic respiratory failure (AHRF) remains a common medical emergency.

In this review, we discuss the physiological mechanisms responsible for AHRF and the challenges involved in its management. We critically examine the current literature focusing on the efficacy of noninvasive ventilation (NIV) in specific settings. The recent findings regarding the possible role of new generation extracorporeal carbon dioxide removal (ECCO2R) devices in patients with hypercapnia are also included.

ACUTE HYPERCAPNIC RESPIRATORY FAILURE

Pathophysiology and causes

The normal level of carbon dioxide (CO_2) tension in the arterial blood ($PaCO_2$) results from the relationship between the rate of CO_2 production and the portion of CO_2 eliminated by the lung with alveolar ventilation [1].

The arterial blood gas analysis is the gold standard for assessing $PaCO_2$ in patients with acute respiratory failure. The determination of a $PaCO_2 > 45$ mmHg is diagnostic of hypercapnia.

Hypercapnic respiratory failure is more commonly determined by the reduction of alveolar ventilation (pump respiratory failure), than by the increase of the rate of CO_2 production, even in high-risk patients with poor pulmonary reserve. A reduction in effective alveolar ventilation may result either from a rise in the dead space or from a reduction of minute ventilation.

A rapid elevation of $PaCO_2$ leads to a drop of arterial blood pH as a consequence of the $HCO_3^-/PaCO_2$ ratio's lowering. Respiratory acidosis ($pH < 7.35$ and concomitant hypercapnia) is the characteristic landmark of acute decompensated

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KEY POINTS

- AHRF is considered an emergency situation and its management has changed during the past decades.
- The role and the efficacy of NIV in specific situations that cause AHRF are well established and NIV is actually the first-line treatment in selected population.
- Recently, ECCO2R devices have been suggested as a new treatment option either in avoiding intubation in COPD patients at risk of NIV failure and in facilitating weaning in mechanically ventilated hypercapnic patients.

ventilatory failure and it is considered an emergency situation.

Principles of management

When a patient develops shortness of breath, a change in mental status, such as hypersomnolence, or oxygen desaturation, the presence of hypercapnia should always be suspected and checked, especially if the patient is at risk for hypoventilation (i.e., use of sedatives), or the patient is affected by chronic lung diseases that increase physiologic dead space [i.e., chronic obstructive pulmonary disease (COPD) exacerbation].

Once the diagnosis of acute hypercapnia is made, the clinician should stabilize the patient by performing a rapid clinical bedside assessment and administering the standard medical therapy. As soon as possible, the clinician should collect the medical history, perform a more accurate physical examination, and other tests like a chest radiograph to determine and treat the specific underlying causes and precipitant factors of AHRF.

Oxygen therapy

Healthcare providers should pay careful attention administering the oxygen therapy in patients with COPD or other known risk factors that can predispose to hypercapnic respiratory failure with acidosis [2,3]. For this subgroup of patients, a target saturation range of 88–92% is recommended to avoid hypoxemia and reduce the risk of oxygen-induced hypercapnia [2–4]. Therefore, oxygen saturation should be monitored continuously and the patient's further treatment should be guided by the results of the arterial blood gas analysis [3]. In fact, if respiratory acidosis persists despite appropriate medical treatment it is mandatory to consider mechanical ventilation [5].

Special reference also needs to be made to the role of high-flow nasal cannulae (HFNC) in patients with hypercapnia. HFNC is a device able to deliver heated and humidified oxygen at high flows (up to 60 l/min) [6▪]. Thanks to higher flow, the system is able to match or exceed the patient's spontaneous inspiratory flow rate, thus attenuating inspiratory resistance within the nasopharynx. Additional potential benefits of HFNC include the washout of upper airway dead space that seems to minimize rebreathing of CO_2. Finally, HFNC generates a low-level positive airway pressure (PEEP effect) that varies according to the flow setting and the breathing [6▪]. For all those reasons, HFNC has been proposed to reduce the work of breathing and respiratory rates, countering intrinsic PEEP, especially in COPD patients [7–9].

Although HFNC is considered the latest trend in the management of various conditions such as hypoxemic respiratory failure [10▪,11▪,12▪▪], further studies are needed to determine if a real advantage of using HFNC in the acute decompensated ventilatory failure exists.

NONINVASIVE MECHANICAL VENTILATION IN THE TREATMENT OF ACUTE HYPERCAPNIC RESPIRATORY FAILURE

The role and the efficacy of NIV in specific situations that cause AHRF are well established. NIV has changed radically the treatment of AHRF shifting its management from invasive mechanical ventilation (IMV) to noninvasive strategy, consequently, decreasing the morbidity and mortality associated with the intubation and IMV.

Physiological effects of noninvasive ventilation

Both invasive and noninvasive ventilation are able to increase alveolar ventilation and reduce the work of breathing, assisting spontaneous respiratory muscle activity. Consequently, in patients with acute respiratory failure, NIV significantly reduces $PaCO_2$ and improves respiratory acidosis. NIV produces a significant increase in tidal volume that is associated to an improvement of the breathing pattern, in particular to a reduction in respiratory rate [13,14].

Several studies have shown that NIV with appropriate levels of inspiratory positive pressure reduces WOB, as demonstrated by a marked reduction in both esophageal pressure and transdiaphragmatic pressure [14]. Additionally, inspiratory positive pressure causes a reduction in the mean pressure–time

product of the inspiratory muscles [13,15], an index of the muscle oxygen consumption. NIV is able to reduce elastic WOB also by using PEEP that supplies all or part of the driving pressure required to overcome intrinsic PEEP, especially in COPD patients.

Moreover, applying positive pressure to the respiratory system ameliorates the gas exchange by increasing functional residual capacity, facilitating the distensibility of lung parenchyma, recruiting areas of atelectasis/dystelectasis, and producing a higher alveolar pressure that contrasts fluid extravasation from the vascular bed. This may improve ventilation/perfusion (Va/Q) mismatching and allows a more uniform distribution of ventilation.

On the other hand, it is important to consider also potential adverse effects on cardiovascular function when administering NIV. It is known that, in normal volunteers, the overall effect of a continuous positive airway pressure (CPAP) of 15 cm H_2O, delivered by a nasal mask, is to 'decrease cardiac output' by 20%–30% [13,16]. Approximately the same reduction has been demonstrated in stable COPD [17] and in patients with decompensated COPD [18] as well.

The magnificent four: any news?

Taking into account particular patients with AHRF, NIV is considered the gold standard in four different settings.

Exacerbation of chronic obstructive pulmonary disease

The most clear evidence on the efficacy of NIV is demonstrated in COPD population. Several controlled randomized studies have shown that NIV, added to standard medical treatment, is effective in reducing mortality, avoiding intubation, reducing the risk of developing pneumonia, improving dyspnoea, reducing hospital length of stay, and reducing costs in COPD patients with acute respiratory failure, when compared with medical management plus oxygen therapy alone [19–23]. Meta-analyses of randomized controlled trials suggested that NIV can reduce the risk of death by up to 55%, revealing itself as the only hospital-based intervention known to improve mortality [24–26,27▪]. This benefit probably results from the prevention of complications associated with IMV, including ventilator-associated pneumonia [28,29]. A recent large retrospective study [30▪] of more than 25 000 patients confirmed that patients hospitalized for COPD exacerbation and initially treated with NIV had better outcomes than those that received invasive ventilation. In particular, NIV was associated with lower risk of mortality [odds ratio 0.54; (95% CI, 0.48–0.61)] and a lower risk of hospital-acquired pneumonia [(odds ratio, 0.53 (95% CI, 0.44–0.64)] [30▪].

Acute pulmonary edema

Acute pulmonary edema (APE) is characterized by the rapid increase in the pulmonary capillary wedge pressure that leads to interstitial and alveolar edema. Consequently, the lung compliance decreases and the WOB increases [31]. Therefore, patients with APE present an acute onset of symptoms and a rapid worsening of the clinical status, characterized by severe respiratory distress that requires direct admission to the emergency department. In addition, around 50% of patients with severe APE are hypercapnic when admitted to the hospital and hypercapnia is a strong predictor of immediate airway intubation [32]. As demonstrated by a recent prospective study [33▪], patients with hypercapnia were more likely to be in severe functional class [New York Heart Association (NYHA) class IV], to have abrupt onset and to present with an usual 'radiologic' appearance of APE compared with hyponormocapnic patients. Another observational study [34▪], after excluding patients with associated underlying chronic lung diseases, showed that patients with severe hypercapnia at admission ($PaCO_2 > 60$ mmHg) needed longer time on NIV (>48 h) than nonhypercapnic patients; no significant difference has been shown between the two groups regarding the intubation rate.

NIV support delivered by either CPAP and pressure support ventilation have shown the same results also in terms of efficacy in patients with APE, rapidly improving patients' symptoms and gas exchange, and reducing the need of invasive mechanical ventilation compared with standard medical therapy alone [35–37]. The two ventilation modalities have similar benefits also in the subgroup of patients affected by APE associated with hypercapnia [38]. However, CPAP is considered cheaper and easier than NIV as it requires limited equipment and minimal staff training and it is often used as first treatment choice in the emergency department or in a prehospital setting.

Weaning from invasive ventilation in chronic obstructive pulmonary disease

Invasive ventilation provides effective and life-saving support for patients with acute respiratory failure. It is indicated when NIV is not recommended or when NIV has failed. Because an endotracheal tube is used as an artificial airway, the cough reflex is suppressed,

increasing the risk of ventilator associated pneumonia, which correlates with both increased morbidity and mortality [39–41]. Other clinical complications related to a prolonged intubation include respiratory muscle weakness, upper airway disorder, and sinusitis. In general, the risk for adverse events rises with the duration of intubation [42].

To reduce these complications, the role of NIV in weaning strategy has been investigated.

Historically, the first study [43] that used NIV in the weaning process was performed in 50 severe COPD patients admitted for an exacerbation. Within 48 h after mechanical ventilation was initiated, patients who failed the T-piece trial were randomized to either extubation and supported with noninvasive pressure support ventilation or to continue conventional weaning with the endotracheal tube. The group of patients who were extubated and received NIV remained ventilated for significantly shorter periods, and had a lower incidence of nosocomial pneumonia as well as a higher 60 days survival rate compared with the control group.

After this first experience, several randomized controlled studies were published [44–50]. Taken together, the randomized controlled trials indicated that using NIV to facilitate weaning is not inferior to invasive weaning in particular in very selected patients such as those with COPD exacerbation where noninvasive support has the same physiological effects and results obtained when NIV is applied as primary treatment in COPD.

In fact, a recent meta-analysis [51▪] on this topic concluded that NIV reduces mortality, ventilator-associated pneumonia, the length of stay in the ICU or hospital, without increasing the risk of weaning failure or reintubation.

Therefore, in accordance with the recent evidences, NIV is recommended to reduce the duration of invasive ventilation facilitating weaning preferentially in patients with COPD and in a highly monitored setting.

Prevention of postextubation respiratory failure in high-risk patients

Postextubation respiratory failure occurs in a percentage of patients varying from 2 to 20% [52], usually within 48–72 h after extubation [53,54]. Several studies have demonstrated that in patients considered at risk, the early application of NIV can reduce the incidence of postextubation respiratory failure, the need for reintubation, and the overall mortality with a varying degree of success according to the nature and severity of the underlying disease [55–59].

Therefore, the early use of NIV is now recommended in the prevention of postextubation failure in selected patients with chronic respiratory disease, cardiac comorbidity, and in those with hypercapnic respiratory failure during a spontaneous breathing trial. In contrast, no clear evidence of benefit has been demonstrated in mixed populations who have already developed postextubation respiratory failure [60▪].

WHEN NONINVASIVE VENTILATION FAILS? THE ROLE OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL

Despite the positive results and the increasing experience with this technique, NIV failure occurs in 25–50% of patients with COPD exacerbation [61–63]. Additionally, COPD patients who require IMV have poor prognosis and an increased risk of difficult weaning and prolonged ventilation [64–66].

In recent years, new generation ECCO2R devices have been proposed in addition to NIV to reduce the rate of endotracheal intubation in COPD patients, suggesting ECCO2R as new therapeutic option. ECCO2R technology is based on a modified continuous venovenous hemofiltration circuit. The devices are equipped with a membrane lung that allows the elimination of CO_2 from the blood. Compared with conventional extracorporeal membrane oxygenation, ECCO2R presents many advantages including a lower blood flow rate (range from 300 up 1500 ml/min) and consequently smaller venovenous catheters (12–14 French). Continuous infusion of heparin is also needed to 'prevent clotting' of the circuit.

Originally, ECCO2R has been suggested in acute respiratory distress syndrome to manage permissive hypercapnia, allowing very small tidal volume [67▪].

Actually, no randomized clinical trials on ECCO2R in the COPD population were published. A recent systematic review [68▪] identified 10 studies (87 patients) about this topic. It included primarily case series and case reports [69–76] and only two case-control studies in which patients treated with ECCO2R were matched to historical controls [77▪▪,78]. In addition, Table 1 shows the currently ongoing studies regarding the use of ECCO2R in hypercapnic respiratory failure patients [79–83].

Results derived from this review demonstrated [68▪] that ECCO2R avoided intubation in 65/70 (93%) patients. Moreover, 9/17 (53%) patients were weaned successfully from invasive ventilation by using ECCO2R. However, many complications have

Table 1. Unpublished and ongoing studies regarding the use of extracorporeal carbon dioxide removal in hypercapnic respiratory failure patients

ClinicalTrials.gov Identifier/Official Title	Study design	Hypothesis/primary outcome	Inclusion criteria	Estimated enrollment	Device	Recruitment status
Prevention of intubation in COPD exacerbation						
NCT02086084 Extra-corporeal CO2 Removal as an Adjunct to Non-Invasive Ventilation in Acute Severe Exacerbations of COPD [79]	Randomized, controlled trial	The hypothesis is that the addition of ECCO2R to NIV will shorten the duration of NIV and reduce likelihood of intubation Primary outcome: time to cessation NIV	Known COPD with an acute exacerbation Patients with a persistent arterial pH <7.30 due primarily to hypercapnic respiratory failure after standard medical therapy and at least 1 h of NIV	24 patients	Hemolung RAS	Recruiting
NCT01784367 Extracorporeal Lung Assist to Avoid Intubation in Patients Failing Noninvasive Ventilation for Acute Hypercapnic Respiratory Failure [80]	Prospective cohort study	Rate of intubation for invasive mechanical ventilation	Acute or acute-on-chronic hypercapnic respiratory insufficiency (pH ≤ 7.35, $PaCO_2 > 45$ mmHg) Failure of noninvasive ventilation Fulfilling criteria for endotracheal intubation	30 patients	ECLA Novalung Germany	Completed
Stable COPD patients with chronic hypercapnic failure						
NCT02260583 Effect of Extracorporeal CO2 Removal in stable COPD patients with Chronic Hypercapnic respiratory failure: a pilot study [81]	Pilot study	The aim of this study is to assess the feasibility and safety of one shot ECCO2R device, in reducing the $PaCO_2$ level Primary outcome: arterial blood gases	COPD Stable $PaCO_2 > 55$ mmHg nonrespondent to long-term NIV (at least 1 week). This means a decrease in $PaCO_2$ during spontaneous breathing, at least 4 h after the termination of NIV, of $<6\%$ pH >7.35 Clinical stability	15 patients	Decap Smart, Hemodec (Salerno, Italy)	Recruiting
Facilitating extubation						
NCT02107222 Multicenter Randomized Control Trial (RCT) to Determine Safety and Efficacy of PALP™ for ECCO2-R in Conjunction With Liberation From Mechanical Ventilation (MV) Compared to MV Alone in COPD Exacerbation and Respiratory Failure [82]	Multicenter, randomized, controlled trial	To evaluate the clinical effect of PALP in reducing the time on invasive ventilation in patients with an exacerbation of COPD requiring invasive mechanical ventilation.	Known history of COPD experiencing an exacerbation P/F ratio >150 mmHg Currently, endotracheally intubated and requiring invasive mechanical ventilation (must have been on invasive mechanical ventilation for 24–48 h) Able to tolerate large bore i.v. cannulation required for proper operation of study device	120 patients	PALP	Not yet recruiting

Table 1 (*Continued*)

ClinicalTrials.gov Identifier/Official Title	Study design	Hypothesis/primary outcome	Inclusion criteria	Estimated enrollment	Device	Recruitment status
NCT02259335 A Pilot Study on the Use of Extracorporeal CO2 Removal During the Weaning Process From Mechanical Ventilation [83]	Pilot study	Weaning success avoiding reintubation after removal of ECCO2R	Patients meeting the criteria for readiness to be weaned At least 2 unsuccessful T-piece weaning trials, excluding the one of the experimental trial Persistence of hypercapnia ($PaCO_2 > 45$ mmHg) during invasive mechanical ventilation	12 patients	ProLUNG [Estor S.p.A. Pero (MI), Italy]	Recruiting

AHRF, acute hypercapnic respiratory failure; COPD, chronic obstructive pulmonary disease; ECLA, extracorporeal lung assist; ECCO2R, extracorporeal carbon dioxide removal; NIV, noninvasive ventilation; $PaCO_2$, carbon dioxide tension; PALP, Pump Assisted Lung Protection; RAS, Remote Access Service.

been described with ECCO2R systems. In particular, adverse events including both major (significant bleeding, vein perforation, pneumothorax, and death) and minor complications (minor bleed, thrombocytopenia, circuit clotting, deep venous thrombosis, pump malfunction, etc.) were observed in almost half of the patients [68▪].

Finally, this meta-analysis does not include the preliminary data related to the effects of ECCO2R on lung mechanics [84▪▪]. As shown in Table 1, our team is conducting a pilot study about the role of ECCO2R in COPD patients who failed spontaneous breathing trials [83]. We demonstrated for the first time that the addition of ECCO2R during unsupported breathing is able to decrease the inspiratory muscle effort, reducing significantly the Pdi swing, the pressure–time products of the transdiaphragmatic pressure, and respiratory rate. Moreover, ECCO2R prevents the increase of rapid shallow breathing index (f/VT) and $PaCO_2$ during a T-piece trial, thereby avoiding respiratory acidosis and accelerating the weaning process in those patients.

The study elucidated the physiologic effects of extracorporeal CO_2 devices, providing the rationale for the application of ECCO2R in patients with AHRF for the first time.

CONCLUSION

The approach to AHRF has changed during the last decades. According to better outcomes and lower mortality rates, NIV has shifted the AHRF management from invasive strategy to noninvasive one. As reviewed in this paper, the evidence about the use of NIV in specific settings and in selected population is strong. The main challenge we face today is to utilize a different way to eliminate the CO_2 by the extracorporeal removal in addition to the 'conventional approach' consisting in the improvement of alveolar ventilation by using a mechanical ventilator working together with the respiratory pump. However, further randomized studies are needed to better understand the role of ECCO2R both in the prevention of intubation and in facilitating weaning in mechanically ventilated hypercapnic respiratory failure patients.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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The article aims to review and summarize current knowledge concerning noninvasive weaning.

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Preliminary data from this pilot study clarifies for the first time the physiologic effects of extracorporeal CO_2 devices in patients that fail weaning from mechanical ventilation.