# Respiratory alkalosis in the acute hypoxemic patient during non-invasive mechanical ventilation: troubleshooting and prognostic relevance

Giancarlo De Leo, Luigi Pinto, Michele Maiellari, Ersilia Tedeschi, Michele Bitetto

Pulmonology Unit, Ente Ecclesiastico Ospedale Generale Regionale "F. Miulli", Acquaviva Delle Fonti, Bari, Italy

## Abstract

Respiratory alkalosis is one of the four basic disturbances to the acid-base equilibrium. Persistent primary respiratory alkalosis during non-invasive mechanical ventilation in patients with hypoxemic respiratory failure could be a risk factor for NIV failure. A 69-year-old man with acute hypoxemic respiratory failure caused by severe COVID-19 pneumonia demonstrated progressive worsening of gas exchange and clinical conditions. Despite a positive response to non-invasive mechanical ventilation, a therapeutic increase in respiratory support was required.

Correspondence: Giancarlo De Leo, Ente Ecclesiastico Ospedale Generale Regionale "F. Miulli", Strada Provinciale 127 Acquaviva - Santeramo, Km 4,100 - 70021 Acquaviva Delle Fonti Bari, Italy.
E-mail: deleogiancarlo@outlook.it

Key words: hypoxemic respiratory failure; non-invasive ventilation; patient-self induced lung injury.

Ethics approval and consent to participate: no ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals. Informed consent was obtained from the patient included in this study.

Patient consent for publication: the patient gave his written consent to use his personal data for the publication of this case report and any accompanying images.

Availability of data and materials: all data underlying the findings are fully available.

Received: 1 December 2024.
Accepted: 7 March 2024.
Early view: 12 April 2024.


*Emergency Care Journal 2024; 20:12152*
*doi:10.4081/ecj.2024.12152*



## Introduction

Non-Invasive Mechanical Ventilation (NIV) is a cornerstone of the management of the acute respiratory failure. The ERS/ATS guidelines[1] for the use of NIV in the acute setting identify the Hypercapnic (type 2) respiratory failure as a main indication for the non-invasive support. On the contrary, the management of the acute hypoxemic (type I) respiratory failure (AHRF) using NIV is still controversial and represents a therapeutic "gray zone" that hides potential harmful risks. In fact, it has been demonstrated that the extensive use of NIV is associated with the delay of orotracheal intubation, a condition that clearly increases patient mortality.[2] For this reason, numerous studies have focused on identifying those risk factors connected to a higher risk of NIV failure in hypoxemic patients. The following is a report of persistent respiratory alkalosis during non-invasive ventilation.

## Case Report

A 69-year-old man, weighing 80kg and 182cm tall, was brought to the Emergency Department (ED) for dyspnoea, fatigue, and fever for 15 days. The medical history of the patient included: granulomatosis with polyangiitis, Interstitial lung disease with NSIP pattern, parossistic atrial fibrillation, and hyperthyroidism. The home medications of the patient included: prednisone 5mg/daily, azathioprine 100mg/daily, atenolol 100mg/daily, methimazole 5mg/daily, edoxaban 60 mg/daily, rituximab infusion 500mg/6 months (temporarily suspended).

On arrival in the ED his oxygen saturation was 94% on air, respiratory rate 24-25 breaths/minute, heart rate 77 beats per minute, arterial blood pressure 118/60mmHg, body temperature 38°C, and GCS 15 (qSOFA score: 1, SAPS II score 24 points). Neither signs of hemodynamic instability nor an acute neurological impairment were observed. The nasal swab for SARS COV 2 resulted positive. In addition, a blood samples for culture were collected, which later resulted negative. Arterial blood gas (ABG) result demonstrated acute respiratory alkalosis and mild hypoxemia: pH 7,59, $pCO_2$ 26 mmHg, $pO_2$ 70 mmHg, HCO3-24.2 mmol/L, $pO_2/FiO_2$ ratio 333, Base Excess +3.2 mmol/L, Lactate 1.1 mmol/L. A standard Chest X-ray showed only mild bilateral opacities. The patient was admitted to the respiratory ward. Subsequently treatment with methylprednisolone (0.5mg/kg/die) and enoxaparin (100UI/Kg every 12 hours), instead of edoxaban, were commenced. Furthermore, because of an increment in procalcitonin level (1.5 ng/ml, n.v. < 0.5 ng/mL), piperacillin/tazobactam and teicoplanin were started with good response. No antiviral therapy was prescribed because of the time past since the onset of the symptoms of the patient. After few hours, oxygen therapy via nasal cannula at the flow of 3L/min was started because of the appearance of unstable oxygen saturation. Subsequently, despite an initial stabilization, a clear worsening of the oxygen saturation was seen and a new ABG (flow: 3L/min, via nasal cannula) demonstrated AHRF and mixed

alkalosis: pH 7,57, $pCO_2$ 26 mmHg, $pO_2$ 50 mmHg, HCO3- 26.8 mmol/L, $pO_2/FiO_2$ ratio 139, Base Excess +1.8 mmol/L, Lactate 2.4 mmol/L. High flow nasal cannula oxygenation was started (Tc 34°C, Tot Flow 50L/min, $FiO_2$ 50%), $SpO_2$=2 94% and RR 24 breath/minute (ROX index: 7.83).

Based on the hyper acute worsening and the ABG result, despite the ongoing anticoagulation therapy, it was decided to have the patient undergo CT pulmonary angiography, which excluded pulmonary embolism but confirmed the presence of COVID-19 pneumonia. However, given the CT Scan findings and the patient history, a blood sample for CMV DNA quantitative detection was sent and resulted negative.

After the exclusion of superimposed acute cardiovascular complications, NIV was started using Monnal T75 (Air Liquide Medical Systems, Paris, France) with pressure support ventilation (PSV) mode and the following setting: pressure support of 8 cmH20, PEEP 8 cmH20, Ti/Ttot 40%, and $FiO_2$ 50% (average expiratory Tidal Volume: approximately 7 mL/kg IBW) (HACOR score: 4).

The case was discussed with ICU physicians, however, because of the improvement after one hour of NIV (ABG result after 1 hour: pH 7,63, $pCO_2$ 26 mmHg, $pO_2$ 87 mmHg, $HCO_3$- 30.3 mmol/L, $pO_2/FiO_2$ ratio 174, latt 1.7 mmol/L), the absence of respiratory distress, and the state of immune deficiency, a decision to not proceed immediately to orotracheal intubation was made and a careful active surveillance approach was followed. Since the respiratory alkalosis persisted, a temporary attempt to reduce PS to 6cm$H_2O$ was made. However, since no change in the tidal volume was seen, the PS was restored to 8 cmH20.

Subsequently, the patient underwent awake prone positioning cycles with $HFNCO_2$ (60% $FiO_2$, 60L/min, 34°C) with benefit. Nonetheless, despite the persistent absence of hemodynamic instability and respiratory distress, gas exchange progressively worsened again (ABG result during awake prone positioning in HNCO2: pH 7,49, $pCO_2$ 36 mmHg, $pO_2$ 55 mmHg, $HCO_3$- 27 mmol/L, $pO_2/FiO_2$ ratio 92, latt 2.2 mmol/L) and the patient was admitted to the medical ICU.

## Discussion

The management of *de novo* AHRF still remains controversial for many aspects. One of these is the choice of the proper non-invasive respiratory support, a topic that is still far from a definitive solution. The European Respiratory Society (ERS) guidelines[3] for the use of $HFNCO_2$ make a conditional suggestion on the use of $HFNCO_2$ over NIV in the management of de novo acute respiratory failure. However, the same guidelines acknowledge the uncertainty and the lack of evidence regarding this topic.

The use of NIV in the AHRF conceals many potential risks. In particular, NIV failure is one the most dangerous because it directly affects the mortality of the patient in case of delay of endotracheal intubation. For this reason, the management of "de novo" AHRF by a trial of NIV should always be performed in a protected environment, where patients can be closely monitored and promptly intubated in case of clinical deterioration.

Numerous studies have been conducted on the risk factors for NIV failure in AHRF. According to Antonelli *et al.* the highest intubation rate was observed in patients with: age > 40 years, SAPS II score ≥ 35, a $PaO_2:FiO_2 \leq 146$ after 1 hour of NIV, and the presence of specific respiratory conditions, *i.e.* ARDS or community-acquired pneumonia. In addition, Carteaux *et al*. found that an expired tidal volume ≥ 9.5 mL/kg IBW predicts NIV failure with a sensitivity of 82% and a specificity of 87% in patients affected by ARDS. Moreover, clinical score, *i.e.* HACOR score, which aims to identify higher risk hypoxemic patients should be part of the daily practice in the emergency setting as much as possible.

Respiratory alkalosis (defined as: pH> 7.45 and $pCO_2$<35mmHg) is one of the four basic disturbances of the acid base equilibrium. It can be due to primary pulmonary disorders, which are the main cause, but also to cardiovascular, metabolic, central nervous system, and drugs toxicity. For this reason, it is mandatory in a mechanical ventilated patient to exclude and eventually manage every extra pulmonary cause of respiratory alkalosis before of any change in the setting of the ventilator.

In this eventuality, the management of the requires different strategies according to the type of ventilation in use.

In order to manage properly the respiratory alkalosis secondary to an inappropriate setting of the ventilator it is important to remember the factors that affect the partial pressure of arterial carbon dioxide. Figure 1 shows schematically these factors.

During controlled ventilation modes, respiratory alkalosis is generally caused by an elevated minute ventilation, secondary to an improper ventilation setting, or an inadequate level of analgosedation of the patient. In this case, by normalizing the minute ventilation, reducing respiratory rate and/or the tidal volume, and/or optimizing the analgesia, or optimizing the sedation level, it is possible to resolve the acid-base disturbance.

A complete different approach is required to resolve the respiratory alkalosis during assisted modes, both in invasive and non-invasive mechanical ventilation. In this case, a hyperactive respiratory centre causing a spontaneous elevated minute ventilation or an overassisting ventilation setting can be the underlying mechanisms. In this scenario, a thorough evaluation of the patient-ventilator interaction, the flow curves and ventilator data can help the physician to manage the patient. Figure 2 shows a possible strategy for the management of respiratory alkalosis during NIV.

The physician should be aware that by reducing the PS in a patient with an hyperactive center of breathing, the decrease in respiratory assistance can cause an increase in the inspiratory effort, transpulmonary pressure, and patient self-induced lung injury (P-SILI). Finally, although it is a controversial topic, a further strategy to manage the respiratory alkalosis during assisted mechanical ventilation is the sedation of the patient.

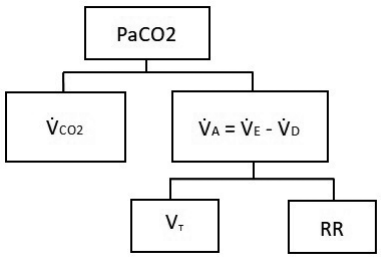


**Figure 1.** Factors that affect the partial pressure of arterial carbon dioxide ($PaCO_2$). $\dot{V}CO_2$ , carbon dioxide production; VA, alveolar ventilation; VE, minute ventilation; VD, dead space ventilation; VT, tidal volume; RR, respiratory rate.

An important question is if primary respiratory alkalosis during mechanical ventilation has a prognostic role. Concerning this point, Carrillo-Aleman *et al.* studied patients affected by acute respiratory failure secondary to cardiogenic acute pulmonary edema undergoing a trial of NIV. A higher rate of NIV failure and a greater in-hospital mortality risk were found in the group with hypocapnia. Similar findings were found by De Vuono *et al.*[9] in patients affected by severe COVID 19 suggesting that hypocapnia could be an early predictor of clinical worsening due to a deep and frequent respiratory pattern possibly related to the generation of excessive transpulmonary pressure swings leading to a self-induced lung injury (P-SILI). On the contrary, Capsoni *et al.*[1] found no correlation between the basal pCO2 values and the rate of endotracheal intubation in patients with acute hypoxemic respiratory failure secondary to interstitial COVID-19 pneumonia. These findings one more time emphasize how controversial is the management of AHRF using non-invasive respiratory supports. However, because the respiratory support was helmet-CPAP, it is important to underline that no data about the tidal volume of the patients were available making their results less comparable with study based on the use of non-invasive mechanical ventilation.

The case report describes a case of severe COVID-19 pneumonia with a persistent respiratory alkalosis despite a good response to NIV.

Two aspects needs to be clarified. Firstly, the choice of administering antibiotic therapy was made considering the immunocompromised state of the patient, despite procalcitonin serum levels have been shown to be not reliable in distinguish viral from bacterial pneumonia.[11]

Secondly, the pre-existing interstitial lung disease may have had a potential role in the development of severe hypoxemia. Patient affected by chronic interstitial lung diseases (ILD), such as Non Specific Interstitial Pneumonia (NSIP), experience a progressive worsening of gas exchange the leads to hypoxemia and in some occasion to chronic respiratory failure. Javaheri *et al.*[12] have demonstrated that patients affected by ILD have an abnormal pattern of breathing characterized by low tidal volume and high respiratory rate. In addition, it is known that aberrant peripheral sensing of the pulmonary vagal C-fibers secondary to interstitial fibrosis may cause chronic hyperventilation in patients affected by ILD.[13] All these pre-existing conditions may have had a role in the severity of the respiratory failure.

Despite being a single case report, these findings agree with the results of De Vuono *et al.*[9] on a possible connection between NIV failure and hypocapnia. Further studies on large group of patients are required to confirm this observation.

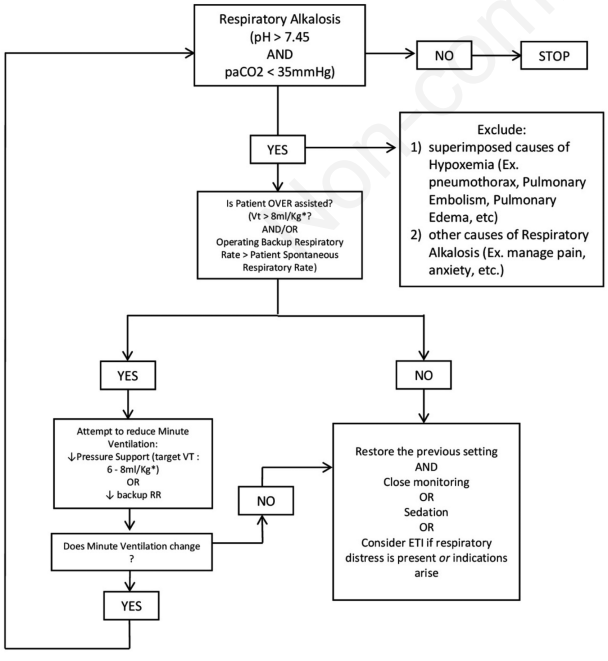


**Figure 2.** Troubleshooting respiratory alkalosis during non-invasive mechanical ventilation.

## References

1. Rochwerg B, Brochard L, Elliott MW , et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50:1602426.
2. Kangelaris KN, Ware LB, Wang CY, et al. Timing of Intubation and Clinical Outcomes in Adults With Acute Respiratory Distress Syndrome. Crit Care Med 2016;44:120-9.
3. Oczkowski S, Ergan B, Bos L, et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. Eur Respir J 2022;59:210157.
4. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med 2001;27:1718-28.
5. Carteaux G, Millán-Guilarte T, De Prost N, et al. Failure of non-invasive ventilation for de novo acute hypoxemic respiratory failure: role of tidal volume. Crit Care Med 2016;44:282-90.
6. Duan J, Han X, Bai L, et al. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. Intensive Care Med 2017;43:192-9.
7. Carteaux G, Parfait M, Combet M, et al. Patient-self inflicted lung injury: a practical review. J Clin Med 2021;10:2738.
8. Carrillo-Aleman L, Carrasco-Gónzalez E, Araújo MJ, et al. Is hypocapnia a risk factor for non-invasive ventilation failure in cardiogenic acute pulmonary edema? J Crit Care 2022;69:153991.
9. De Vuono S, Berisha S, Settimi L, et al. Hypocapnia as a predictor of the need for non-invasive mechanical ventilation in subjects with SARS-CoV-2 related pneumonia. Emerg Care J 2023;19:11237.
10. Capsoni N, Privitera D, Airoldi C, et al. Evaluation of PaCO2 trend in COVID-19 patients undergoing helmet CPAP in the emergency department. Emerg Care J 2023;19:11274.
11. Kamat IS, Ramachandran V, Eswaran H, et al. Procalcitonin to distinguish viral from bacterial pneumonia: a systematic review and meta-analysis. Clin Infect Dis 2020;70:538-42.
12. Javaheri S, Sicilian L. Lung function, breathing pattern, and gas exchange in interstitial lung disease. Thorax 1992;47:93-7.
13. Jonkman AH, de Vries HJ, Heunks LMA. Physiology of the respiratory drive in ICU patients: implications for diagnosis and treatment. Crit Care 2020;24:104.
14. Jareonsettasin P, Zeicu C, Diehl B, et al. Inappropriate ventilatory homeostatic responses in hospitalized COVID-19 patients. Front Neurol 2022;13:909915.