EC PULMONOLOGY AND RESPIRATORY MEDICINE
Perspective

Integrated Strategies to Reduce NIV Failure

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Received: February 19, 2019; **Published:** March 19, 2019

The use of non-invasive ventilation (NIV) to treat acute respiratory failure (ARF) has been tremendously expanded in the last two decades, and therefore, NIV is now considered the ventilation modality of first choice for a large proportion of patients with ARF, such as exacerbation of chronic obstructive pulmonary disease (COPD), acute cardiogenic pulmonary edema, pulmonary infiltrates in immunocompromised status, as well as after endotracheal intubation (ETI) in the transition from invasive ventilation to spontaneous breathing in chronic hypercapnic respiratory failure [1]. The main advantage of NIV is due to the chance of delivering an efficient ventilator support without the life-threatening complications correlated with conventional mechanical ventilation (CMV) delivered via endotracheal intubation (ETI). Other benefits achievable with NIV as compared to CMV is the "wider window" in terms of both timing and settings of applications (i.e. NIV as prevention of CMV, NIV as facilitation of weaning from CMV, NIV in other than ICU environments), as well as "ceiling ventilator treatment" and as "pure palliative support" [1,2].

Despite its large application and its benefit, unfortunately NIV failure occurred in up to 60% of patients with ARF and, therefore ETI is required in no- do not intubate status. The likelihood of failure is greater in hypoxaemic *de novo* ARF occurring in patients without pre-existing cardiorespiratory diseases (i.e. ARDS) as compared to hypercapnic ARF occurring in patients with pre-existing chronic respiratory disorders (i.e. COPD, chest wall deformities, neuromuscular diseases and CHF) [1-4]. The main drivers of NIV failure are: severe acidosis (i.e. pH < 7.25) and/or de novo hypoxaemia (i.e. P_{aO2}/F_{IO2} < 200 mmHg), respiratory distress signs (i.e. f_R > 25 breaths·min^{-1}) and non-pulmonary organ failure are strong predictors of NIV failure [1-3]. To avoid a potentially dangerous delay in ETI and CMV it's crucial to early detect predictors of NIV failure to avoid an inappropriate poor prognosis.

According to the timing of occurrence, NIV failure may be distinguished as 1) immediate failure (within minutes to < 1h), due to inefficient clearing of secretions, hypercapnic encephalopathy syndrome (HES), intolerance/agitation and patient-ventilator asynchrony; 2) early failure (1 - 48h), due to poor blood gas exchange and an the inability to correct them promptly, increased severity of acute illness and the persistence of a high respiratory rate with respiratory muscle distress; and 3) late failure (> 48h), occurring after an initial favourable response to NIV and related to sleep disturbance and severe comorbidities [3,4].

NIV-integrated therapeutic strategies may be attempted by expert teams to counterbalance the drawbacks of NIV such as poor compliance, mucus accumulation, ineffective gas exchange correction [4,5].

The inefficient autonomous capability of patients in clearing bronchial secretions is strongly correlated with NIV failure especially level of consciousness and cough are severely impaired [6]. In this scenario some integrated strategies with NIV may be tried to reduce the need of ETI or death [1-3,6,7]. Conjunct use of NIV with different non-invasive techniques such as mechanical and manual cough assist devices [8,9], high-frequency chest wall oscillation [10-14] and intrapulmonary percussive ventilation (IPV) could be successful in improving the mobilisation and removal of abundant secretions from airways and, thus, avoiding the requirement of ETI in a large population of neuromuscular, COPD and bronchiectasis patients. In the acute setting, the use of IPV before or in combination with NIV has been shown to may reduce the risk of treatment failure and the need of ETI and in COPD patients with difficulties in spontaneously removing secretions [13,14]. Moreover, the early application of fibre-optic bronchoscopy (FBO) in COPD exacerbated patients at high risk of NIV failure for inefficient spontaneous management of respiratory secretions is a safe and effective alternative to the conventional invasive strategy (FBO after ETI) with the advantage of being associated with lower rate of infective complications [15].

A part for mild to moderate hypercapnic encephalopathy (HES), altered level of consciousness is an independent predictor of NIV failure. This especially true for encephalopathy not correlated with hypercapnia and acidosis [6,16,17]. While patients usually get on well with NIV when sensorium is severely depressed (i.e. coma), agitation and delirium are associated with poor adherence to mask ventilation and need for ETI. In this scenario, the combined use of NIV with mild analgosedation (i.e. opioids, propofol and α2-agonists) in an high intensive care setting could be effective in improving the compliance to mask ventilation [18,19]. The risk of side effects and oversedation should be always kept in mind and intubation must be prompted available. Analgosedation may be combined with the "interface rotational strategy" by expert teams working in highly monitored settings with the aim to manage poorly tolerant NIV acute patients [20].

Another integrated strategy to reduce NIV failure due to discomfort for patient-ventilator dyssincronies is to optimised the ventilator settings on the basis of the lecture of ventilator waveforms, by adjusting trigger sensitivity, increasing PEEP, minimising air leaks or using different modes or more sophisticated ventilators [21]. New modes of ventilation, such as neutrally adjusted ventilator assist (NAVA), have been documented to reduce asynchrony even in the presence of air leaks; however, the large scale application in the clinical practice of NAVA is still prevented by the difficulties in setting the ventilator in inexpert hands [22].

Integrated therapeutic option aiming at correcting gases exchanges in severely hypoxaemic or hypercapnic acute patients who are likely to fail NIV treatment during both NIV supported or unsupported sessions are High flow nasal cannula (HFNC) and extracorporeal carbon dioxide removal ($ECCO_2R$), respectively [2].

HFNC is able to deliver inspiratory flows of up to 60 $L \cdot min^{-1}$ of air up combined with 100% heated and humidified oxygen via a nasal cannula [23]. HFNC has several physiological advantages over conventional oxygen therapy: 1) capability of administering precise values of F_{IO2} ranging from 21% to 100%; 2) efficient clearance of carbon dioxide (CO_2) correlated with high flushing of pharyngeal dead space; 3) good efficiency in humidifying and heating the delivered oxygen-air mixture with an improved capacity of removing secretions; 4) greater patient comfort with a treatment that does not interfere with eating, drinking and speaking; 5) adequate matching between the flow rate provided by the device and the patient's inspiratory demand; and 6) a "stenting effect" on upper airways and alveolar recruitment due to the generation of flow-dependent low PEEP levels (up to a median 7.4 cmH_2O at 60 $L \cdot min^{-1}$). An increasing amount of clinical data have been accumulated about the feasibility, efficacy and tolerance of HFNC as alternative or as integrative respiratory support to NIV especially in hypoxaemic ARF of different aetiologies [23].

$ECCO_2R$ is an extracorporeal lung assist device which has developed from the traditional extracorporeal membrane oxygenation (ECMO) [24]. ECMO is a "total extracorporeal support" capable of oxygenating severely hypoxaemic patients and removing up to 50% of total body CO_2 production. In the opposite, $ECCO_2R$ is a "partial extracorporeal support" which may remove a lower amount of CO_2 without substantial impact on oxygenation. The advantage of $ECCO_2R$ is correlated to the less invasivity and risks as compared to the traditional ECMO (lower blood flows, lower diameter cannulation and lower doses of heparin) [24]. As well as in ARDS and as bridge to transplant, $ECCO_2R$ could be an alternative or an integrated therapeutic option in patients with acute hypercapnic acidotic ARF who are failing NIV or in those who have been intubated and are at risk of extubation failure [25-27]. Despite some preliminary encouraging results, the large scale application of $ECCO_2R$ as rescue strategy in NIV failing patients of as facilitating tools for extubation is prevented by some dangerous risks (i.e. bleeding) correlated with this extracorporeal lung assist technique. This concept has been highlighted by a systematic review that reported the lack of robustness of evidence in terms of the effectiveness and safety of $ECCO_2R$ to avoid ETI or reduce length of CMV in hypercapnic respiratory failure due to COPD exacerbations. Therefore, higher quality studies are required to deeply assess the risk-benefit balance of $ECCO_2R$ [26].

In conclusions, despite the large scale application of NIV in ARF several pitfalls of the ventilator techniques are on the base of "treatment failure" depending on different clinical and physiopathology scenarios. The implementation of integrated therapeutic strategy associated to NIV by means of expert teams in high-intensity of care settings may be of help in reducing the likelihood of failure even if ETI -CMV or terminal palliative care should be always quickly available if this rescue strategy would not work.

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Volume 8 Issue 4 April 2019