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Articolo di revisione / *Review article*

Respiratory support in acute exacerbation of idiopathic pulmonary fibrosis

Supporto respiratorio nella fibrosi polmonare idiopatica in fase di riacutizzazione

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Summary

Acute Exacerbation of Idiopathic Pulmonary Fibrosis (AE-IPF) is characterized by evidence of a rapid deterioration of clinical course (especially of dyspnea) without an obvious cause, by a lower value of arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2)(P/F) and/or by a faster decrease of PaO_2 value than in non-exacerbation IPF patients. This can lead to "*refractory*" hypoxemia requiring mechanical ventilation (MV). Because of the severe alterations in lung mechanics, in order to maximise alveolar recruitment, high tidal volume (VT) values should be applied, when performing conventional mechanical ventilation (iMV). A high risk of baro/volutrauma due to MV-iper-inflating healthy areas, and ultimately the establishment of high Ventilator Induced Lung Injury (VILI) can occur. Alleviation of the load of the respiratory muscles by non-invasive ventilation (NIV) reduces breathlessness, although the risk of patient Induced Lung Injury (P-SILI) cannot be excluded in the presence of high respiratory frequencies.
Recently, High Flow Oxygen Therapy (HFOT) has become available in daily practice and has proven useful for the management of AE-IPF, which is less invasive and more comfortable for the majority of patients. Other advanced therapies, such as invasive ventilation and extracorporeal membrane oxygenation (ECMO), are usually only used as a bridge to lung transplantation (LTX). NIV or HFOT may be also useful for compassionate use, providing relief from dyspnoea and avoiding more aggressive approaches.

Key words: Acute Exacerbation of Idiopathic Pulmonary Fibrosis, Acute Respiratory Distress Syndrome, Non-Invasive Mechanical Ventilation, Ventilator Induced Lung Injury, High Flow Oxygen Therapy, Extracorporeal Membrane Oxygenation

Riassunto

La Fibrosi Polmonare Idiopatica (IPF) è una malattia polmonare progressiva a prognosi infausta, con una sopravvivenza dopo la diagnosi variabile dai due ai cinque anni. Sebbene nella maggior parte dei pazienti la IPF si presenti con un decorso gradualmente progressivo, ogni anno il 10-20% circa va incontro ad un peggioramento acuto della dispnea non riconducibile ad una causa nota, in presenza di nuove alterazioni radiologiche alla tomografia computerizzata del polmone (addensamenti bilaterali a tipo "ground glass"/consolidazioni) su un "pattern" di Usual Interstitial Pneumonia. Tale entità nosografica è stata definita IPF riacutizzata (AE-IPF) e presenta un'insufficienza respiratoria ipossiemica, spesso "refrattaria" alla semplice somministrazione di O_2 in respiro spontaneo, di entità tale da necessitare di ventilazione artificiale (VM); sebbene già nel 2011 la ATS/ERS/JRS/ALAT ne sconsigliasse l'impiego, se non in casi particolari e solo per pazienti in attesa di trapianto; ciò poichè la necessità di impiegare alti flussi ventilatori al fine di massimizzare il reclutamento alveolare, eleva di molto il rischio di baro/volu-trauma. Pertanto, in caso di impiego della ventilazione meccanica previa intubazione (iMV), è consigliabile utilizzare bassi valori di Volume Corrente e di Pressione Positiva di Fine Espirazione ("lung resting strategy"). La Ventilazione Non-Invasiva (NIV) è di uso routinario in questi pazienti, migliorando gli scambi gassosi e correggendo l'acidosi respiratoria, frequente nelle fasi avanzate di AE-IPF; inoltre è impiegata a fini palliativi per ridurre la dispnea, da sola in associazione agli oppioidi. In una recente survey internazionale è risultato che i pazienti AE-IPF vengono trattati con NIV in una % del 74% e con cannula nasale ad alto flusso di O_2 (HFNC) nell'81%. HFNC non sostituisce la iMV nè la NIV in pazienti in situazioni critiche. La ossigenazione extracorporea, potendo essere applicata unicamente in Centri all'uopo attrezzati, esige un'attenta valutazione del rapporto costo/beneficio per singolo paziente esaminato.

***Parole chiave**: Fibrosi Polmonare Idiopatica riacutizzata, Sindrome da distress respiratorio, Ventilazione meccanica non invasiva, Danno polmonare da ventilazione meccanica, Cannula nasale ad alto flusso, Ossigenazione extracorporea*

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Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive inflammatory interstitial lung disease of unknown cause, that occurs primarily in older adults. It is characterized by relative unresponsiveness to therapy and a poor prognosis with a survival median after diagnosis ranging from 2 to 4 years, with short-term mortality around 50%. It is the most common fibrotic lung disease of all idiopathic interstitial pneumonia [1,2] (Fig. 1).

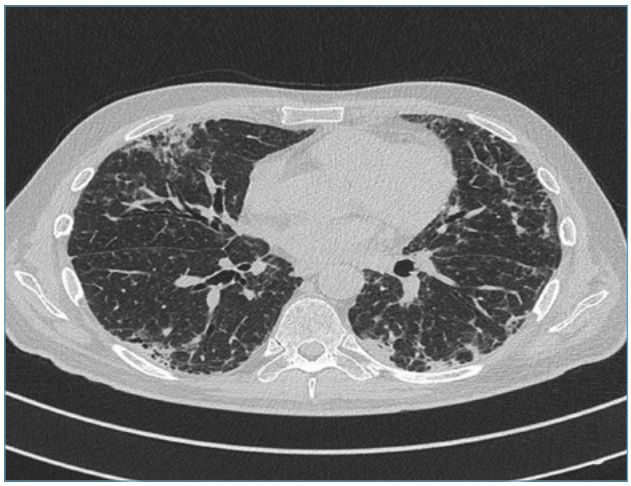

Figure 1. A patient's baseline HRCT images, showing reduced lung volumes, diffuse fibrosis, architectural distortion with bronchiectasis juxtapleural honeycombing. Reprinted from Mollica, et al. 2022 [2].

Although most IPF patients display a gradually progressive course, each year approximately 10 to 20% of patients with IPF have an acute exacerbation (AE-IPF) without displaying any obvious cause or evidence of new radiologic abnormality on high-resolution computerized tomography (HRCT) (i.e., bilateral ground-glass opacification/consolidation) on a Usual Interstitial Pneumonia (UIP) pattern [3] (Fig. 2). AE-IPF may be triggered (e.g. infection, lung biopsy, or aspiration) or idiopathic: i.e. in absence of heart congestive failure, infection or fluid overload, pulmonary embolism. Indeed, it is a diagnosis of exclusion. Nevertheless, as pointed out by Richeldi [4], because a number of studies have shown that the features and prognosis of AE-IPF are similar to other causes of acute respiratory worsening, often in the absence of specific precipitating factors "*…the proposed definition of AE-IP* [5] *focuses the most on clinical and radiological findings consistent with an underlying pathobiology of diffuse alveolar damage (DAD) and places less emphasis on the search for the etiological cause*"[4]. Moreover, a recent international survey called for harmonisation in the AE-IPF definition, assesses the global variability in prevention, diagnostic and treatment strategies for AE-IPF [6].

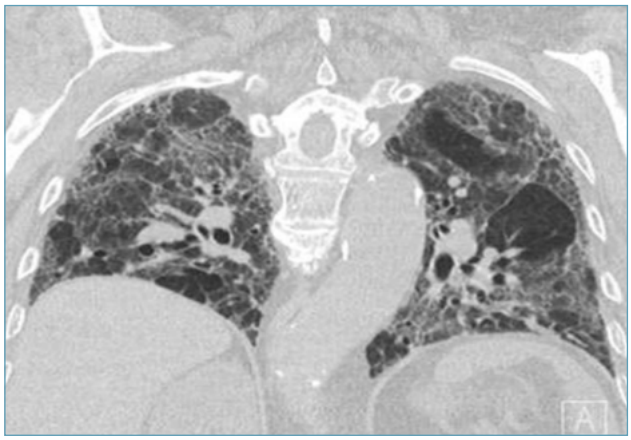

Figure 2. Exacerbation and acceleration of the underlying disease, showing progressive fibrosis and honeycombing, bronchiectasis and widespread ground-glass opacities. Reprinted from Mollica, et al. 2022 [2].

Patho-physiological aspects

DAD's proliferative stage may evolve into lung fibrosis, causing altered pulmonary gas exchange mainly by lung-diffusing capacity ($D_{L)}$ impairment and ventilation-perfusion (V/Q) mismatch.

It is well known indeed that defects in oxygenation are not necessarily due to "alveolar-capillary block" [7] but are caused by ventilation-perfusion inequalities [8]. Additionally, it has been shown that the distribution of ratios of ventilation to blood flow in IPF lungs is bimodal, with most lung units falling within a narrow range similar to normal and a minority with very low ventilation/blood flow, i.e., effectively non-ventilated [8].

V/Q lung scans also demonstrate that fibrotic lesions, and honeycomb lesions in particular, are very poorly perfused although they still receive some ventilation [9].

Thus in AE-IPF patients hypoxia is due to: a V/Q mismatch, a lower D_L in the presence of an elevated alveolar-arterial difference of PO_2 ($AaPO_2$), and/or a true right-to-left (RL) shunting [10].

In the early stage it appears that at the IPF, pneumonia induces high permeability-type pulmonary oedema with a large "*capillary leak syndrome*" (*repeated flares of massive leakage of plasma from blood vessels*) and a significant venous admixture (poorly aerated-perfused lung regions) concomitant with a loss of hypoxic pulmonary vasoconstriction (HPV)(Euler-Liljestrand mech-

anism) [11]. Impaired HPV, whether due to disease (eg, COPD, sepsis) or vasodilator drugs, promotes systemic hypoxemia. The influence and effects of hypoxia on the lung beyond vasoconstriction and regional blood flow control play an essential role in the pathogenesis as well as in the physio-pathological and clinical outcomes of IPF [12]. Note that in cardio-vascular diseases the presence of Group 3-pulmonary hypertension IPF-linked (between 30-50%) is still responsible for up to 10% of deaths [13].

As it happens, hypoxia, likely via VEGF, recruiting bone marrow precursor cells to the lung and affecting the behavior of immune cells causes both depolarization and constriction in small pulmonary arteries myocyte [14]. Sustained hypoxia activates vasoconstriction, and hypoxia-inducible factor (HIF)-1α, leading to adverse pulmonary vascular remodelling and pulmonary hypertension (PH) [15].

HPV is reduced in IPF/ early ARDS; however, the residual HPV improves Ventilation-Perfusion ratio (Va/Q) and reduces shunting. During pneumonia or atelectasis, HPV optimizes systemic oxygen delivery by reducing perfusion of the hypoxic segment [16].

In IPF pts exercise is limited by a reduced ventilatory capacity, despite the adoption of a short inspiratory time (Ti) and high inspiratory flow rate, both of which serve to optimise tidal volume (VT) and breathing frequency while presumably reducing both the force developed by inspiratory muscles and the sensation of breathlessness [17]. This confirms the clinical value of lung-diffusing capacity and the six-minute walking test (6MWT) that are strong predictors of mortality in these pts [18], although it is still debated whether concomitant PH reduces 6MWT in patients with IPF [19,20].

Note that the prevalence of pulmonary arterial hypertension [mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg] is higher in a combined pulmonary fibrosis and emphysema syndrome (CPFE) than in IPF alone (47-90% *vs* 31-46%) [21].

The increased physiological dead space ventilation (increased ratio of dead space volume to tidal volume (VD/VT), due to a rapid shallow breathing pattern [i.e. a small-tidal volume (VT)/high-respiratory-rate (RR)], in combination with the reduced lung compliance, require higher effort to increase ventilation and produces a lower ventilatory efficiency [22]. Moreover, patients with higher dead space usually need higher minute ventilation to avoid hypercarbia, leading to an increase in lung injury due to higher dynamic mechanical power [22]. Furthermore increased respiratory drive, secondary both to the increased elastic load and the higher ventilation levels required by abnormal pulmonary gas exchange, contribute more to dyspnoea in patients with IPF, that have a greater diaphragmatic activity [23].

In the first phase of IPF, alveolar hypoventilation and hypercapnia is not a common finding, very likely because of respiratory muscle adaptation to the increased respiratory workload, as a consequence of the reduction in lung compliance [24].

In this phase, exercise induced hypoxaemia and the higher alveolar-arterial oxygen difference ($AaDO_2$) gradient (approximately 30%) [25] can be due to a marked O_2-diffusion limitation, that results from parenchymal and vascular lesions, with no change in the V/Q mismatch, as patients with IPF fail to reduce VD/VT at exercise [26].

In this phase, the carbon dioxide arterial pressure ($PaCO_2$) remains normal because CO_2 diffusion rate across the alveolar-capillary membrane is facilitated in accordance with Graham's law.

This is the reason why in the early IPF phase O_2-therapy is sufficient to ensure adequate tissue oxygenation [27].

The profound alterations in elastic and resistive mechanical properties ('*stiffness*') at the late stage of the disease, may be responsible for the onset of significant CO_2 retention, both in spontaneous breathing [27], and during mechanical ventilation in patients with end stage IPF [24].

Alterations in lung mechanics

The course of most ILDs is characterized by a progressive decline in lung function due to gas exchange impairment and reduced lung compliance, and the decline rate is directly proportional to the dysregulation of fibroblasts [28].

The Pressure/Volume (P/V) curve of IPF pts shows a reduction in lung compliance; the curve is displaced downwards and to the right if compared with normal subjects [29,30] (Fig. 3); this reduction increases respiratory effort because ventilatory pump must generate a larger pressure rate to obtain the same level of inflation lung volume [31].

Failure occurs when the demands placed on the ventilatory muscles prevent adequate ventilation and respiration [32]. Thus, the increased expiratory volumes required to maintain $PaCO_2$ at normal levels are responsible for increased ventilatory drive and dyspnoea [33].

Prolonged increased respiratory workload, causes respiratory fatigue leading to carbon dioxide (CO_2) retention and Acute on Chronic Respiratory Failure (ACRF) (Type II ARF) [34].

As the disease progresses to the end stage, hypoxic respiratory failure ensues and mechanical ventilation (MV) may be required, especially in patients awaiting lung transplantation [35].

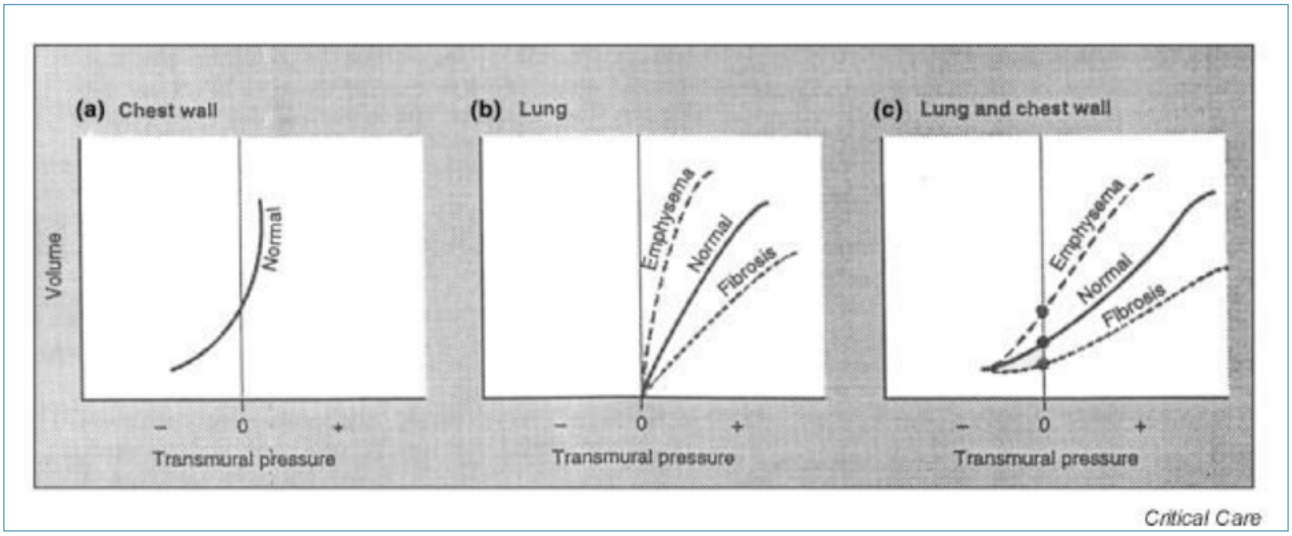

Figure 3. Compliance in emphysema and fibrosis. Shown are changes in the compliance of the inspiratory limb of the pressure-volume curve with respect to (a) chest wall, (b) lungs, and (c) combined lung-chest wall system in patients with emphysema and fibrosis. The functional residual capacity (FRC), represented on the vertical axis at a transmural pressure of 0, is elevated in emphysema, which can lead to dynamic hyperinflation. (Reprinted from Grinnan et al. 2005 [29] with permission from Elsevier).

Mechanical ventilation in AE-IPF

Usually Mechanical Ventilation (MV) is administered in order to improve oxygenation in hypoxaemic respiratory failure (*), when high flow oxygen-therapy is not enough, and/or we witness an increase in $PaCO_2$ levels and a pH shifting towards acidosis are also observed [36].

(*) *Hypoxaemic respiratory failure is usually defined as significant hypoxaemia (PIF ≤ 200), tachypnoea (respiratory rate > 30-35 breaths·min^{-1}) or use of accessory respiratory muscles or paradoxical abdominal motion, and a non-COPD diagnosis (e.g. pneumonia and/or acute respiratory distress syndrome (ARDS).*

Current IPF guidelines recommend that: "*…mechanical ventilation should not be used in the majority of patients with IPF but may be a reasonable choice in a minority.*" [1].

The rationale for these indications lies in the fact that both the structural lung disease and the precipitating condition causing ARF are irreversible and progressive [1].

Other reasons for denying MV are: poor prognosis, not improved by MV; not omogeneous lung structure ("*patchy lesions*"), as in ARDS [37]; the need of high MV flow (in Volume/Pressure mode) to maximize alveolar recruitment; a high risk of baro-/volu-trauma due to MV-iper-inflating healthy areas, and ultimately the establishment of high "ventilator induced lung injury" (VILI) [38].

VILI is a widely recognized potential side effect of mechanical ventilation, commonly attributed to the application of excessive tidal volume (VT) ("*volutrauma*") or airway pressure ("*barotrauma*") [39]. However, *volutrauma* and *barotrauma* are primarily caused by un-physiologic lung distortion or "strain" [the ratio between VT and functional residual capacity (FRC)] and "stress" (the transpulmonary pressure) acting either globally or locally, at the interface between open and closed pulmonary units [39,40].

The forces of strain, stress, and respiratory rate are primarily applied to the Extracellular Matrix (ECM) to which both the epithelial and endothelial cells are anchored. The strain of these two cell populations contributes through a cytokine release to a further recruitment of inflammatory cells, causing bio-trauma [41]. The interfaces between open and closed lung regions may have then acted as "stress raisers," locally multiplying the applied insult [40].

Because of the high mortality, Invasive Mechanical Ventilation (iMV) should not be systematically denied in IPF but discussed on a case-by-case basis, since MV can be appropriate as a bridge to lung transplantation. Thus, the use of iMV in patients with IPF with AE has important ethical connotations [42,43].

Main reason for MV treatment in these pts is mechanical ventilation (iMV)/NIV) reducing dispnoea [3].

Invasive Mechanical Ventilation (iMV) Settings

The decision to intubate is generally made on the basis of marked deterioration in blood gas tensions with hypercapnia (pH ≤ 7.30 with $PaCO_2$ ≥ 49.50) and the presence of severe dyspnoea and tachypnoea, with alteration of mental status, unless previous willingness not to be resuscitated is declared by the patient. Sedation is generally made by means of midazolam or phentalyn; to obtain a better adaptation to MV patients also can receive vecuronium or pancuronium.

In order to reduce the risk of barotrauma, protective ventilatory strategies have been performed in ARDS [44], and more recently in AE-IPF patients, obtaining encouraging results [43,45]. Indeed as reported by Marchioni et al. [46], in the presence of Diffuse Alveolar Damage (DAD) there is a partial overlap between AE-IPF pts and a fair percentage of ARDS pts [46]. "*Lung protective*" strategies during iMV in ARDS pts are generally carried out by: a) low VT < 6-8 ml/Kg; b) high respiratory rate; c) high PEEP level > 10 mmHg; d) a Plateau Pression ≤ 30 mmHg [47].

Similarly to the type of ARDS pts who had a low percentage of the recruitable lung, in AE-IPF pts the use of higher Positive End Expiratory Pressure (PEEP) value may provide some benefits but may be harmful, since all it takes is to overinflate lung regions that are already open [48].

This as in patients with AE-IPF "*the use of high PEEP to keep alveolar units opened during expiration exposes the lung at risk of injury by forming 'squishy ball' lung areas that aggravate the end-inspiratory transpulmonary pressure effects*" [45]. Indeed the inhomogeneity of the lung ("*patchy multifocal consolidations*") might act as a regional localized "*stress raiser*", increasing the pressure applied to the respiratory units surrounded by non-aerated units. Consequently, in IPF, alveolar collapse and consolidation that are responsible for permanent de-recruitment, do not improve with the application of positive pressure to the airways.

Thus the application of a high PEEP to these lungs cannot result in recruitment of hypo-ventilated areas, but can lead to overinflation in the patchy areas of the lung, with further deterioration of its mechanical properties [45].

Indeed the use of iMV in AE-IPF pts is associated with high in-hospital mortality rate (86-100%) when it is performed at high VT (> 8 ml/Kg of Predictive Body Weight (PBW) [49-51]. Thus, Marchioni et al. suggests using a "*lung resting strategy*", as opposed to "*open lung approach*" in AE-IPF pts, "*regardless of the underlying etiology*" [45]. It follows that using iMV, low VT and low PEEP should be employed regardless of the mode of ventilation ("*volume/pressure controlled*") [49,50]; even if this topic is still under discussion in ARDS [47].

Therefore, PEEP should be set at low-moderate levels (4-6 cmH_2O), taking into account that the intrinsic low potential ability of lung recruitment could involve a high risk of hyperinflation [51]. Mechanisms of ventilation-induced lung injury in patients with AE-IPF owing to an increasing in transpulmonary pressure are described [46]. Moreover, PEEP has to be set in order to obtain the best oxygenation with the smallest side effect on haemodynamics [52].

Pressure Controlled Ventilation (PCV) by using constant inspiratory flow, widely adopted in case of ARDS, is also administered in AE-IPF patients suitable for lung transplantation (LTX), as a bridge to LTX or in very selected other cases [6]. Aside from bridge for LTX, additional reasons to use PCV are the following:

1. incidence of associated Cardio-Vascular-Diseases [13];
2. a decision by the patients to forego intubation, while still receiving salvage NIV therapy for the sake of surviving hospitalization [53];
3. the case of patients seeking alleviation from symptoms, e.g. dyspnoea, and in short-term life prolongation, while maintaining cognition and the ability to communicate with others, as they await for their relatives or intend to finalise their affairs [53].

Poor prognosis associated with a higher risk of infections occurring during conventional mechanical ventilation may suggest the use of non-invasive mechanical ventilation; alternatively, "protective" ventilation in iMV must be performed, unless the patient had previously declared a wish not to be resuscitated (DNR) [50].

Non-Invasive Ventilation (NIV) setting

"*Noninvasive positive pressure ventilation may be appropriate in some patients. In rare circumstances, mechanical ventilation may be appropriate as a bridge to lung transplantation*" [1]. While a multi-center study carried on predictors of failure of NIV in 5 IPF pts with ARF, NIV had discouraging outcomes [54], recent literature has shown that the survival of ILDs patients receiving NIV seems to be higher in comparison to those who require iMV [55]. NIV is generally initiated in any patients showing CO_2 retention ($PaCO_2 \geq 45$ mmHg) and signs of respiratory muscle fatigue. In IPF pts, to avoid the risk of pneumothorax, the pressure support (PS) levels have not to exceed 25 cmH_2O. By the same token, PEEP is usually set at 5 cmH_2O, raising by 1-2 cmH_2O without exceeding 6-8 cmH_2O. The oxygen flow rate is set to achieve an arterial $SaO_2 > 92\%$ or $PaO_2 > 65$ mmHg [55].

Stratifying the results on the basis of the causes of ARF and the radiological pattern of ILD, Aliberti et al. evaluated NIV responsiveness in pts with ILD and ARF [56]. The results show that NIV improved oxygenation in pts with pneumonia, yet not in those with AE-IPF, without differences in terms of radiological pattern. Despite the high rate of NIV failure in patients with ARF in ILDs, in patients with less severe respiratory failure an early NIV trial may facilitate the recognition of NIV-responders with a better short-term clinical outcome [56,57].

In addition, the reduction in respiratory muscle load by NIV during submaximal exercise leads to an increase in endurance time and reductions in breathlessness [58]. Besides, as IPF typically affects older patients and smokers, COPD and pulmonary emphysema can

affect patients with IPF. NIV is the first-line intervention in these co-morbidities [53].

Moreover, proportional assist ventilation (PAV) can increase exercise tolerance and decreases dyspnoea and cardiac effort in patients with IPF [59].

NIV Mode: PSV vs CPAP

NIV is generally performed in PSV ("*Pressure Support Ventilation*") mode (range: 5-15 cmH_2O), or in CPAP ("*Continuous Positive Air Pressure*") mode (range: 8-10 cmH_2O), titrated to provide a moderate VT (6-8 ml/Kg of PBW). Inspired oxygen fraction (FiO_2) is set at the lowest value to keep PaO_2 at more than 60 mmHg. In the absence of respiratory acidosis, the early NIV mode is often a CPAP. During CPAP, which involves exclusively the application of a PEEP in a tight-fitting pressurized system (helmet or mask), all the respiratory work is performed by the patient and the only positive result consists in the recruitment of hypo-ventilated lung areas. CPAP is thus effective for treating hypoxemia with tachypnea, but does not improve hypercapnia (and acidosis), insofar as it does not correct hypoventilation. Conversely, alveolar hypoventilation and hypercapnia do not occur frequently in the early stage of AE-IPF [24]. In the end stages of the disease, the onset of respiratory fatigue may lead to CO_2 retention and respiratory acidosis (pH < 7.35, $PaCO_2 \geq 45$ mmHg) that forces to perform PSV in assisted/controlled ventilation by face-mask (FM) to correct hypercapnia and to unload respiratory muscles, along with the use of PEEP, up to 12 cmH_2O to keep the lung open [60].

NIV Interface: helmet vs face-mask

In IPF patients FM or helmet are employed. However, in hypoxemic patients, who required prolonged MV, FM treatment is not well tolerated and a helmet is usually used as an interface [61] (Fig. 4). When NIV-helmet is applied, PS and PEEP baseline levels are respectively set at

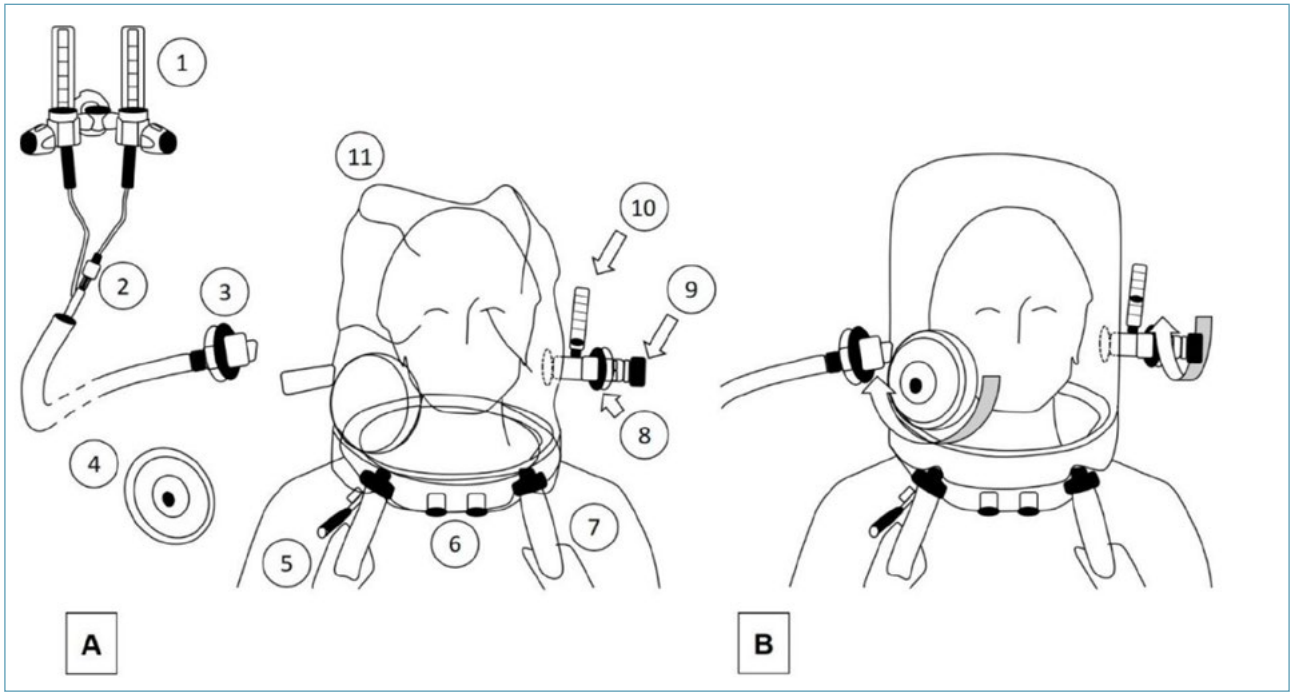

Figure 4 Schematic representation of the helmet CPAP equipment. (A) shows the mounted deflated helmet just before being connected to the high flow oxygen circuit. When connected to gas flow (B) the antisuffocation valve must be in place and the helmet must remain inflated during inspiratory efforts. 1 = double oxygen flow meter (maximal flows of 5 and 30 L, respectively). The right combination of flows to obtain the desired FiO_2 depending on the PEEP setting is usually reported in a leaflet and depends on the available high-flow mechanism (e.g., air + oxygen blender). 2 = venturimeter valve must be closed to obtain 100% FiO_2. 3 = anti-bacterial filter. 4 = antisuffocation valve (compare with (B); valve in place. The curved arrow indicates a screw like mechanism); 5 = inflatable air pillow that runs around patients' neck for improved comfort and air seal; 6 = small additional operational ports to allow the passage of the nasal gastric tube or for maintaining the seal and reduce contamination while the patient drinks by means of a straw; 7 = armpit straps for anchoring the helmet; 8 = 100% anti-viral and anti-bacterial filter; 9 = PEEP valve, which can be regulated with a spring mechanism (see also the curved arrow in (B)); 10 = manometer column, to have a direct reading of the real-time pressure changes inside the helmet; depending on the helmet design, it can be replaced by spot reading by means of a hend-held manometer through a small port usually placed on the filter crown; 11 = plastic hood (deflated). CPAP = continuous positive airway pressure; FiO_2 = inspired oxygen fraction; PEEP = positive end-expiratory pressure. From: Radovanovic, et al. 2020 [61] (courtesy of the Authors).

10 and 5 cmH_2O, both raising in increments of 2-3 cmH_2O. *Helmet advantages versus face mask*: no skin lesions due to the helmet's lack of contact with the face; effective application of higher PEEP (i.e., 8-12 cmH_2O) with minimal air leaks during prolonged treatments without interruptions. Moreover, feasibility of bronchoscopy and brochoalveolar lavage (BAL). However close monitoring and ready availability of equipment for emergency intubation are necessary during these maneuvers. Furthermore the passage of a nasogastric tube permits the patient to drink through a straw or to be fed a liquid diet [62].

Disadvantages: standard helmet's large inner volume (12-15 L) results in a compressible volume, which interferes with circuit pressurization, trigger sensitivity, and Work Of Breathing (WOB), thus facilitating rebreathing and worsening patient-ventilator synchrony. A new helmet for a decade now introduced into clinical practice features an annular openable ring which, placed underneath an inflatable cushion, secures the helmet without the need of armpit braces, as opposed to the standard helmet. The new design improves comfort, rate of pressurization, and triggering performance, while the procedure can be used in clinical practice in order to determine an improvement in clinical outcome, especially in the most severe pts requiring NIV for prolonged periods [63]. When helmet CPAP (H-CPAP) is delivered through gas flow rates up to 50 L/min, a heat and moisture exchanger (HME) placed on the helmet inlet gas port can reduce noise inside the helmet and improves patients' comfort [63].

Moreover to reduce re-breathing during NIV in ARDS pts, NIV can be delivered through different interfaces with different internal volumes, both for CPAP [64] and bi-level positive-pressure ventilation [65]. As well as a face mask with a two-limb ventilation circuit and separate access for inflow and outflow gas reduces rebreathing [66]: nevertheless there are no evidence/studies in this regard in AE-IPF pts.

During NIV by helmet, the high internal volume can promote higher CO_2 rebreathing, patient ventilator asynchrony and lower reductions in WOB compared to the FM, due to less efficiency in decreasing inspiratory effort [67].

Higher levels of pressure support and faster pressurization rates, however, could improve the efficiency of the helmet to be comparable to the face mask. In conclusion: providing NIV with helmet in CPAP mode and face-mask in PSV provides relief from dyspnoea and avoids endo-tracheal intubation (ETI) [60].

Moreover, in IPF with a low PaO_2/FiO_2 are at high risk for developing respiratory failure during fibreoptic bronchoscopy. Two randomised trials showed that non-invasive ventilation given via a full face mask reduced post-procedure respiratory failure in patients with severe hypoxaemia. Similar findings with the helmet were reported [62].

NIV Failure

May be distinguished in "*immediate/early*" failure (1-4 hrs), mainly due to intolerance of device (mask or helmet), permanence of ARF, inability to correct gas exchanges and the persistence of a high respiratory rate; and "*late*" failure (> 48 h), occurring after an initial favourable response to NIV and related to sleep disturbance and severe comorbidities [60].

As shown in the analysis conducted by Scala et al., two risk factors were found to be significant for NIV failure of ILD in the ICU: an APACHE II score > 20 and a continuous NIV demand [60].

When switch to iMV is obliged

In the presence of acute alteration of consciousness (Glasgow coma scale score < 8), cardiac arrest, poor mask compliance, inability to clear secretions, or hemodynamic instability with systolic blood pressure < 70 mmHg [53].

Predictors of MV failure in IPF

In a retrospective study on a few number of IPF pts in end-stage lung, undergoing iMV, the in-hospital mortality was 85%: moreover patients were older and at higher risk of infections than subjects treated with NIV [68]. Conversely, in a large national cohort, the in-hospital mortality of patients with IPF who are mechanically ventilated was approximately 50% [69]. MV and NIV mortality rates for patients with primary diagnosis of IPF were lower than in other studies [42,43]. Moreover, patients receiving iMV had higher mortality, were younger and had longer hospital stays, compared to those receiving NIV [69]. This study has been criticised because the decision to include all patients with a diagnostic code for IPF, beyond a rate of 33% of patients intubated also for other procedures, rather than solely those with the primary diagnosis of IPF exacerbation, such as patients with sepsis, respiratory failure, pneumonia and cardiac arrest, might have influenced the mortality rate and the final results of the study [70].

Thus, the severity of illness at the time of ICU admission (high APACHE score), severe hypoxemia (low baseline PaO_2/FiO_2 ratio), high PEEP during the first 24 hours of MV, and older age stand as independent predictors for both hospital and one-year survival [71].

Retrospective studies show a moderate success of NIV compared to IMV with a lower mortality in responder pts; a percentage between 85 and 100% died within

3 months, regardless of endo-tracheal intubation (ETI) being imposed [72-74].

Moreover, the presence of diffuse ILD ("*widespread opacification*") [56,57], a SAPS II > 34 [75], and the inability to improve PaO_2/FiO_2 after 1hr of NIV, later requiring to switch to IMV, have shown to correlate with higher mortality 68%-69% of pts submitted to NIV [73,74].

However, NIV responsiveness did not have a relevant impact on the poor prognosis related to the disease: one-year mortality rate in NIV-responders was ≥ 70% in all the evaluated studies [72-75]. On the contrary, an early start of NIV during AE-IPF is associated with better 30-day survival, improving patients' management and short-term outcomes [72]. As regard to MV setting in ILDs patients, since high PEEP has no effect on fibrotic, un-recruitable areas, thus promoting VILI, an high in-hospital mortality rate is referred when high levels of PEEP (> 10 cmH_2O), and and high Vt (> 8 ml/Kg) are applied [55]. Aliberti et al. evaluated NIV responsiveness in patients with ILD and ARF in a multicenter study, stratifying the results according to the cause of ARF and radiological pattern of ILD [56]. NIV showed to improve oxygenation in patients with pneumonia, but not in those with AE-IPF, without differences in terms of radiological pattern. The results suggest that NIV outcomes does not result from radiological pattern or cause of ARF. Despite the high rate of NIV failure in patients with ARF in ILDs, in patients with less severe respiratory failure an early NIV trial may facilitate the recognition of NIV-responders with a better short-term clinical outcome [56].

The use of NIV instead of iMV for management of life-threatening AE-IPF shows a better 60-day survival rate, a shorter high-care unit stay, and preserved oral communication with better quality of life and usage of medical resources. Further, NIV may be applied in selected pts, such as those with less severe ARF, to early recognition of NIV-responder pts and to treat the causes of ARF, minimizing complications and the poor outcome linked to endotracheal intubation ETI and iMV [53].

Patient Induced Lung Injury (P-SILI)

In non-intubated patients with AE-IPF, there is a significant hyperactivation of the respiratory drive with a pleural swing reaching -30 cmH_2O. Inspiratory muscle activities can lower the pleural components surrounding the lung, leading to an increase in trans-pulmonary pressure. When spontaneous effort is modest and lung injury is less severe, the increased trans-pulmonary pressure provides various benefits for gas exchange, ventilation pattern, and lung aeration. When the contribution to the large tidal volumes and the total trans-pulmonary pressure is predominantly obtained with high inspiratory pressure and excessive spontaneous effort by the patient, then injurious lung inflation pattern of "pendelluft" (i.e., the translocation of air from nondependent lung regions to dependent lung regions) occurs. Therefore, spontaneous breathing may be more injurious in patients with a high respiratory drive [76,77].

Therefore, in patients to whom NIV is unable to reduce the excessive inspiratory effort, the condition of persistent increased lung stress and strain may be associated with the development or worsening of patient Self-Induced Lung Injury (P-SILI) [78]. On the contrary, a protective low VT, useful to avoid the triggering/worsening of ventilator-induced lung injury (VILI), may be difficult to achieve in most patients receiving NIV [79].

HFOT/HFNC

High-flow oxygen therapy by nasal cannula (HFNC) may be a reasonable alternative for patients with acute hypoxemic respiratory failure without hypercapnia who are not able to achieve an adequate saturation of peripheral oxygen (SpO_2) with low-flow oxygen. HFNC is a system that is able to deliver up to 100% heated and humidified oxygen at a maximum flow of 60 L·min-1 of gas via a nasal cannula. It has become available in daily practice and has proven useful for the management of AE-IPF because is less invasive and more comfortable for the majority of patients [80].

Several advantages over conventional oxygen therapy and an increasing amount of clinical data, even if derived mostly from uncontrolled trials, are accumulating about the feasibility, efficacy and tolerance of HFNC in ARF [81]. High Flow Nasal Oxygen (HFNO) is also better tolerated than NIV and allows deteriorating patients to eat and converse and may have utility as a palliative treatment in those patients not suitable for intubation [82].

Several high-quality trials recently demonstrated a major clinical impact of HFNC in patients with hypoxemic respiratory failure [83].

An international panel of experts assessed the physiological effects and potential clinical benefits of HFNC in different areas of ARF management [84].

Patients with ARF not responding to conventional oxygen therapy seemed to benefit from this device. His beneficial effects allow some patients with severe ARF to avoid intubation and improve their outcome [84]. Since failure of HFNC might cause delayed intubation and worse clinical outcomes in patients with respiratory failure, not delaying intubation during HFNC is an important concern.

The diagnostic accuracy of "ROX index" (*termed defined as the ratio of oxygen saturation as measured by pulse oximetry (SpO_2)/FiO_2 to respiratory rate*) for determining HFNC outcome (need or not for intubation) has been validated [84,85].

However, use of modified ROX criteria using PaO_2/FiO_2 rather than SpO_2/FiO_2 in patients with different severity of respiratory failure was estimated to have a more contributory prediction of HFNC failure [86]. A treatment algorithm defined as a step-by-step protocol for the management of healthcare in patients with AE-IPF admitted to a Respiratory Intensive Care Unit (RICU) was also developed; it included: *conventional Oxygen therapy, HFNC oxygen therapy, NIV, $ECCO_2R$, ECMO, iMV.* Short-term mortality falls to below 50% when this treatment algorithm incorporating HFNC was implemented [87]. Moreover, HFNC proved to be so effective that it was proposed as an extension of the Berlin Definition [88].

Helmet-NIV vs HFNC

In the end, the role of noninvasive respiratory support in patients with acute hypoxemic respiratory failure is debated [53].

Because high-flow nasal oxygen is simple to use and has clinical and physiological effects, it is recommended as the first-line intervention for respiratory support in patients with hypoxemia.

Benefits of Helmet-NIV include the possibility to prolong treatments with higher levels of PEEP, which may be crucial to improve hypoxemia. Moreover this technique can offer physiological advantages if compared with HFNC high-flow oxygen [89], but the real clinical efficacy has to be demonstrated. Among patients with COVID-19 and moderate to severe hypoxemia, treatment with Helmet-NIV, compared with HFOT/HFNC, resulted in no significant difference in the number of days free of respiratory support within 28 days [90].

In a retrospective observational study carried out in AE-IPF in ARF, comparing the effects of HFNC therapy with a gas flow rate of 40-50 liters per minute and an FiO_2 of 1.0 (at initiation) *vs* NIV delivered to the pts through a face mask in CPAP mode (connected to a BiPAP ventilator) and/or in Pressure Support, there was neither a significant difference in the intubation rate at day 30 nor in the length of stay in the ICU between the two groups [91].

In an international survey, critically ill patients with AE-IPF (total number = 434 pts) were offered high-flow oxygen by 81% and non-invasive ventilation (NIV) by 74%, yet the result lends to suspect an overlap among the groups [6].

$ECMO/ECCO_2R$

Extracorporeal lung support technologies i.e. extracorporeal membrane oxygenation (ECMO) and Extracorporeal CO_2 removal ($ECCO_2R$) have been advocated for use in the treatment of patients with irreversible end-stage lung disease as a bridge to lung transplantation (LTx). These techniques do not treat the underlying lung condition; rather, they improve gas exchange while enabling the implantation of a protective ventilation strategy to prevent further damage to the lung tissues imposed by the ventilator [92].

Since a NIV treatment failure in IPF pts requiring iMV has a high mortality rate, $ECCO_2R$ can be an option, although further studies are warranted focusing on the $ECCO_2R$ system's tolerability, safety, and efficacy in these patients [93,94].

In an International survey ECMO was offered to patients suitable for LTX as a bridge to LTX by 44%, mostly in Europe (57%) and the fewest in Oceania (24%) [6].

Prone position

Prone position (PP) has been used since the 1970s to treat severe hypoxemia in patients with ARDS because of its effectiveness at improving gas exchange [95]. Prone position is used to recruit collapsed dependent lung regions, by improving lung elastance and lung gas content. The possible mechanisms involved in oxygenation improvement during prone position in ARDS patients are: 1) increased lung volumes; 2) redistribution of lung perfusion; 3) recruitment of dorsal spaces with more homogeneous ventilation and perfusion distribution [96].

PP provides a survival advantage only in patients with relatively severe ARDS (PaO_2/FiO_2 < 150 mmHg), when managed with a smaller tidal volume (≤ 8 mL/kg), higher PEEP (10-13 cmH_2O), and longer duration of PP sessions (> 10-12 h/session). In contrast, the presence of fibrosis, as in late ARDS and pulmonary fibrosis, predisposes to non-responsiveness to prone positioning [97], while it appears useful both in association with ECMO in ARDS pts [98], both in pts affected by COVID-19 pneumonia together with recruitment manoeuvres [99], or in spontaneous breathing [100].

Palliative care

The complicated and time-consuming diagnostic, together with the few treatment options, make IPF comparable to many forms of cancer (in terms of survival and death rates) [101]. In a recent International Survey, palliative care was considered by 65% [6]. Differences in these approaches were again significant between continents. Therefore, current guidelines recommend early-integrated palliative care to IPF patients in addition to early referrals to lung transplantation and pharmacological treatment to decrease lung function decline [6]. For some patients, treating hypoxemia with supplemental oxygen is sufficient to treat dyspnea, but dyspnea due to IPF may be refractory. Palliative care strategies may help alleviate dyspnea.

The use of opioids is an indicator of an intention to relieve symptoms, but end-of-life decisions are frequently still made very late. Note that NIV is more effective compared with oxygen in reducing dyspnea and decreasing the doses of morphine needed in patients with end-stage lung (cancer and IPF). In the end, palliative care consult is a useful adjuvant for patients and their caregivers. Goals of care should be discussed with all IPF patients in outpatient settings [102].

Outcome

Most patients with an IPF acute exacerbation die from ARF. MV does not appear to have a significant impact on the survival of patients with end-stage IPF. Therefore, the international guidelines recommend avoiding the ICU in patients with AE-IPF ("*weak recommendation*") [1]. Differently from ARDS, no studies have yet concluded on the optimal ventilatory strategy and management in AE-IPF patients admitted to the ICU/RICU. Notwithstanding, a protective ventilation strategy in iMV with low tidal volume and low driving pressure could be recommended similarly to ARDS. The beneficial effect of high levels of positive end-expiratory pressure and prone positioning has still to be elucidated in AE-IPF patients, as well as the precise role of other types of respiratory assistance (e.g., extracorporeal membrane oxygenation). NIV use in acute hypoxaemic respiratory failure is still under debate. Nevertheless, NIV, compared with iMV, has fewer side effects (ventilator-acquired pneumonia and sepsis). High-flow oxygen therapy is started too shortly and data on this are limited. Other advanced therapies, such as invasive ventilation and ECMO, are usually only used as a bridge to LTX [103]. NIV or HFOT may be useful for compassionate use, providing relief from dyspnea and avoiding more aggressive approaches. Pulmonary rehabilitation probably improves functional exercise capacity, dyspnoea and quality of life in the short term, with benefits also probable in IPF [104].

Take home messages

- In AE-IPF patients hypoxia is due to a ventilation/perfusion mismatch (Va/Q), a low diffusion capacity in the presence of an elevated alveolar-arterial difference of PO_2 ($AaPO_2$), and/or a true right-to-left (RL) shunting;
- Reduction in lung compliance occur early in IPF, and may be tightly correlated with the degree of lung fibrosis;
- Parameters of lung distensibility and exercise-induced gas exchange alterations may be useful in staging the severity of disease in IPF;
- Currently, there is no definitive long-term treatment proven effective for IPF and there is even less data on prevention and treatment of AE-IPF;
- Approaches to the prevention, diagnosis and treatment of AE-IPF vary worldwide.

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