ERS International Congress, Madrid, 2019: highlights from the Respiratory Intensive Care Assembly

Celal Satici[1], Daniel López-Padilla[2], Annia Schreiber[3], Aileen Kharat[4], Ema Swingwood[5], Luigi Pisani[6], Maxime Patout[7], Lieuwe D. Bos[6,8], Raffaele Scala[9], Marcus J. Schultz[6,10,11] and Leo Heunks[12]

Affiliations: [1]Respiratory Medicine, Istanbul Gaziosmanpasa Training and Research Hospital, Health Science University, Istanbul, Turkey. [2]Respiratory Dept, Gregorio Marañón University Hospital, Spanish Sleep Network, Madrid, Spain. [3]Interdepartmental Division of Critical Care, University of Toronto, Unity Health Toronto (St Michael's Hospital) and the Li Ka Shing Knowledge Institute, Toronto, Canada. [4]Pulmonology Dept, Hôpitaux Universitaires de Genève, Geneva, Switzerland. [5]University Hospitals Bristol NHS Foundation Trust, Adult Therapy Services, Bristol Royal Infirmary, Bristol, UK. [6]Intensive Care, Amsterdam UMC, Location AMC, University of Amsterdam, Amsterdam, the Netherlands. [7]Rouen University Hospital, Rouen, France. [8]Respiratory Medicine, Amsterdam UMC, Location AMC, University of Amsterdam, Amsterdam, the Netherlands. [9]Pulmonology and Respiratory Intensive Care Unit, S. Donato Hospital, Arezzo, Italy. [10]Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand. [11]Nuffield Dept of Medicine, University of Oxford, Oxford, UK. [12]Intensive Care, Amsterdam UMC, Location VUmc, Amsterdam, the Netherlands.

Correspondence: Lieuwe D. Bos, Intensive Care, Amsterdam UMC, Location AMC, University of Amsterdam, Meibergdreef 9 M0-127, Amsterdam 1105AZ, the Netherlands. E-mail: l.d.bos@amc.uva.nl

ABSTRACT The Respiratory Intensive Care Assembly of the European Respiratory Society is delighted to present the highlights from the 2019 International Congress in Madrid, Spain. We have selected four sessions that discussed recent advances in a wide range of topics: from acute respiratory failure to cough augmentation in neuromuscular disorders and from extra-corporeal life support to difficult ventilator weaning. The subjects are summarised by early career members in close collaboration with the Assembly leadership. We aim to give the reader an update on the most important developments discussed at the conference. Each session is further summarised into a short list of take-home messages.

@ERSpublications
The #ERSCongress in Madrid had some great sessions on respiratory intensive care. This article highlights the most important sessions. http://bit.ly/2GtT0qL

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Hot topic: acute respiratory failure

A European Respiratory Society statement on chest imaging in acute respiratory failure

Paolo Navalesi summarised the main findings of a European Respiratory Society (ERS) Task Force, that was recently published as an ERS statement on chest imaging in acute respiratory failure in the *European Respiratory Journal* [1]. The statement highlights the characteristics, clinical indications and limitations of five imaging techniques: chest radiography, chest computed tomography (CT), lung ultrasound (LUS), positron emission tomography (PET), and electrical impedance tomography.

The accuracy of the portable chest radiograph to detect pulmonary abnormalities consistent with acute respiratory distress syndrome (ARDS) is severely limited [2]. The gold standard in diagnosing ARDS is the chest CT, which can reveal typical abnormalities like parenchymal distortions, reticular opacities, ground-glass opacifications and consolidations [1]. More recently, LUS has been evaluated for the diagnosis of ARDS. The typical LUS pattern of ARDS is characterised by multiple B-lines usually coalescent and not well separated; this is different from the B-lines seen with cardiogenic pulmonary oedema. LUS may also encompass pleural line and subpleural abnormalities, consolidations and spared areas in ARDS [3]. Positron emission tomography has a very limited role in bedside management of ARDS [1].

The correlation between changes in lung water and changes on chest radiography, *e.g.* in the context of cardiac failure, is poor [4]. However, absence of multiple bilateral B-lines on LUS, a sign of increased extravascular lung water, excludes cardiogenic pulmonary oedema with a very high negative-predictive value [5]. Therefore, LUS may be more sensitive for detecting increased extravascular lung water than chest radiography.

Since CT is more sensitive than chest radiography in detecting pulmonary infiltrates in patients with a clinical suspicion of pneumonia, CT modifies the likelihood of diagnosing community-acquired pneumonia (CAP) in almost two-third of cases [6]. The pooled sensitivity and specificity of LUS for pneumonia are very high [7]. Therefore, it may seem timely to include LUS and/or chest CT in the diagnostic processes of CAP.

Both LUS and chest radiography are highly specific for detection of a pneumothorax. Additionally, while the specificity of LUS and CXR for pneumothorax is quite comparable, the sensitivity of LUS is much higher than that of CXR [8]. CT remains the gold standard, but it requires transportation to the scanner and risks associated with radiation exposure. While LUS is very useful for detecting pneumothorax [9], there is discussion about the reliability of LUS to determine the extension and exact location. LUS seems superior to chest radiography when compared to CT, but it remains unclear when LUS examination is sufficient to withhold CT examination for this purpose [10, 11].

Take-home messages

- LUS and chest CT are increasingly taking a prominent role in the diagnostic process of ARDS and pneumonia;
- LUS is more sensitive for the detection of pneumothorax than chest radiography, but cannot determine the extent of the pneumothorax requiring additional investigation with chest CT.

A worldwide perspective of ventilator management

Marcus Schultz summarised the findings of three recent large service reviews of ventilator management in intensive care unit (ICU) patients: 1) the "Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure" (LUNG SAFE) [12]; 2) the "PRactice of VENTilation in patients without ARDS" (PRoVENT) study [13]; and 3) the recently finished "PRactice of VENTilation in Middle-income Countries" (PRoVENT-iMiC) study [14].

There is convincing evidence for benefit of ventilation with a low tidal volume (V_T) in patients with ARDS [15]. Ventilation with a low V_T may also benefit patients without ARDS, especially when a low V_T is compared to a high V_T [16]. A recent randomised controlled trial of ventilation with a low V_T *versus* ventilation with an intermediate V_T showed no benefit of V_T reduction in patients without ARDS [17]. It should be noted, though, that most patients in this study were receiving spontaneous ventilation during which setting the support to achieve a target V_T is difficult if not impossible, attenuating the gap between the two study groups [18]. Thus, caution should be used when extrapolating the findings of this study concerning the potential clinical impact of larger V_T differences. Overall, the evidence favours the use of ventilation with a low V_T to improve outcomes in invasive mechanically ventilated patients who have a variety of diseases other than ARDS [19].

While high positive end-expiratory pressure (PEEP) may protect patients with moderate-to-severe ARDS [20], this may not be the case in patients with mild ARDS in whom it could actually be harmful. Evidence for benefit of high PEEP, and actually of PEEP at any level, is currently lacking for patients not having ARDS [21].

Approximately half of patients with ARDS in LUNG SAFE [22] and patients without ARDS in PRoVENT [23] received lung protective ventilation with a low V_T and PEEP. While awaiting a detailed report on PRoVENT–iMiC [14], it can already be concluded that lung protective ventilation is also used in ICUs where resources are low.

There is increasing interest in driving pressure, the difference between the end-inspiratory plateau pressure and PEEP, as this parameter has a strong association with mortality and morbidity in patients with [22, 24], as well as in patients without, ARDS [23].

One recently published *post hoc* analysis of LUNG SAFE revealed that female ARDS patients are at a higher risk of receiving ventilation with a too high a V_T than male ARDS patients (figure 1) [25]. One of the reasons for this alarming sex difference could be the use of a (too large) fixed V_T in men and women, but also the difference in height between males and females could play a role [26]. Most strikingly, compared to males the mortality rates were significantly higher in females when ARDS was severe, and it could very well be that V_T settings play a role.

Take-home messages

- Low V_T ventilation is likely to benefit all patients, not only those with ARDS;
- It is uncertain if a high PEEP strategy in patients without ARDS is beneficial;
- Female patients with ARDS are possibly harmed by too high a V_T due to fixed V_T settings on mechanical ventilators.

A worldwide perspective on weaning from mechanical ventilation

Leo Heunks presented a preliminary analysis of the "Worldwide Assessment of Separation of Patients from Ventilatory Assistance" (WEAN SAFE) study, which is currently being analysed.

Longer duration of ventilation after the first separation attempt is associated with increased mortality and longer length of ICU stay [27, 28]. Weaning is a costly and critical process that comprises numerous hurdles [29–32], and there is a remarkable lack of standardisation in definitions or evidence-based practices of what should be the best course to take [27, 32, 34].

The WEAN SAFE study will answer several questions regarding weaning practices. The WEAN SAFE study ran in up to 500 centres worldwide, more than half of them located in Europe, and enrolled over 6000 patients receiving invasive ventilation for >2 days. The WEAN SAFE study collected detailed information regarding ventilation, the weaning process, presence of comorbidities and previous health status in terms of frailty. Barbara Johnson, representative for the European Lung Foundation and co-presenter with Leo Heunks, emphasised the importance of the patients' perspective in this type of study, including patient relevant outcome measures.

Take-home messages

- There is variable practice in weaning due to a lack of standardisation;
- The WEAN-SAFE study will provide insights into the common practices. This information is important to inform future intervention studies.

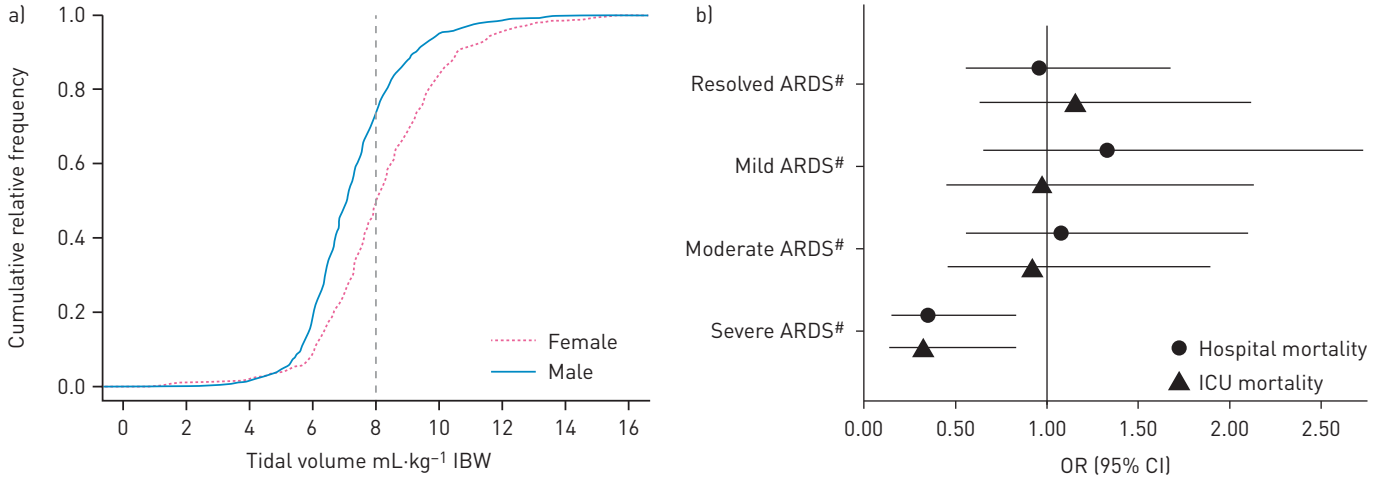

FIGURE 1 Results from a recent *post hoc* analysis of LUNG SAFE. a) Cumulative frequency distribution of tidal volume in males and females. b) Odds ratios (OR) for intensive care unit (ICU) and hospital mortality of males *versus* females by ARDS severity at day 2 (resolved, mild, moderate and severe). #: male (ref. female). Reproduced from [25] with permission.

A bridge to lung transplantation in end-stage right-sided heart failure

Olaf Mercier summarised the current evidence for the benefit of extracorporeal life support (ECLS) as a bridge to lung transplantation for pulmonary arterial hypertension (PAH) leading to refractory right-sided heart failure (RHF).

Lung transplantation is the gold standard treatment for refractory RHF caused by PAH. Candidate selection should be performed by centres with extensive expertise, given the complexity of decisions and the demanding surgical procedure [35]. PAH triggers right ventricle remodelling to which some patients adapt worse than others [36]. Thus, ECLS should be initiated when secondary organ failures and/or terminal RHF is imminent despite optimised medical therapy [37]. Lung transplantation presents as a definitive solution for unloading the RV [38]. Timely decisions are crucial. Lower stroke volumes and higher right atrial pressures are associated with worse outcomes. Biomarkers are not useful to enlist a patient for lung transplantation [39].

Veno-arterial extracorporeal membrane oxygenation (ECMO) is the most commonly used type of ECLS as a bridge to lung transplantation for PAH patients [40]. Other ECLS techniques, such as pulmonary artery-left atrium communications, are also used, though much less often. The logical case is to propose ECLS as bridge to lung transplantation and activate an emergency organ allocation, which has been a successful formula for long-term survival [40–43]. Adequate time under ECLS prior to lung transplantation is still a matter of ongoing debate [44].

Take-home messages

- Lung transplantation is the only treatment for refractory RHF due to PAH;
- Veno-arterial ECMO can be initiated as a bridge to transplantation, but timing remains an important issue.

State-of-the-art session: respiratory critical care

Non-pharmacological strategies to prevent hospitalisation in advanced stable COPD

Annalisa Carlucci first addressed the topic of preventing readmission after a first exacerbation and then talked about how to prevent hospitalisation, independently of a previous exacerbation.

Preventing the readmission of COPD patients after a first exacerbation

Some factors can have a role in preventing patient's readmission following a COPD exacerbation.

Peri-exacerbation pulmonary rehabilitation

According to the European COPD Audit, a previous hospital admission is the strongest risk factor for readmission [45] and has a greater impact than age and comorbidities. The reason of this can be found in several insults occurring during the hospitalisation itself, including immobility, systemic inflammation, treatment with corticosteroids, reduced dietary intake, and catabolic/anabolic imbalance, which generate sarcopenia, rapid deconditioning and increased disability. Pulmonary rehabilitation seems to be crucial to contrasting these factors and has proven to significantly reduce hospital readmission and mortality [46]. Unfortunately, the majority of patients who could benefit from a rehabilitative treatment after an exacerbation are not referred to a rehabilitation centre [47]. Furthermore, almost 60% of them are non-adherent to rehabilitation, mainly because they are not interested or they feel too sick/frail [48].

Home noninvasive ventilation

Home noninvasive ventilation (NIV) after an acute COPD exacerbation, in case of persistent hypercapnia (arterial carbon dioxide tension >53 mmHg) 2–4 weeks after resolution of respiratory acidaemia, can improve admission-free survival as compared to home oxygen alone, according to Murphy *et al.* [49]. In contrast, Struik *et al.* [50] found no difference in terms of exacerbation rate and survival between patients randomised to NIV and patients randomised to standard treatment. However, the two studies differ in the time of starting NIV as in the latter study NIV was started 48 h after recovery from the acute event, which could explain the discordant results.

Treatment of concomitant obstructive sleep apnea

The incidence of obstructive sleep apnoea (OSA) in patients with pre-existing COPD hospitalised for pulmonary rehabilitation was found to reach 45% in patients screened with a polysomnography [51]. Concomitant OSA is an important risk factor for the need for invasive or noninvasive mechanical ventilation and longer hospital stays in hospitalised patients with COPD [52]. Furthermore, patients with both OSA and COPD showed a higher exacerbation rate (15% *versus* 8%, p=0.04) and lower survival ($p<0.001$) compared to COPD only patients with the same severity of obstruction and medical treatment [53]. Continuous positive airway pressure treatment was able to reduce the risk of exacerbation and improve survival to the level of that of patients with COPD alone.

Care bundles

Care bundles are a set of interventions and evidence-based practices that, when used together, significantly improve the process of care and patient outcomes (www.ihi.org).

A recent systematic review found that the use of care bundles reduced the risk of hospital readmissions compared to usual care [54]. In a randomised study [55] health coaching significantly reduced the rate of re-hospitalisation at 1, 3 and 6 months compared to usual care.

In summary, a suggested flowchart after an acute exacerbation requiring mechanical ventilation could be as follows. 1) Check for residual functional activity and consider rehabilitation. 2) Perform polygraphic/polysomnographic screening once the patient is stable to exclude the presence of OSA that can be treated with continuous positive airway pressure as a first level of treatment. 3) In cases of persistent hypercapnia (⩾53 mmHg) wait 2–4 weeks and re-perform an arterial blood gas analysis and, if hypercapnia persists, treat with home NIV. 4) Care bundles have the potential to reduce the risk of hospital readmissions.

Prevention of exacerbation and hospitalisation in severe COPD, irrespective of a previous exacerbation

Although supported by less evidence, there are factors that can contribute to exacerbations and be modified.

The ability to use inhalers

In a recent study, a considerable percentage of patients made critical errors while using inhalers and in these patients the risk of exacerbation was significantly higher than in patients taking the drug correctly [56]. Therefore, training patients and regularly verifying their proficiency in the use of inhaler devices appears crucial to reducing the risk of exacerbations and hospitalisation.

Role of high-flow nasal cannula

In patients with chronic hypoxemic respiratory failure secondary to COPD, when used for at least 8 h·day^{-1}, high-flow nasal cannula (HFNC) significantly reduced the risk of exacerbation and hospitalisation, as compared to standard oxygen therapy. This result was mainly ascribed to the effect of HFNC on improving clearance of secretions [57].

Preventing pneumonia

More than 30% of COPD exacerbations were found to be related to pneumonia [58]. These pneumonic exacerbations were associated with higher 30-day mortality as compared to non-pneumonic exacerbations (12% *versus* 8%, equivalent to an adjusted HR of 1.21).

The following factors may increase the risk of pneumonia. 1) The use of inhaled corticosteroids [59]. In fact, a recent panel expert recommendation paper [60] in patients with no exacerbations in the last 3 months and a normal blood eosinophil count, recommended inhaled corticosteroid withdrawal. 2) The presence of swallowing dysfunction. Its prevalence was found to correlate with the level of obstruction [61] reaching a higher rate in patients with more severe obstruction and with the frequency of exacerbation [62].

Role of tele-assistance

The use of telemedicine was found to prevent hospitalisation in COPD patients [63]. However, data are still controversial as in another randomised controlled trial [64] telemedicine did not prevent admissions compared to the control group.

Take-home messages

- Education training in inhaler device use is crucial;
- HFNC for >8 h a day may help to reduce exacerbations;
- Assess possible withdrawal of ICS in patients with no exacerbations in the last 3 months and the risk of swallowing dysfunction, especially in patients with frequent exacerbations and more severe obstruction;
- Further studies are needed to establish which patients can really benefit from telemedicine.

Non-invasive respiratory assistance to prevent intubation in acute respiratory failure

Professor Stefano Nava outlined the evidence on noninvasive respiratory support strategies for acute respiratory failure, which include supplementary oxygen, HFNC and NIV. Invasive tools comprise invasive ventilation and extracorporeal carbon dioxide removal ($ECCO_2R$).

Hypercapnic respiratory failure

Supplemental oxygen must be used with caution in COPD patients, ideally targeting an oxygen saturation measured pulse oximetry of 88–92% [65]. High levels of oxygen are potentially dangerous especially in out of hospital settings [66], while abrupt withdrawal may induce a dangerous rebound hypoxaemia [67].

HFNC can reduce dead space fraction and as such reduce work of breathing in patients with COPD, although less effectively compared to NIV [68, 69]. Other potential beneficial effects of HFNC include humidification resulting in improved airway clearance. In addition, high inspiratory oxygen fraction can be delivered, although it is often not necessary in patients with acute exacerbation of COPD (AECOPD).

The only randomised controlled trial comparing HFNC with NIV in COPD with acute moderate hypercapnic failure showed that both strategies are equally effective [70], but trials are ongoing (*e.g.* ClinicalTrials.gov NCT03370666). Of note, HFNC has been used between NIV sessions, resulting in reduced dyspnoea sensation, although no reduction in total time on NIV [71].

The use of NIV in COPD patients with acute or acute on chronic respiratory failure with acidosis (pH<7.35 with no lower limit) remains the best practice [72], except for patients immediately meeting criteria for endotracheal intubation.

$ECCO_2R$, or lung dialysis, is a technique that allows removal of arterial carbon dioxide, using a low flow veno-venous device [73]. It has been proposed in patients with COPD at high risk of failing NIV, or to expedite extubation in hypercapnic patients. Meta-analysis of pioneer studies suggest that the combined use of $ECCO_2R$ and NIV reduces arterial carbon dioxide tension, increases pH and lowers respiratory rate, but adverse events such as haemorrhage, thrombocytopenia, circuit clotting and pump malfunctions are relatively frequent [74]. $ECCO_2R$ was further discussed in the symposium on extra-corporeal support, which is summarised below.

Hypoxic respiratory failure

The role of NIV is limited, irrespective of the underlying disease and the oxygenation defect in ARDS [75], as the risk of NIV failure is high and delayed intubation increases the risk of death [76]. Importantly, higher V_T are associated with NIV failure [77].

HFNC is superior to oxygen therapy for re-intubation prevention in low-risk patients [78] and is equivalent to NIV in patients at high risk [79] and in cardiothoracic surgery patients [80]. In CAP patients there was no difference between treatments in the primary analysis but benefits of HFNC *versus* NIV or standard oxygen were seen in a *post hoc* analysis in patients with arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) <200 mmHg [81]. Jean-Pierre Frat discussed the current evidence for HFNC in another symposium, which is summarised below.

Take-home messages

- Noninvasive mechanical ventilation has the best evidence for acute hypercapnic respiratory failure. In moderate hypercapnia, HFNC may be an alternative;
- For acute hypoxemic respiratory failure, HFNC is generally preferred over NIV.

Strategies to prevent diaphragm and lung injury in ventilated patients during partially supported ventilation

After reviewing the physiology of respiratory drive [82], Leo Heunks addressed the topic of partially supported modes of ventilation and the risk of lung injury in patients with ARDS. According to data from the LUNG SAFE observational study [83], around 70% of patients with mild ARDS are ventilated using a partially supported mode, and almost 50% of patients with severe ARDS (P_{aO_2}/F_{IO_2} ratio <100) exhibit a spontaneous breathing effort.

It is known that the match between severe lung injury and spontaneous breathing with high breathing effort is injurious. In a study by Yoshida *et al.* [84] rabbits were divided into four different groups according to the level of lung injury (mild or severe) and to the ventilator mode used (assisted or controlled). After 4 h of ventilation in rabbits with mild lung injury there were no differences in the mode used. While in those with severe lung injury, the presence of spontaneous breathing efforts dramatically increased the severity of lung injury.

Four mechanisms play a role in lung injury related to spontaneous breathing efforts: 1) transpulmonary pressure [85]; 2) transvascular pressure [86]; 3) patient ventilator asynchronies; and 4) pendelluft.

Leo Heunks then discussed the concept of patient self-inflicted lung injury (P-SILI) [87] as a mechanism of lung injury related to spontaneous breathing effort and explained how increased pressure swings caused by the patient's increased respiratory drive generate this injury.

Diaphragm injury

It is already well known that excessive unloading of the diaphragm by mechanical ventilation with no (or too low) residual effort by the patient leads to disuse atrophy, loss of muscle mass and weakness [88].

Only 3–4 days of mechanical ventilation were enough to determine a decrease in pressure generating capacity of the diaphragm of 25% [89]. Furthermore, disuse atrophy was evident after 2–3 days of controlled mechanical ventilation in brain dead patients [90]. It is less recognised that also insufficient loading by the ventilator (too low support) causes injury of the diaphragm and weakness. In a study by HOOIJMAN *et al.* [91] biopsies of the diaphragm were performed in patients ventilated for a few days and who underwent thoracic surgery. The biopsies revealed fibre atrophy with tissue injury and inflammation and sarcomeric disruption, consistent with load-induced injury. Therefore, in patients with high respiratory drive, partially supported modes may result in both patient P-SILI and patient self-inflicted respiratory muscle injury.

How do we protect the diaphragm and lung in in those patients? How could we control the respiratory drive?

Modulation of drive: change assist

Reducing the level of pressure support may not change tidal volume, as the patient will increase the effort and the respiratory drive [92]. Therefore, the transpulmonary pressure will remain unchanged, as will the damage to the lung.

Modulation of drive: sedation with propofol and the use of neuromuscular blockers

Sedation with propofol can reduce V_T and respiratory drive [93]. While, remifentanil (or any other opioid) is only able to change the respiratory rate and not modulate the respiratory drive [94]. If we are not able to control the respiratory drive with high doses of propofol, the introduction of neuromuscular blockers is probably useful. In fact, the use of neuromuscular blockers in the early stages of ARDS was found to reduce mortality in one study [92], although this was disputed in a larger and more recent randomised controlled trial [95].

Modulation of drive: partial relaxation

By titrating rocuronium we can probably modulate the respiratory drive. This would lead to a reduction of the V_T to a safe range and the work of breathing to a physiological range.

Modulation of drive: $ECCO_2R$

This could be a further experimental way to modulate the respiratory drive. In fact, in patients with ARDS, increasing ECMO flow can decrease V_T and the pressure generated by the respiratory muscles [96].

To summarise, in a patient with high respiratory drive, a reasonable approach could be: 1) to reduce the level of pressure support, monitoring the V_T; 2) if the V_T does not change, increase the level of sedation; and 3) if the respiratory drive is not controlled with sedation, introduce neuromuscular blockers, being aware that by inducing muscle inactivity they potentially increase the risk of respiratory muscle dysfunction. However, excessive activity of the diaphragm is probably more damaging than inactivity.

Improving outcomes in interstitial lung disease patients mechanically ventilated in the ICU

Alexandre Demoule focused on outcomes and treatment strategies for interstitial lung disease (ILD) patients in the ICU. "We can only improve" was the take home message as the mortality of ILD patients exceeds 50% [97], with mechanical ventilation as a primary risk factor [98]. NIV and HFNC are scarcely explored and should not delay intubation. NIV probably retains more risks than benefits [99], and P-SILI (see above) is possible also with HFNC.

How to ventilate our ILD patient?

The decision to "not intubate" should be considered if there is no plan for recovery or transplantation. If intubation is performed, we are still lacking guidelines on ventilation settings and strategies. Translation from ARDS literature may not be feasible as we face similarities (bilateral lung injury, hypoxaemia, low compliance) but also key differences (lung recruitment and poorer reversibility). Lung protective ventilation with low PEEP may lead the way [100] as the potential for recruitability is probably low. ECMO is an option in candidates for lung transplantation [101]. Diagnostic workout must be aggressive in order to recognise and treat exacerbation factors for idiopathic pulmonary fibrosis/ILD.

Take-home messages

- Patients with ILD undergoing mechanical ventilation are at a very high likelihood of mortality;
- Advance care directives should be set for patients in whom there is no chance of recovery and no possibility for transplantation;
- Mechanical ventilation in patients with pre-existent ILD should not aim at recruitment of lung with high PEEP.

Integrated strategies for acute NIV

Bronchoscopy during NIV

Raffaele Scala presented the current evidence for bronchoscopy as a diagnostic tool in patients undergoing NIV, especially in immunocompromised patients or in patients with ILD or in patients with hospital-acquired pneumonia [102]. Bronchoscopy is also used as a therapeutic tool to treat atelectasis or to perform airway clearance. However, bronchoscopy increases airway resistance by reducing tracheal lumen by 20% and by inducing bronchospasm. That results in an increased work of breathing that may affect the patient up to 2 h following the bronchoscopy [103]. Respiratory deterioration can occur in up to 35% of patients [102]. It has been shown that bronchoscopy in immunocompromised patients may worsen their outcome probably because it was performed after intubation during invasive ventilation in 61% of the cases [104].

As NIV decreases the work of breathing, its use during bronchoscopy may improve patients' outcome. It has been shown that the use of NIV during bronchoalveolar lavage in patients with acute respiratory failure improved its diagnostic yield [105]. However, there is still a lack of data to support such management. Performing bronchoscopy in patients with acute respiratory failure under NIV needs to be discussed and the risk–benefit balance assessed. If bronchoscopy is decided, the ventilator settings should be adjusted, as well as the interface [106]. The bronchoscopy needs to be performed by an experienced team regarding bronchoscopy and NIV. If necessary, the patient can be sedated using propofol during the procedure [107].

Take-home messages

- Bronchoscopy during NIV can be used for diagnostic and therapeutic purposes and the two are complementary under specific circumstances;
- There is sparse data on the safety and added value of bronchoscopy during NIV specifically;
- Studies in immunocompromised ICU patients show that bronchoscopy may not be as safe as once thought especially if performed after intubation.

Acute respiratory failure: high-flow nasal oxygen and NIV

Jeanne-Pierre Frat presented the current approach to acute respiratory failure using NIV and HFNC. In patients with acute hypoxaemic respiratory failure, there is no recommendation for or against the use of NIV [72]. It has been suggested that the use of NIV may contribute to P-SILI [87]. Indeed, some patients with hypoxaemic respiratory failure exhibit a high respiratory drive and therefore have a high V_T during NIV [108].

HFNC has predictable effects on end-expiratory pressure [109], reduces the anatomical dead space [110] and so decreases the work of breathing [111] in patients with acute hypoxaemic failure. It's use in these patients has been evaluated in a prospective randomised controlled trial that showed an improvement in survival with the use of HFNC [80]. In this study, intubation rate was not statistically different with the use of HFNC in the all population. However, subgroup analysis showed a benefit in the cohort of patients with the most severe hypoxaemic failure (P_{aO_2}/F_{IO_2} ratio<200 mmHg). In immunocompromised patients, no benefit was shown for the use of HFNC on intubation rate or mortality [112]. However, a meta-analysis does suggest a benefit in this group of patients [113].

Take-home messages

- NIV is not recommended in acute hypoxaemic respiratory failure;
- HFNC is a safe alternative to standard oxygen in hypoxaemic acute respiratory failure;
- There is conflicting evidence regarding the benefit of HFNC, especially in immunocompromised patients.

Mechanical insufflation–exsufflation devices and NIV

Miguel Goncalves explored the benefits and implementation options of using mechanical insufflation–exsufflation (MI-E) as a combined treatment option. It is well documented that NIV is the optimal treatment choice for hypercapnic respiratory failure (see summary of previous symposium). In this vulnerable patient group, secretion encumbrance is often present due to either an ineffective cough, or a defect to the muco-ciliary escalator. As a result, a comprehensive cough assessment in this specific population may be warranted and beneficial to informing timely treatment interventions.

Cough is as essential defence mechanism and previous research has highlighted critical thresholds where treatment is indicated. In a patient with a peak cough flow of $\leqslant 270\ L{\cdot}min^{-1}$ prophylactic cough augmentation is recommended due to the impact of a chest infection resulting in a further reduction in cough strength to $\leqslant 180\ L{\cdot}min^{-1}$ when no effective airway clearance will occur. In this situation a patient is at increased risk of retained secretions, ineffective secretion clearance and, therefore, repeated chest infections.

MI-E is a device that aids secretion clearance. This device augments inspiratory and expiratory flow to improve secretion mobilisation, through rapidly alternating positive and negative pressure, approximating

TABLE 1 Relative and absolute contraindications to the use of mechanical insufflation–exsufflation

Relative contraindications	Absolute contraindications
Application after meals	Bulbous emphysema
Rapid increase in respiratory rate	Pneumothorax
Haemodynamic instability	Recent barotrauma
Severe bronchospasm during the session	Non-controlled asthma exacerbation
Severe chest wall pain	Severe hypotension
	Significant pulmonary bleeding

normal cough [114]. Its possible benefits are clearing retained secretions and managing secretion load. These overlap with the contra-indications for NIV, giving rise to the question: could MI-E augment NIV?

The evidence base for MI-E is growing but is predominantly based in a neuromuscular population at present. It is known whether this device augments peak cough flow [114, 115]. Complications during home use are rare and include abdominal distension, pneumothoraxes, bradycardia and nausea [116–119].

More recently the safety of MI-E has been examined in endotracheally intubated patients. An observational study [120] reported no adverse events during MI-E use in these patients. The study authors concluded that MI-E may be safe and effective in the intubated population, but further work is required [120]. There are some commonly accepted contra-indications for the use of MI-E (table 1).

Miguel Goncalves went on to explore the wider application of MI-E in four main clinical situations. It requires emphasis that there is a very small evidence base for the application of MI-E in any of these situations at this moment in time: 1) early application to prevent intubation in the emergency department; 2) following early extubation and to facilitate rapid weaning; 3) the prevention/resolution of post-extubation failure; 4) in patients with chronic home mechanical ventilation to prevent hospitalisation.

Early MI-E application to prevent intubation in the emergency department

NIV is often used in the emergency department. Miguel Goncalves speculated that this is an opportunity for MI-E use with the aim of preventing intubation. Servera *et al.* [121] demonstrated the ability of NIV and MI-E to avoid the need for intubation in a group of neuromuscular patients with acute respiratory failure. A cohort prospective study completed in 17 patients (24 care episodes) reported that the noninvasive management was successful in preventing intubation in 79% of the episodes. Severe bulbar impairment was also found to be a limiting factor. An important limitation of the study was the small sample size and the lack of a randomised control group.

MI-E use following early extubation to facilitate rapid weaning and prevent post-extubation failure

A definition of "readiness to wean" as part of an extubation criteria often includes a manageable secretion load [122]. Early extubation may be challenging if there is a remaining secretion load. The need to await normalisation of secretions was very much challenged during this talk and a pro-active approach was championed. In those patients with secretions it was questioned whether they ever meet the criteria of a true manageable secretion load, thus making them "unweanable". Miguel Goncalves hypothesised that there is a role for MI-E under these circumstances, especially in conjunction with NIV [123].

A randomised controlled trial examined the added value of MI-E in 75 critically ill adults intubated for >48 h [124]. They found significant reductions in re-intubation rate (48% *versus* 17%), mechanical ventilation duration and ICU length of stay. More recent trials demonstrate the superiority of MI-E in aspirated sputum weight, static lung compliance, airway resistance and work of breathing [125, 126]. Limitations of these studies impact their applicability. There is a general lack of long-term follow-up, and no investigation concerning patient and clinician perceived barriers and facilitators to use of MI-E in ventilated patients.

A recent Cochrane review [127] of cough augmentation techniques for extubation/weaning from mechanical ventilation identified only three trials for inclusion. The authors concluded that the role of cough augmentation techniques in prevention of extubation failure is unclear and additional robust research, including understanding intervention safety and intensity, is essential. Furthermore, despite emerging evidence in the intubated population a recent UK survey has highlighted limited adoption of this device in the intubated population [128].

Take-home messages

- MI-E seems to be a safe intervention for home use in patients with neuromuscular disease;
- There is less evidence for the use of MI-E in conjunction with invasive or noninvasive mechanical ventilation;
- Future applications of MI-E might be to prevent intubation in patients with otherwise unmanageable secretions by allowing NIV or to facilitate early extubation and mediate weaning failure.

Analgo-sedation and NIV

Lara Pisani provided a clear overview of the available medications and the role they should play to facilitate NIV.

Sedation may sometimes be necessary but we have to ensure the respiratory drive is not abolished. Furthermore, the right drug needs to be used for the right patient. The key features of "the right" drug in combination with NIV are to: 1) improve comfort, reduce anxiety and increase tolerance; 2) perform procedures; 3) alleviate dyspnoea and achieve comfort in the palliative care setting.

Ideally, clinicians are looking for a drug that is short-acting, has a constant half-life, no accumulation in case of renal or liver failure, no impact on respiratory drive or haemodynamic status and has both anxiolytic and analgesic properties. Brochard *et al.* [129] reviewed common analgesics used in the ICU (table 2). Treatment effects should be monitored using the Richmond Agitation Sedation Scale or the Ramsay Sedation Scale.

A survey of sedation practices during NIV was performed more than a decade ago [130] with the aim of establishing what was the current practice towards sedation use during NIV. Authors reported that clinicians were using sedation and analgesic therapy infrequently but also highlighted that clinical practice was found to vary depending on clinical specialty and geographical area. There were seldom protocols in place and there was no assessment of outcomes to guide ongoing prescription titrations. It should be noted that this survey is now over 10 years old and so may not accurately reflect the practice of today.

TABLE 2 Common analgesics used in the intensive care unit

Drug name	Characteristics	Half-life	Advantages	Disadvantages
Morphine	The reference drug, recommended as bolus regimes because of the long half-life and active metabolites	3–7 h	Reduces acute/chronic pain	Histamine release can cause hypotension
			Reduces respiratory drive	Continuous titration of effective dose
			Hydrophilic agents (ideal for obsess patients)	Risk of accumulation (especially in acute/chronic renal failure)
			Synergic effect with α_2-agonist	Abolishes REM sleep stage
			Cheap	
Remifentanil	Ultra-short-acting drug, can only be administered by infusion	3–10 min	Fast elimination with no accumulation	Risk of muscle rigidity with rapid infusion
			Reduces pain	High risk of withdrawal symptoms because of short half-life
			Reduces respiratory rate (in a dose-dependent way)	Intravenous bolus not indicated
			Synergic effect with α_2-agonist	Expensive
Midazolam	Active metabolites especially with renal failure	3–11 h	Rapid onset	
			Synergic effect with α_1-agonist	
Propofol	Risk of propofol infusion syndrome at high doses/ prolonged periods	3–12 h	Rapid onset time (90 s)	Dose-dependent cardio-circulatory effects
			Reduced cerebral metabolic rate of oxygen and anticonvulsant effect	Respiratory depression and loss of upper airway patency
Dexmedetomidine	Cannot be used for deep sedation	2 h	Selective α_2-agonist	Bradycardia
			pioid and sedative sparing effect	Hypotension
			Short distribution and elimination	Intravenous bolus not indicated
			May help reduce delirium in critically ill	

REM: rapid eye movement. Reproduced from [129] with permission from the publisher.

Take-home messages
- Sedation is not always required during NIV;
- There is not a single drug of choice and the drug should be matched with the patient;
- Analgesic sedation may reduce agitation due to NIV and improve tolerability;
- Once analgesic sedation is started, the effect should be monitored using validated sedation scales and this should guide subsequent treatment decisions.

ECMO

ECMO in ARDS

Benjamin Seeliger started this symposium by outlining the evidence for veno-venous ECMO in severe ARDS. As discussed previously in this highlight paper, ARDS is a common cause of acute respiratory failure with a high mortality and, currently, only strategies that limit ventilator induced lung injury have shown to improve outcomes [12].

The emergence of severe ARDS with severe refractory hypoxaemia such as seen in the H1N1 pandemic was accompanied with an increased use of veno-venous ECMO. With this, the CESAR trial was published comparing ECMO *versus* conventional management in severe ARDS [131]. The results showed no significant difference in the survival between the treatments. The primary end-point was a composite end-point considering survival at 6 months without disability. It is important to underline a particularity in the design of the study: only one centre in the UK provided the ECMO technique which may have induced a centre-effect bias.

The high mortality of ARDS and questioning surrounding the positive effect of ECMO use led to the conception of the EOLIA trial [132]. This multicentre randomised clinical trial with a rescue therapy cross-over possibility compared early initiation of ECMO therapy to standard therapy in patients with severe ARDS. 68 centres across France participated, with a total of 249 patients undergoing randomisation. The inclusion criteria were patients with severe ARDS on mechanical ventilation for <7 days, persistent low P_{aO_2}/F_{IO_2} despite standard ARDS treatment (*e.g.* protective ventilation, prone position, neuromuscular blocker use). The randomisation was stratified by centre and on the duration of the ventilation (cut-off 72 h). Patients in the control group were allowed to cross over to ECMO therapy (rescue therapy) if they had persistent severe hypoxaemia and on the discretion of the physician in charge. The primary end-point of mortality at 60 days was not statistically significant (−11% absolute risk) based on an estimated mortality of 60% in the conventional group and a power of 80%. It is important to specify that 35 patients underwent rescue ECMO therapy, which corresponds to 28% of the control group. These patients can account for a possible dilution effect of ECMO therapy in this intention to treat trial. The expected mortality of these patients without cross-over to ECMO therapy would probably be higher than the mortality of 60% presented for the statistical analysis. The secondary end-points, among which were treatment failure at 60 days, length of stay and days free of mechanical ventilation, were significantly better in the ECMO group. The safety profile of ECMO use was good and there were no significant differences between groups on bleedings. The trial was also stopped prematurely (the sample size needed was 75%) as the effect of ECMO could not be achieved. This could be due to the ambitious estimated effect size of 20% on the mortality due to treatment with ECMO. A Bayesian re-analyses of this trial showed that there is a likely positive effect of ECMO under a broad set of assumptions [133]. In clinical practice, this translates to the adoption of ECMO for very severe ARDS in expert centres.

Take-home messages
Veno-venous ECMO is an accepted rescue treatment for ARDS patients with persistent severe hypoxaemia;
The currently available evidence suggests a reduction in mortality in patients treated with veno-venous ECMO.

$ECCO_2R$: a method for the future?

Vito Fanelli talked about the potential indications regarding $ECCO_2R$. These include: AECOPD, ARDS and acute kidney failure requiring renal substitution therapy. The mechanism of $ECCO_2R$ is to clear the arterial carbon dioxide through a venous canula with a blood flow of 350–1000 mL·min^{-1}. Importantly, it has no significant effect on oxygenation.

The aim of $ECCO_2R$ in ARDS is to provide carbon dioxide control in order to reduce the need for a larger V_T to minimise ventilator-induced lung injury. As discussed in the previous sections of this article, ventilator-induced lung injury prevention is the most important treatment in ARDS. The SUPERNOVA trial assessed the feasibility and efficacy of the association of $ECCO_2R$ to ultra-protective ventilation in patients with moderate ARDS and an expected mechanical ventilation >24 h [134]. The use of $ECCO_2R$ facilitated the achievement of ultra-protective ventilation. The V_T, plateau pressure and driving pressure were diminished while maintaining the same level of arterial carbon dioxide. Complications described with $ECCO_2R$ were canula haemorrhage requiring incidental blood transfusion.

AECOPD is a frequent complication that is typically associated with hypercapnia. In recent years, NIV has become a cornerstone in the treatment of hypercapnic exacerbation (see previous sections) with a positive effect on mortality. With the development of $ECCO_2R$, its role in AECOPD treatment was questioned, especially considering the existing high rate of NIV failure [135]. In 2014, Del Sorbo *et al.* [136] studied the use of $ECCO_2R$ in AECOPD patients at risk of NIV failure to avoid oro-tracheal intubation. This match–control cohort study established that $ECCO_2R$ seemed to be safe and efficient in this group of patients. These observations need to be confirmed with future randomised control trials.

Recently, the place of $ECCO_2R$ in acute kidney failure requiring continuous renal replacement therapy has been studied. Acute kidney failure can be associated with multiple organ dysfunction syndrome and need for mechanical ventilation. All these elements lead to inflammation, cell apoptosis and humoral mediators release. In an open-label interventional clinical trial, Fanelli *et al.* [137] showed that there could be an improvement in renal function and lower levels of inflammatory mediators using $ECCO_2R$ and continuous renal replacement therapy in patients with ARDS and acute kidney failure. The hypothesis is a possible "cross-talk" between the lung and kidney leading to reduced mechanical stress and, therefore, less inflammatory response.

Take-home messages

- $ECCO_2R$ can reduce the risk of ventilator-induced lung injury in moderate ARDS allowing achievement of protective mechanical ventilation by clearing the arterial carbon dioxide tension;
- It may diminish the need for mechanical ventilation in patients with hypercapnic exacerbation of COPD if associated to NIV;
- $ECCO_2R$ may interrupt the cross-talk lung/kidney interaction in patients with acute kidney failure which could result in a lower level of inflammation;
- All these findings are preliminary and require validation in larger randomised controlled trials.

Mechanical ventilation in ECMO

Christoph Fisser spoke on how to set the ventilator during ECMO in ARDS. The standard care for all patients with ARDS involves the concept of "baby lung". Protective ventilation is considered protective when a V_T of 6 mL·kg^{-1} (ideal weight)/min and a plateau pressure <30 cmH_20 are used. In real life it can be difficult to achieve this, as shown in a large observational international study (LUNG SAFE) [12] and as discussed in the talk by Marcus Schultz (see previous section in this article).

Gattinoni *et al.* [138] developed an equation called mechanical power which can be a surrogate for lung stress and, therefore, ventilator-related lung injury:

$$\text{Power}_{rs} = 0.098 \cdot \text{RR} \cdot \left\{ \Delta V^2 \cdot \left[\frac{1}{2} \cdot \text{EL}_{rs} + \text{RR} \cdot \frac{(1+ I{:}E)}{60 \cdot I{:}E} \cdot R_{aw} \right] + \Delta V \cdot \text{PEEP} \right\}$$

where ΔV is the tidal volume, RR is the respiratory rate, EL_{rs} is the elastance of the respiratory system, I:E is the inspiratory-to-expiratory time ratio, and R_{aw} is the airway resistance. In theory, at least different variables of this equation can be adapted and improved with optimal ventilatory settings. For example, we know that V_T reduction effectively limits lung injury [15]. Data suggest that ventilation with very low V_T (3 mL·kg^{-1} predicted body weight) during ECMO [139] could be effective in the reduction of the inflammatory response. The respiratory rate is also a variable in the equation. Based on the data available in the LUNG SAFE study, patients with a lower respiratory rate had better survival [12]. Taking these two variables together, animal data indeed suggest that near apnoeic ventilation would have a reductive effect on lung inflammation [140].

With the limited evidence available for V_T and respiratory rate it seems that the lower is the better. But it is important to bear in mind that the lowest is not the best. There are some side-effects of very low driving pressure and respiratory rate such as de-recruitment, which may result in oxygenation disturbances requiring a higher ECMO blood flow.

As discussed in the lecture by Leo Heunks in a previous sections, Christoph Fisser further emphasised the importance of navigating the balance between P-SILI and minimisation of sedation and muscle relaxation. The weaning of patients on ECMO and mechanical ventilation should be anticipated and discussed at the moment of cannulation. There are various algorithms available produced by different centres, but there are no evidence-based guidelines.

Take-home messages

- Veno-venous ECMO could facilitate more protective mechanical ventilation and hereby limit lung injury and improve outcomes;
- Calculation of mechanical power is an attractive method to estimate the damage that is potentially done by mechanical ventilation and provides a rationale for decreasing V_T and respiratory rate;
- More evidence is needed regarding the optimal ventilator settings during ECMO.

Neuro-prognostication in ECMO

Mirko Belliato discussed the prognostication of neurological outcome during ECMO. It is widely accepted that ECMO with arterio-venous cannulation is associated with 15% of neurological complications. In ECMO with veno-venous cannulation, the possible neurological complication can be linked to a reduced cerebral flow secondary to a rapid carbon dioxide level correction. With the increasing use of veno-venous ECMO in acute respiratory failure, there is more and more attention focused on the neurocognitive (dys) function of patients receiving ECMO and much can be learned from studies in a post-cardiac arrest indication. Different predictors of survival and neurological outcome are developed that aim is to help identify patients at risk of neurological complication and determinate level of impairment.

Electroencephalogram

In the first 24 h of ECMO, the presence of crisis, micro-voltage and reduced cerebral activity or micro-burst suppression contributes to early prediction of poor outcome [141].

Near-infrared-spectroscopy

This noninvasive technique measures the change in brain oxygenation. It can suggest a difference in the cerebral perfusion. A low near-infrared-spectroscopy is associated with a rapid onset poor outcome (risk of cerebral oedema development) and might be used to guide treatment in patients undergoing ECMO [142].

Biomarkers

The evidence for biomarkers in prognostication of neurological outcomes is premature. One biomarker that is frequently studied is neuron specific enolases. Levels of this molecule >75 $\mu g \cdot L^{-1}$ in the first 24–72 h is a sign of severe neuronal lesion [143]. Another molecule that was studied is the S-100 protein, but it has a low sensitivity which limits the potential application.

To date, none of these markers can be used clinically and should be used in a research setting.

Take-home messages

- Prognostication of neurological outcomes during ECMO is difficult and most evidence comes from post-cardiac arrest veno-arterial ECMO;
- Electroencephalogram, near-infrared-spectroscopy and biomarkers are being developed as prognostic tests but have not been validated sufficiently to allow for clinical application;
- The findings in post-cardiac arrest patients are not directly applicable to ARDS patients undergoing veno-venous ECMO.

Closing remarks

This highlight paper discussed the most important sessions of the ERS Respiratory Intensive Care Assembly at the 2019 International Congress in Madrid. We summarised the recent advances in several topics that are highly relevant for pulmonologists, intensivists, nurses and researchers. We hope to see you next year at the International Congress in Vienna, Austria, and in the meantime follow us on Twitter @ERSAssembly2 or the ERS website.

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