ERS International Congress 2022: highlights from the Respiratory Intensive Care Assembly

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Shareable abstract (@ERSpublications)
The Early Career Members of Assembly 2 (Respiratory Intensive Care) attended the #ERSCongress 2022 in Barcelona. They report on sessions related to the theme of this assembly: in particular, ARDS and mechanical ventilation. https://bit.ly/3QwQVxy

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Abstract

Early Career Members of Assembly 2 (Respiratory Intensive Care) attended the 2022 European Respiratory Society (ERS) International Congress in Barcelona, Spain. The conference covered acute and chronic respiratory failure. Sessions of interest to our Assembly members and to those interested in respiratory critical care included the state-of-the-art session on respiratory critical care, the journal session (ERS/*Lancet*) on acute respiratory distress syndrome (ARDS) phenotyping into precision medicine, and sessions on specificity of coronavirus disease 2019 ARDS and its post-critical care. A symposium on treatment of acute respiratory failure in patients with COPD and innovations in mechanical ventilation either in the intensive care unit or at home were also reported upon. These sessions are summarised in this article.

Introduction

Assembly 2 of the European Respiratory Society (ERS) encompasses the broad fields of respiratory critical care. Our assembly is divided into two groups, those of acute critical care and of non-invasive support. Currently, Christian Karagiannidis heads our assembly, João Winck has the role of secretary, and Christoph Fisser is our Early Career Representative. The acute critical care subgroup is chaired by Ignacio Martin-Loeches, with Ana Cysneiros as secretary. The non-invasive support group is chaired by Marieke Duiverman, and Claudia Crimi is secretary. At the time of publication, we have 1672 Assembly 2 members, 36% of whom are early career members and 50% of them are female. In this review, we present highlights from the ERS International Congress 2022 of interest to Assembly 2 members and those interested in critical care and mechanical ventilation. The sessions we have reported on include the symposia on acute respiratory distress syndrome (ARDS) phenotypes, non-invasive ventilation (NIV) in hypoxaemic respiratory failure and new developments in mechanical ventilation and weaning, and the guidelines session on high-flow nasal cannula (HFNC) in adults with acute respiratory failure.

ARDS: the path to precision medicine (a joint ERS/*Lancet* session)

Lorraine Ware (Nashville, TN, USA) began the session by highlighting that ARDS is a heterogenous clinical syndrome. Different methods have been employed to subclassify ARDS based on aetiology, severity, radiological distribution and biological markers [1]. The hyperinflammatory phenotype characterised by Calfee *et al.* [2] has demonstrated a higher mortality and differential response to treatment. Further advances in ARDS phenotyping may hold promise for future personalised medicine.

Danny McAuley (Belfast, UK) emphasised the limitations of current Berlin definition of ARDS. He suggested incorporating ultrasound to identify lung infiltrates, using the ratio of oxygen saturation measured by pulse oximetry to inspiratory oxygen fraction (S_{pO_2}/F_{IO_2} ratio) as a non-invasive marker of oxygenation and removing minimal positive end-expiratory pressure (PEEP) requirement with the advent of high flow nasal oxygen. The cornerstone of ARDS management includes lung protective ventilation, prone positioning and restrictive fluid strategy [3–5]. The recent REST trial explored extracorporeal CO_2 removal ($ECCO_2R$) to further lower tidal volumes, without mortality benefit [6]. Additionally, there is an urgent need to assess the long-term outcomes post-ARDS.

Martin Kneyber (Groningen, the Netherlands) presented the paediatric-specific definition and management of ARDS [7]. Interestingly, in the paediatric population, studies have not shown a strong correlation between tidal volume and mortality [8]. However, mortality was higher in children managed with lower PEEP than recommended by the ARDSNet protocol [9]. Increased driving pressure was associated with prolonged time to extubation [10]. More randomised controlled trials are needed to guide individualised therapy in paediatric ARDS.

Michael A. Matthay (San Francisco, CA, USA) concluded the session with lessons learned from past clinical trials. Moving forward, he recommended designing ARDS trials that reduce heterogeneity by targeting treatable traits, yet applicable to diverse global population [11]. A global definition of ARDS was proposed at an international consensus conference to address these goals.

Take-home message

- Given the heterogeneity of ARDS, further phenotyping into treatable traits is key to precision medicine in both adults and children.

Beyond COVID-19: translating COVID-19 treatment successes to all-cause ARDS

Tiffanie Jones (Philadelphia, PA, USA) reflected on the need to identify and translate coronavirus disease 2019 (COVID-19) biomarkers into ARDS' treatable traits [12, 13]. Alveolar/endothelial injury contributes to ARDS at different stages [14]; the receptor for advanced glycation endproducts (RAGE) is defined as an alveolar/epithelial injury marker, and its soluble form (sRAGE), a possible treatable trait, is associated with the risk of ARDS [15–19]. Anti-RAGE therapies have been tested in preclinical models with success [20, 21].

Manu Shankar-Hari (Edinburgh, UK) described a molecular signature with a cytokine pattern connected to each ARDS phenotype [22–24]. Targeting inflammation positively impacts mortality. As such, interleukin (IL)-6 antagonist reduced mortality in patients with COVID-19 [25], anti-TNF-α therapy increased survival in septic patients [26], and reparixin appeared to be effective for the treatment of patients with COVID-19 pneumonia [27]. The success of a therapy might be associated with the dominant activated pathway at the moment of the treatment, according to the patient's phenotype.

Jurjan Aman (Amsterdam, the Netherlands) defined the necessity to measure vascular stability and leakage as a critical player for ARDS due to COVID-19 [14, 28–31]. In this regards, angipoietin-2 has been suggested as a marker [32]. To improve alveolocapillary function, imatinib (a tyrosine kinase inhibitor) has been used in COVID-19 patients [33]. Imatinib trials, COUNTER-COVID and INVENT-COVID, exhibited an improvement in the clinical outcome in severe COVID-19 and reduced extravascular lung water index (EVLWi) in subgroups of ARDS due to COVID-19 patients, measured by pulse contour cardiac output monitoring [33–36].

Trials in critical care are challenging due to heterogeneity of the patient population and inefficiencies in obtaining data, including long-term outcomes. Carolyn Calfee (San Francisco, CA, USA) introduced adaptive trials (trials with pre-planned capabilities to adjust design factors) as a proposal to deal with the ARDS phenotype heterogeneity, the stratified randomisation and a response adaptation [37–39]. They had a considerable impact during COVID-19: for example, RECOVERY evaluated 10 treatments in 47 879

participants in 199 sites, and I-SPY-COVID is an adaptive platform for a phase 2 clinical trial to identify agents with potential therapeutic benefit [40, 41].

Take-home messages

- The need for finding new biomarkers and treatable traits to develop new therapies targeted against ARDS is evident. Most treatments of ARDS are directed against inflammation, but we must not miss the treatment for vascular leakage.
- Adaptive clinical trials have proven to be a useful tool in finding targeted treatments for ARDS.

State-of-the-art: respiratory critical care

Carolyn Calfee (San Francisco, CA, USA) presented the clinical implications of phenotyping ARDS. Several ways of phenotyping have been proposed and have demonstrated acceptable results in different settings according to the aetiology or the severity of the underlying disease (*e.g.* COVID-19 ARDS [42]). Biomarker models have identified a hyperinflammatory phenotype [1, 2, 43, 44] that have been validated in different cohorts [45, 46]. This might help in the future treatment because hyperinflammatory ARDS might respond to higher PEEP or corticosteroids [42, 46]. However, prospective studies evaluating this concept are still needed.

Laurent Brochard (Toronto, ON, Canada) discussed the clinical implications of patient self-inflicted lung injury (p-SILI). Experimental studies have demonstrated p-SILI [47, 48]; however, in clinical practice it is still a concept. There is indirect clinical evidence of p-SILI such as a high expired tidal volume that is independently associated with NIV failure in patient with acute hypoxaemic respiratory failure [49]. Monitoring techniques including airway occlusion pressure (P_{occ}) [50] could help to better understand it, although oesophageal pressure (P_{oes}) is the gold standard [51]. Clinical implications hypothesises that mortality is higher with NIV than with HFNC due to p-SILI [52]. Partial neuromuscular blockade, ventilation with higher PEEP and higher F_{IO_2} presents as a promising treatment for p-SILI [53–55].

Lise Piquilloud (Lausanne, Switzerland) commented on the advanced respiratory monitoring in acute respiratory failure. Current recommendations do not address potential phenotypes, chest wall compliance or p-SILI risk [56]. A well targeted P_{oes} ventilation strategy potentially improves ARDS outcomes, especially in patients with lower APACHE-II scores [57, 58]. Respiratory drive and effort monitoring is relatively easy and indicates patient demand during assisted mechanical ventilation [50, 59]. P_{occ} at 100 ms ($P_{0.1}$) is a not-so-new technique but useful [60–64] and might predict relapse in COVID-19 ARDS patients [65].

Stefano Nava (Bologna, Italy) presented whether HFNC or NIV should be used for acute hypoxaemic respiratory failure. There are contradictory results on this matter. While the FLORALI study found lower mortality with HFNC in the severe subgroup of patients [52], it failed to reduce therapeutic escalation compared to standard oxygen therapy in mild hypoxaemic COVID-19 patients [66]. Helmet NIV reduced the incidence of intubation compared with HFNC in COVID-19 [67] and other studies found them to be equivalent [68]. Nonetheless, a trial of NIV might be offered to treat *de novo* acute hypoxaemic respiratory failure, when treated by an experienced team [69].

Take-home messages

- ARDS phenotypes are already treated differently, in terms of severity and COVID-19 *versus* non-COVID-19 distress.
- New methods for identifying molecular phenotypes using biomarkers and/or clinical data have been developed, although clinical testing is still needed.

COVID-19 acute respiratory distress syndrome

The usefulness of day 1 chest X-ray score for predicting mortality and intensive care unit (ICU) admission in COVID-19 patients was reported by Trieu-Nghi Hoang-Thi (Ho Chi Minh City, Vietnam). In 219 patients hospitalised for COVID-19 pneumonia, a simple severity score based on lung consolidation observed on chest X-ray, with a maximal score of 24, was assessed. Each point increase in this score increased the risk of death over time by 1.33 (HR 1.33, 95% CI 1.10–1.62) and was a strong predictor of mortality in the first 25 days (figure 1). This score had a good sensitivity and specificity and could be a useful tool in hospitals where computed tomography is not readily available [70].

Elizabeth Rohrs and Thiago Bassi (Burnaby, BC, Canada) presented reports on the value of temporary transvenous diaphragm neurostimulation (TTDN) in ARDS. The studies were conducted on a model of

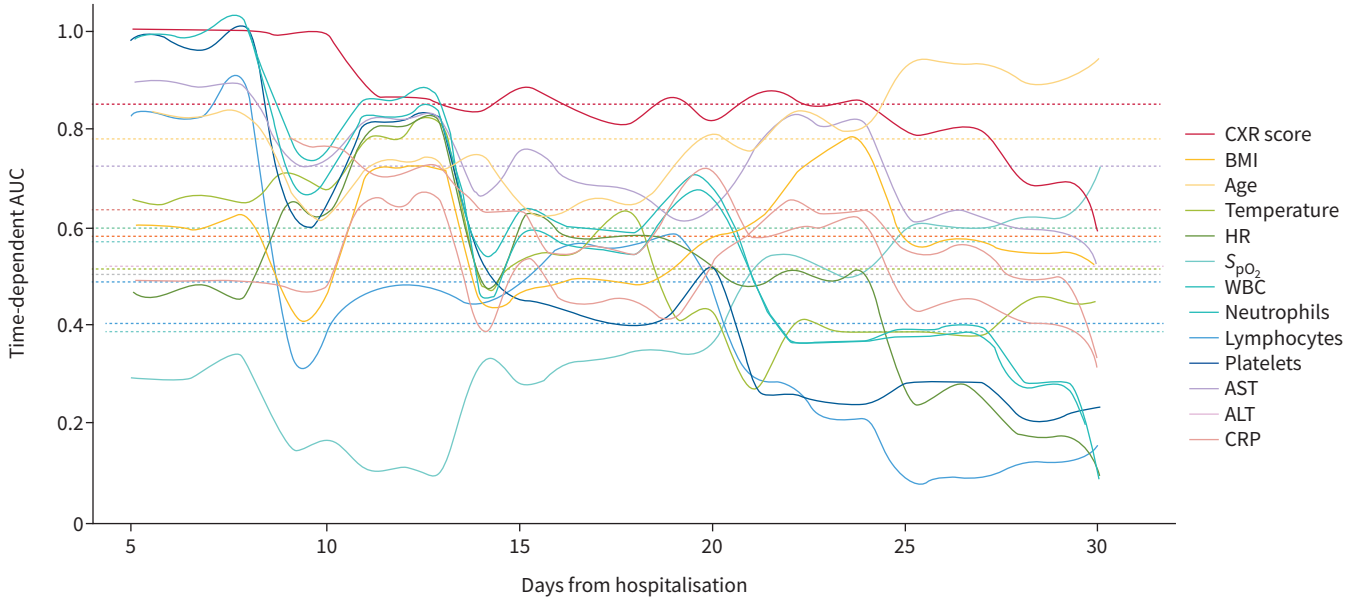

FIGURE 1 Time-dependent area under receiver operating characteristics curve (AUC) for predicting death within 30 days among 13 clinical parameters. CXR: chest X-ray; BMI: body mass index; HR: heart rate; S_{pO_2}: oxygen saturation measured by pulse oximetry; WBC: white blood cells; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein. Reproduced and modified from [70] with permission.

moderate ARDS in deeply sedated pigs. TTDN significantly reduced the total mechanical work of breathing by 19%. Neurostimulation of the diaphragm with each breath modulated the neuroinflammation associated with moderate ARDS by attenuating the proportion of pro-inflammatory microglia in the hippocampus compared to mechanical ventilation alone [71]. Finally, TTDN resulted in 41% less atelectasis and improved homogeneity of alveolar expansion in pigs with moderate ARDS [72]. These results support TTDN as a new tool to improve ARDS outcomes.

Leila Atmowihardjo (Maastricht, the Netherlands) introduced the efficacy and safety of intravenous imatinib in invasively ventilated patients with moderate to severe COVID-19 ARDS, in a multicentre randomised double-blind, phase 2 study. Imatinib was administered twice daily *versus* placebo and EVLWi (primary outcome) was measured once daily by Pulse Contour Cardiac Output monitoring. 33 patients, mainly men, with a moderate ARDS, were included in each group. There was no significant effect of imatinib on variation of EVLWi or on clinical outcomes between day 1 and day 7, but a biological sub-phenotype of patients (n=20) has been identified, characterised by high levels of alveolar epithelial injury markers that had a decrease of EVLWi over time and needs further characterisation. There were no safety concerns in this population.

Ofir Deri (Tel Hashomer, Israël) reported on the outcomes of patients with COVID-19-associated respiratory failure being registered on the lung transplantation list (n=20), in a single-centre retrospective study. Among these 20 patients (12 males), median age was 49.5 (43.8–57.5) years and median body mass index was 30.5 (28.9–31.1) $kg \cdot m^{-2}$. Four patients underwent lung transplantation and seven died while waiting on the list. The surviving patients were younger (p=0.016) and spent less time under extracorporeal membrane oxygenation (ECMO) (p=0.044).

Jessica Gonzalez Gutierrez (Lleida, Spain) presented an overview and follow-up in a post-COVID-19 consultation of critically ill patients (*i.e.* with ICU admission) in a prospective observational cohort. At 12-month follow-up (n=97), one-third of patients needed to continue follow-up due to low diffusing capacity of the lung for carbon monoxide, chest computed tomography abnormalities or persistent symptoms, leading to a high use of healthcare resources.

Take-home messages

- A new score, based only on the first-day chest X-ray, may be useful in hospitalised patients with COVID-19 if computed tomography is not available.

- Temporary transvenous neurostimulation of the diaphragm improved ARDS outcomes in preclinical studies and needs to be evaluated in patients.
- A sub-phenotype of invasively ventilated COVID-19 patients may benefit from imatinib and need further characterisation.

Post-critical care long COVID: reducing the physical and emotional toll

The pathophysiology of post-ICU COVID-19 symptoms was presented by Negin Hajizadeh (New York, NY, USA). 25% to 75% of post-ICU COVID-19 patients reported new disabilities, mainly fatigue, exertional dyspnoea and mental health problems, often irrespective of the severity of the acute illness [73]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) not only causes direct alveolar damage, but also promotes aberrant angiogenesis and microthrombi formation [28]. However, COVID-19 lung lesions only partly explain the dyspnoea and fatigue of some of these patients. Indeed, skeletal muscle wasting promoted by inflammatory cytokines (IL-6 and TNF-α) and myalgic encephalomyelitis due to mitochondrial dysfunction could contribute to the post-COVID-19 hyperventilation syndrome (figure 2) [74].

Nicholas Hart (London, UK) opened his presentation on prolonged mechanical ventilation (PMV) in COVID-19 patients by pointing out the heterogeneity of PMV definitions across the scientific literature, which urgently requires a standardisation [75]. The effects of evolving standard-of-care, vaccination and virus biology greatly reflected on critical care occupancy and the need for PMV. Indeed, data from the Guy's and St Thomas' NHS Hospital (London, UK) showed that the survival of critical COVID-19 patients progressively increased (from 70% of wave one (April 2020) to 87% of wave four (April 2022)). Nevertheless, during waves three and four, the proportion of patients requiring ECMO doubled, mainly due to the more frequent admission of unvaccinated pregnant women. The recovery process should be focused on "reverse the reversible", treating each sequela due to SARS-CoV-2 infection that could be addressed.

Tracy Vannorsdall (Baltimore, MD, USA) presented a topic called "Managing anxiety, depression and cognitive impairment to promote recovery". Higher rates of depressive symptoms were noticed after the start of the pandemic and they were more common in those with lower income, less savings and more stressors [76]. Interestingly, the rate of objective cognitive dysfunction was much lower than subjective

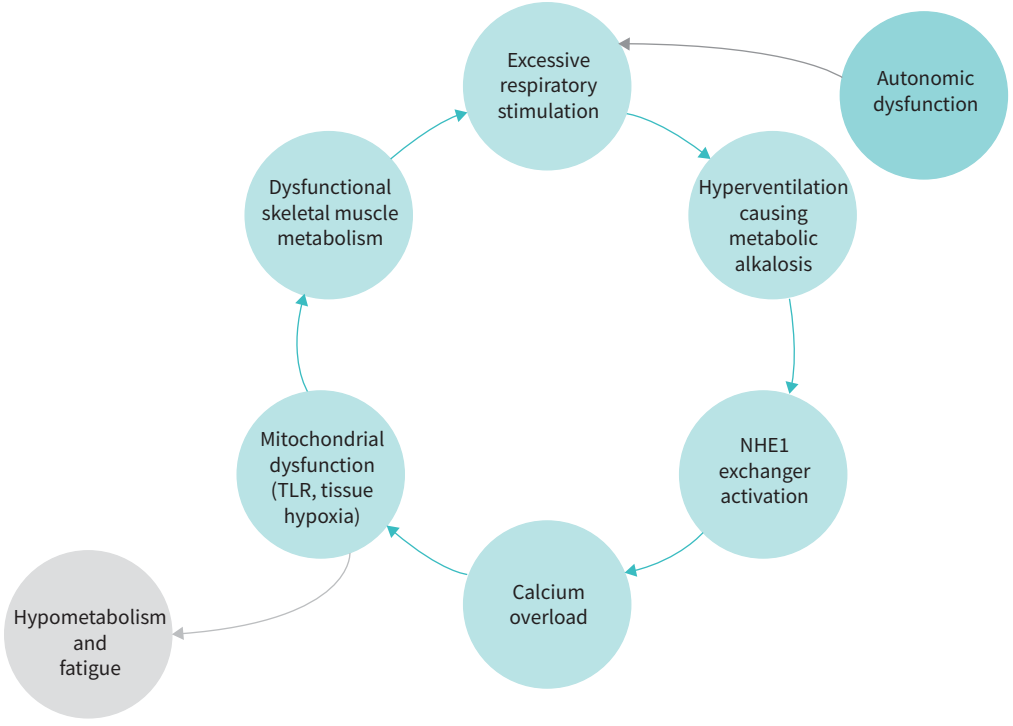

FIGURE 2 Proposed hyperventilation syndrome and post-acute COVID-19 dyspnoea vicious cycle. NHE1: sodium-hydrogen antiporter 1; TLR: Toll-like receptors.

complaints. Thus, clinicians should also target other factors such as anxiety, depression or fatigue in order to improve objective and subjective functioning. Data from a long COVID clinic showed that 4 months after leaving ICU, patients had significant levels of psychiatric stress and their cognitive scores decreased [77].

Mara Paneroni (Brescia, Italy) talked about rehabilitation modalities to address physical morbidity and support recovery. Multinational task force recommends early, bedside rehabilitation for patients affected by severe COVID-19 [78]. A global protocolised weaning strategy, started early in the ICU and followed by intensive rehabilitation in a specialised centre, accelerated the physical recovery and psychological status in ICU survivors from COVID-19 ARDS [79].

Take-home messages

- Long-term impairment is common in post-acute COVID-19 patients.
- Discrepancies between COVID-19 lung parenchymal damage and dyspnoea severity can be explained by myalgic encephalomyelitis and hyperventilation syndrome.
- The progressive improvement of the standard of care and the evolving virus biology resulted in a reduction of patients requiring intensive treatment and prolonged mechanical ventilation.
- Psychiatric and cognitive disorders became more frequent during the SARS-CoV-2 pandemic.
- Early physical rehabilitation is crucial for the optimal recovery of COVID-19 patients.

Treatment of acute respiratory failure in COPD patients

Marieke Duiverman (Groningen, the Netherlands) presented NIV as the first-line intervention to relieve work of breathing in patients with COPD presenting with acute hypercapnic respiratory failure. NIV clinical practice varies widely across hospitals [80]. Evidence-based use improves exacerbation outcomes, including mortality, endotracheal intubation, hospitalisation duration, gas exchange and complications [81, 82], whereas delayed NIV implementation increases mortality [83]. The Non-invasive Ventilation Outcomes (NIVO) score serves as an outcome-prediction tool for in-hospital mortality [84, 85]. NIV settings [86] and patient comfort [87] should be optimised to prevent patient–ventilator asynchrony and intolerance. Home NIV should be considered as an earlier intervention for persistent hypercapnia [88, 89].

Paolo Navalesi (Padua, Italy) presented the role of HFNC in facilitating CO_2 wash-out [90], relieving work of breathing through PEEP [91] and delivering humidified, warm air [92, 93]. Although better tolerated than NIV [94], HFNC is not an alternative [95–97] but an ancillary treatment during NIV breaks or withdrawal [98]. Regarding compensated hypercapnic respiratory failure, HFNC shows superiority over conventional oxygen therapy in improving hypercapnia [99] and need for NIV [100]. Post-extubation HFNC is recommended, but NIV remains pivotal for high-risk patients [97, 101].

Christian Karagiannidis (Cologne, Germany) illustrated the decreasing number of patients with COPD under invasive mechanical ventilation (IMV) during the COVID-19 pandemic. IMV poses higher risk of mortality, endotracheal intubation, complications and longer hospitalisation duration than NIV [102, 103]. $ECCO_2R$ may prevent or shorten duration of IMV by alleviating acidosis and respiratory rate [104, 105] and may improve right ventricle function by reducing pulmonary artery pressure [106]. However, application of $ECCO_2R$ raises technical issues related to recirculation rate [107] and bleeding/thromboembolic complications that limit its current use and therefore should only be used in clinical trials [105, 108].

Rebecca D'Cruz (London, UK) reflected on COPD exacerbations' detrimental impact on long-term outcomes, with higher mortality in patients requiring mechanical ventilation [109–111]. Interestingly, eosinophilic exacerbations show more favourable outcomes, including need for NIV and mortality [112]. R. D'Cruz highlighted the lung function decline and potential progression to respiratory failure associated with exacerbations [113, 114]. Extrapulmonary sequelae and comorbidities warrant a holistic approach [115–123].

Take-home messages

- NIV remains the first-line intervention for acute hypercapnic respiratory failure in patients with exacerbated COPD. The NIVO score is a validated outcome-prediction tool.
- HFNC facilitates NIV breaks or withdrawal, showing superiority over conventional oxygen therapy.
- $ECCO_2R$ alleviates acidosis and respiratory rate, but further clinical trials on its safety and effectiveness are needed.
- Extrapulmonary sequelae warrant a holistic approach to COPD exacerbations.

Innovations in non-invasive respiratory support

Nicole Sheers (Heidelberg, Australia) opened the session by presenting a randomised controlled trial that examined the feasibility of setting up NIV at home in patients with motor neuron disease. The patients were randomised to the NIV home model (single-day NIV initiation at home with remote usage monitoring, and weekly telephone follow-up) or a usual care control (single-day in-hospital NIV initiation with in-laboratory polysomnography follow-up). No significant between-group difference was observed in symptoms, quality of life, care burden or adherence.

Ana Díez Izquierdo (Barcelona, Spain) shared data from a retrospective review of 10 children with chronic lung diseases or neurological conditions necessitating home HFNC therapy. The review was conducted over 12 months with the aim of assessing the long-term benefits and safety of HFNC use. During follow-up, it was identified that home HFNC in children resulted in early discharge (40%) and reduction in hospital readmission (30%). This was attributed to the ability to treat exacerbations of disease at home. No adverse events were observed.

Chiara Torregiani (Trieste, Italy) presented a study investigating the utility of forced oscillatory technique as a potential marker of lung compliance in patients with COVID-19. The study enrolled 32 patients with moderate to severe COVID-19 ARDS who underwent NIV and alternated to HFNC. The study identified that forced oscillatory technique measurements can be used to identify abnormal respiratory reactance and could be used to assess patients. Currently, forced oscillatory technique is mainly applied in neonatology to expand the pathophysiological understanding of ARDS and in pre-clinical studies.

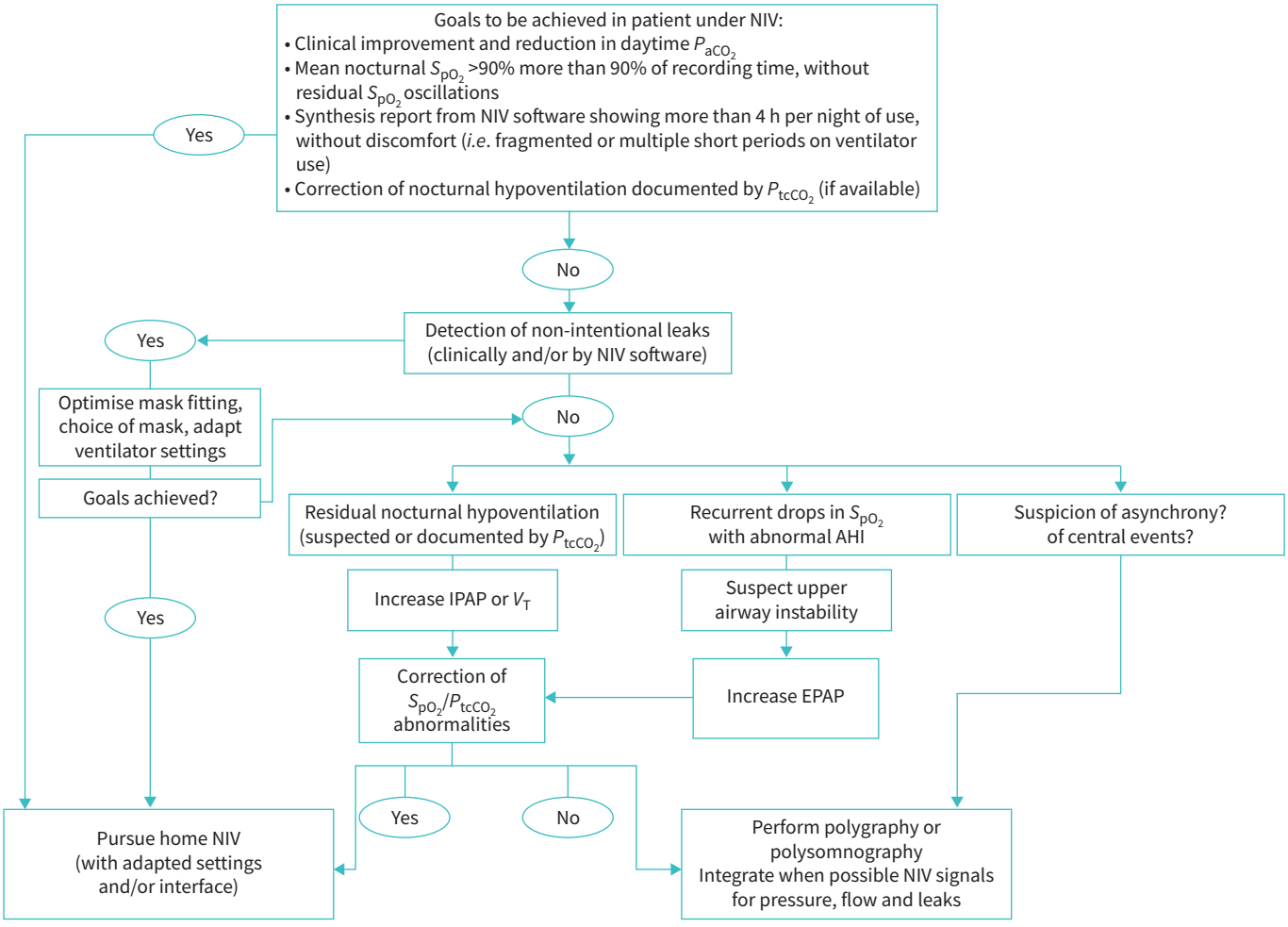

FIGURE 3 Goals to be achieved in a patient under home NIV. NIV: non-invasive ventilation; S_{pO_2}: oxygen saturation measured by pulse oximetry; P_{tcCO_2}: transcutaneous carbon dioxide tension; AHI: apnoea–hypopnoea index; IPAP: inspiratory positive airway pressure; V_T: tidal volume; EPAP: expiratory positive airway pressure. Reproduced and modified from [131] with permission.

David Berlowitz (Heidelberg, Australia) concluded the session with an explanation of an artificial intelligence model which could be used to detect patient–ventilator asynchrony during NIV. The models, which used Multidimensional Matrix Profiles, were able to filter and de-noise polysomnography data to identify asynchronies. Their proposed model had 0.80 sensitivity and specificity for identifying patient–ventilator asynchrony.

Take-home message

- Recent research has identified methods to increase the ease of use and optimisation of NIV in both the home and the hospital.

State-of-the-art in home mechanical ventilation

Barbara Garabelli (Milan, Italy) focused her presentation on alternative treatments of NIV support for chronic respiratory failure in neuromuscular diseases. Long-term mechanical ventilation improves survival and increases or maintains health-related quality of life (HRQoL) [124, 125]; however, dependency of the ventilator can affect quality of life especially in patients having continuously a mask on their face. Other types of NIV support can reduce side-effects related to prolonged ventilation such as mouthpiece ventilation or intermittent abdominal pressure ventilation. Mouthpiece ventilation with a volume mode is the preferable choice because it allows air-stacking and there is no leak compensation during patient disconnection [126, 127]. The settings usually suggested are no PEEP or back-up respiratory rate, a low trigger and a tidal volume according to the respiratory abilities and needs of the patient (500–1500 mL). Regarding intermittent abdominal pressure ventilation [128, 129], there is a lack of expert consensus guidelines on its indication, titration, management, and follow-up.

Jean-Paul Janssens (Geneva, Switzerland) highlighted the different structural options for home NIV follow-up that depends on the local healthcare structures, legislations and geographical considerations. Home NIV follow-up should also be tailored for specific groups of patients or situations requiring multidisciplinary assessment. There are numerous tools for home NIV monitoring (*e.g.* symptom scores, arterial blood gases, nocturnal pulse oximetry) and side-effects of NIV should be systematically assessed using a checklist. A recent study explored different strategies for home NIV monitoring, attempting to efficiently identify patients who were inappropriately ventilated, using ventilator software integrated with overnight capnography [130]. Several goals should be achieved in patients under NIV (figure 3) [131, 132] due to its impact on HRQoL and survival in certain groups of patients [133–135]. Different studies have shown the feasibility, safety and cost-effectiveness of initiating NIV at home [136, 137] with a specialised team of nurses, the use of capnography and telemonitoring.

Take-home messages

- NIV supports such as mouthpiece ventilation or intermittent abdominal pressure ventilation can reduce side-effects related to prolonged ventilation.
- The impact of NIV support on HRQoL should be tested in clinical trials, especially for intermittent abdominal pressure ventilation.
- Logistics for home NIV follow-up are country and healthcare system dependent. The implementation of NIV at home seems feasible and safe.
- Monitoring of home NIV is mandatory to ensure efficacy and comfort, guided by several goals to be achieved in patients under NIV.

Provenance: Commissioned article, peer reviewed.

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