Chapter 4

ACUTE RESPIRATORY FAILURE

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Acute Respiratory Failure (ARF) is a critical medical condition characterized by abnormal pulmonary mechanics, impaired gas exchange, or disturbances in pulmonary circulation. In this condition, the concentration of oxygen in the blood can be insufficient for the body›s metabolic demands, caused by various diseases. Lack of adequate treatment can lead to irreversible consequences and fatal complications, requiring immediate medical intervention and highlighting its high clinical relevance (Yang; Esper, 2024).

ARF is among the most common causes of critical illness, with a hospital mortality rate of approximately 30% (Yang; Esper, 2024). In the United States, more than one million patients admitted annually to intensive care units (ICUs) require mechanical ventilation for acute respiratory failure. Advances in intensive care have reduced mortality rates, resulting in an increasing number of survivors. However, 65% of these survivors experience significant functional disability, negatively affecting quality of life and potentially persisting for years after hospitalization for ARF. Despite evidence that functional disability is a common problem for ARF survivors, early identification and management are still poorly studied and understood. Identifying the various subtypes of ARF patients early in the ICU stay can help personalize interventions and strategically plan the prognosis to improve quality of life after hospitalization (Potter *et al.*, 2023).

ARF is one of the conditions with the highest incidence in ICUs, representing 56% to 69% of admissions, in addition to having a high financial cost for the healthcare system (Yang; Esper, 2024). The main causes of death in patients with ARF are linked to sepsis, pulmonary, and neurological dysfunction, demonstrating that therapies focused on reducing sepsis complications increase the survival of these patients (Ketcham et al., 2020). Rapid diagnosis is essential, given the impact of functional disability and high mortality in emergencies (Potter *et al.*, 2023). However, early identification is challenging due to the rapid progression of the condition, the wide variety of causes, clinical presentation, and patient heterogeneity (Yang; Esper, 2024).

Strategies for managing ARF consist of nonspecific supportive measures and individualized treatment approaches. The use of latent class analysis to identify patterns of functional impairment and mobility allows for a more personalized and effective approach. Additionally, interventions to improve physical function post-ICU have been explored, although they need more evidence-based investigations. Recent studies highlight strategies such as the adoption of lung-protective ventilation with reduced tidal volumes to minimize ventilator-induced lung injuries. Early mobilization of ICU patients, including physical and occupational therapy, has shown benefits in reducing muscle weakness and improving physical function post-ICU (Ketcham *et al.*, 2020).

Another important trend is the use of biomarkers for the identification and monitoring of conditions associated with ARF, such as inflammatory cytokines and lung injury markers. These biomarkers can aid in early diagnosis, prognosis, and the development of targeted therapies. Additional supportive therapies, such as high-flow oxygen therapy, positional therapy, and pulmonary rehabilitation, are being integrated into ARF management to optimize patient recovery (Yang; Esper, 2024).

The use of adjunct therapies, such as prone positioning in patients with Acute Respiratory Distress Syndrome (ARDS), aggressive management of sepsis associated with ARF, and promotion of early mobilization in patients on mechanical ventilation, aims to reduce complications and improve rehabilitation. The multidisciplinary and individualized approach to ARF patients, including specialized intensive care teams, is crucial for improving clinical outcomes (Ketcham *et al.*, 2020).

EPIDEMIOLOGY

According to recent data, the incidence of Acute Respiratory Distress Syndrome (ARDS) varies significantly across different regions of the world. In 2014, the incidence in Brazil was 10.1 per 100,000 inhabitants per year, while in the United States, it was 82 per 100,000 inhabitants per year in 2005. Respiratory failure is one of the leading causes of mortality in ICUs worldwide. In Scandinavia, the mortality rate for ARDS is 41%, and for acute lung injury (ALI) it is 42.2%. In the United States, the mortality rate varied from 5.01 per 100,000 people in 1999 to 2.82 per 100,000 inhabitants in 2013 (Ernest, 2020; Hendrickson, Peltan, and Brown, 2021).

In recent years, there have been changes in the incidence and mortality of respiratory failure, attributed to advances in diagnostic methods, an increase in patients with chronic comorbidities, a decrease in individuals over 70 years old, and the admission of patients with greater severity. There was a 197% increase in incidence, from 429 to 1,275 cases per 100,000 adults per year, and a 57% decrease in mortality, from 28% to 12%. This indicates that mortality has improved despite the increased severity and incidence of the disease, possibly due to improvements in intensive care (Kempker *et al.*, 2020).

In certain studies, during the analysis period, hospital mortality decreased from 34% to 23%. This variation is attributed to changes in patient characteristics over the study period. A decrease in the proportion of patients aged 70 years or older, an increase in the proportion of patients with chronic comorbidities, an increase in the proportion of patients at higher risk of disease severity, and an increase in the proportion discharged to intermediate care units were observed, along with a reduction in hospital length of stay (Kempker *et al.*, 2020).

The risk factors for respiratory failure interact in a complex manner. Chronic alcohol use causes pulmonary immunodepression, epithelial dysfunction, and an inability to contain reactive oxygen species, resulting in high permeability pulmonary edema and hyaline membrane formation. Smoking, on the other hand, increases the expression of the inflammatory cascade, leading to ARDS conditions. Advanced age is related to an increased incidence, however, it has not been found to be associated with increased mortality. Diabetes is associated with a lower incidence of the disease, possibly contributing to the attenuation of the systemic inflammatory response (Hendrickson, Peltan, and Brown, 2021).

DIAGNOSIS

Acute Respiratory Failure (ARF) can be caused by various primary conditions such as bacterial pneumonia, viral infections, drug-induced lung injury, and acute exacerbation of interstitial lung disease. Early diagnosis and immediate intervention are crucial for saving lives (Anan *et al.*, 2022). The management of ARF consists of a cyclical process involving

three stages: verification, treatment, and maintenance. In the verification stage, the level of consciousness, respiratory rate, pulse oximetry, blood gas analysis, and underlying cause are assessed (See, 2022).

Acute hypoxemic respiratory failure is characterized by a sudden decrease in the partial pressure of arterial oxygen (PaO_2) to <60 mmHg, corresponding to an arterial oxygen saturation <90% and reflecting SpO_2 <90%. Additionally, it may be accompanied by an elevation in $PaCO_2$ to >45 mmHg and a decrease in blood pH to <7.35 (i.e., acidemia), leading to acute hypercapnic respiratory failure. This state is potentially fatal, as the concentration of oxygen in the blood may be insufficient for organ demands, resulting in tissue hypoxia (See, 2022).

Initially, ARF can be identified by a decreased level of consciousness or abnormal respiratory rate, caused by either hypoxemia or hypercapnia. Pulse oximetry, a non-invasive method, is used to confirm hypoxemia by detecting pulsatile flow and calculating the ratio of oxygenated to deoxygenated hemoglobin. Arterial blood gas analysis is used to evaluate hypercapnia by checking the acid-base balance. The severity of ARF can be estimated by the ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (See, 2022).

In critically ill patients with ARF, lung ultrasound is a useful tool for rapid diagnosis and therapeutic management. It diagnoses conditions such as pneumothorax, acute respiratory distress syndrome (ARDS), cardiogenic pulmonary edema, pneumonia, and acute pulmonary embolism by evaluating the four intercostal spaces in each hemithorax, looking for the pleural line, A-lines, B-lines, alveolar consolidation, and pleural effusion (Islam *et al.*, 2020).

Cellular analysis through bronchoalveolar lavage (BAL) can be a useful diagnostic method, especially for uncommon causes of ARF, such as pneumocystis pneumonia and invasive pulmonary aspergillosis. BAL is safe even in patients with severe ARF, including those on mechanical ventilation, with a low risk of death, severe cardiovascular complications, and bleeding. However, the patient›s preexisting comorbidities, especially cardiovascular ones, should be considered as they can cause hemodynamic instability during the procedure (Anan *et al.*, 2022).

Lung biopsy can be useful in diagnosing ARF and ARDS, although its feasibility and safety still need to be better established. Recent studies indicate that lung biopsy for ARDS or ARF is safe, with fewer than 5% of severe complications such as bleeding, infections, and persistent air leaks, and no related deaths reported (Sugimoto *et al.*, 2023).

The biomarker MV-miR-223 emerges as a new option for evaluating the prognosis in patients with ARDS. These microRNAs regulate the hematopoiesis of myeloid lineage cells and granulocytic degranulation and are strong markers of inflammatory response in acute lung injury. The ALTA study concluded that elevated levels of MV-miR-223 are associated with severe lung injury and worse prognosis. However, limitations such as differences between control and ARDS plasma samples and the small sample size make the study less conclusive (Almuntashiri *et al.*, 2022).

TREATMENT

Given the prevalence of hypoxemic acute respiratory failure (ARF), which accounts for a high number of intensive care unit (ICU) admissions, effective management is essential to improve patient survival (Grieco *et al.*, 2021). Intubation and the use of non-invasive mechanical ventilation are evident in two-thirds of these cases, with a mortality rate exceeding 50%, emphasizing the importance of oxygenation therapies that aim to avoid intubation (Coudroy *et al.*, 2019). The use of non-invasive oxygenation, such as high-flow nasal oxygen (HFNO), non-invasive ventilation (NIV) with a helmet or facial mask, and continuous positive airway pressure (CPAP), are frequently employed in these patients. These methods have shown benefits compared to standard oxygen therapy, avoiding endotracheal intubation in patients with mild hypoxemia (Grieco *et al.*, 2021).

Non-invasive ventilation can be performed using bilevel positive airway pressure (BPAP) or continuous positive airway pressure (CPAP). It can be offered through different interfaces, such as facial masks and helmets, depending on the patient, the objective, and comorbidities. Below are the main benefits of these modalities:

High-Flow Nasal Cannula (HFNC)

- Settings: FiO_2 0.21 – 1; airflow 40-60 lpm; temperature 31-37ºC.
- Benefits: Matches inspiratory flow; delivers total FiO_2; provides conditioned gas; improves comfort; provides positive pressure up to 4 cmH_2O; washes out dead space in the nasopharynx and reduces inspiratory effort.
- Obstacle: Limited amount of PEEP provided.

Facial Mask:

- Settings: PSV requires a ventilator; FiO_2 0.12 – 1; PEEP 5-8 cmH_2O; PS 7-10 cmH_2O; CPAP, continuous flow >30 l/min.
- Benefits: Provides defined FiO_2; conditioned gas; PEEP allows alveolar recruitment; PS unloads inspiratory muscles; tidal volume monitoring.
- Obstacles: Skin ulcers; air leakage; difficulty with high PEEP; low tolerance; increased transpulmonary pressure and tidal volume.

Helmet:

- Settings: PSV requires a ventilator; FiO_2 0.21 – 1; PEEP 10-12 cmH_2O; PS 10-12 cmH_2O; no need for humidification; rapid pressurization with CPAP; continuous flow >60 l/min.
- Benefits: Provides defined FiO_2; alveolar recruitment with high PEEP; good tolerance; PS reduces inspiratory effort; asynchronous PS can prevent increased transpulmonary pressure.

- Obstacles: Inability to measure tidal volume; upper limb edema with potential venous thrombosis.

Benefits of NIV:

BPAP is widely used in patients with acute hypercapnic respiratory failure, such as those with exacerbation of chronic obstructive pulmonary disease (COPD) or disorders that evolve with acute hypoventilation. Patients with acute hypoxemic non-hypercapnic respiratory failure, such as those with asthma, acute respiratory distress syndrome (ARDS), and pneumonia, also benefit from BPAP. On the other hand, CPAP is primarily designated for patients with acute cardiogenic pulmonary edema (Hyzy; McSparron, 2020).

The use of non-invasive therapies allows patients to benefit from spontaneous breathing, preserving physiology and reducing complications related to invasive mechanical ventilation, such as diaphragmatic atrophy. However, spontaneous breathing can cause damage due to unregulated respiratory effort and lung mechanics, resulting in patient self-inflicted lung injury (P-SILI). Thus, patients with greater severity and a tendency to fail NIV may be less benefited by its use (Grieco *et al.*, 2021).

High-Flow Nasal Oxygen Therapy (HFNO):

High-flow nasal oxygen therapy (HFNO) has gained prominence due to its clinical efficacy, providing a high flow mixture of humidified and heated air. HFNO can increase airway pressure proportionally to the end-expiratory volume, leading to efficient alveolar recruitment and reducing inspiratory effort and respiratory rate. Compared to conventional devices, HFNO allows for a higher inspiratory flow, eliminating anatomical dead space and improving functional residual capacity (Vega & Pisani, 2021; Ricard *et al.*, 2020).

Rigorous monitoring is essential to avoid delays in endotracheal intubation when there are signs of clinical deterioration, such as muscle fatigue, need for vasoactive drugs, cardiac dysfunction, and organ failure (Ricard et al., 2020). Parameters such as oxygenation through pulse oximetry, arterial blood gas analysis, ROX index, HCOR scale, expired tidal volume, and inspiratory effort are used for monitoring (Grieco *et al.*, 2021).

Indicators of Failure in NIV and HFNO:

- SpO_2/FiO_2: Risk of failure when <120 or worsening trend.
- PaO_2/FiO_2: Risk of failure when <150-200 mmHg or worsening trend.
- Respiratory Rate: Risk of failure when >25-30 or not decreasing with support.
- Expired Tidal Volume: Risk of failure when >9-9.5 ml/kg of predicted body weight.
- Transpulmonary Pressure: Risk of failure when >15 cmH_2O or reduction of <10 cmH_2O during NIV.

- ROX Index: Risk of failure when <2.85 at 2 hours, <3.47 at 6 hours, or <3.85 at 12 hours of HFNO initiation.
- HCOR Scale: Risk of failure when >5 one hour after NIV initiation.

An innovative pillar in the treatment of ARF is the study of microbiomes, suggesting that respiratory microbiota patterns are predictive of increased mortality among critically ill patients. Oropharyngeal swab and endotracheal aspirate samples were analyzed with 16s ribosomal RNA gene sequencing, along with inflammatory biomarkers such as receptor for advanced glycation end products and interleukin-10. Future therapies may be guided by patterns of dysbiosis or direct manipulation of the host microbiome (Ali & Sweeney, 2020).

High-Flow Nasal Cannula (HFNC)

HFNC is indicated for acute hypoxemic respiratory failure as an alternative to NIV, during NIV intervals, in postoperative patients at risk of pulmonary complications, and in cases of extubation failure. HFNC has shown similar efficacy to NIV in terms of intubation rate, mortality, and treatment failure, along with better patient tolerance, which reduces the rate of therapeutic failure (Oczkowski et al., 2022; Xu et al., 2023).

Invasive Mechanical Ventilation (IMV)

IMV, in turn, is indicated in cases of severe hypoxemic or hypercapnic respiratory failure that do not respond to NIV. Evidence-based practice (EBP) associated with IMV is linked to lower mortality rates. Interventions such as daily sedation interruptions, mobility exercises, and spontaneous breathing trials help reduce the duration of IMV and improve clinical outcomes (Ervin *et al.*, 2020).

Indications:

- Acute hypercapnic respiratory failure (exacerbation of COPD)
- Acute respiratory failure due to cardiogenic pulmonary edema
- Acute hypoxemic non-hypercapnic respiratory failure
- Asthma exacerbation, among others.

Contraindications:

- Need for emergency intubation
- Acute non-respiratory organ failure with life-threatening risk
- Facial abnormalities
- Significant airway obstruction
- Inability to protect the airways
- Prolonged duration of ventilatory support (Hyzy; McSparron, 2022).

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