Epidemiology of Acute Respiratory Failure and Mechanical Ventilation

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Introduction

Acute respiratory failure, and the need for mechanical ventilation, remains one of the most common reasons for admission to the intensive care unit (ICU). The burden of acute respiratory failure is high in terms of mortality and morbidity as well as the cost of its principal treatment, mechanical ventilation. Very few epidemiologic studies have evaluated the prevalence and outcome of acute respiratory failure and mechanical ventilation in general. Most of the published literature has focused on specific forms of acute respiratory failure, particularly acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). In this chapter, we provide a brief review of the pathophysiology of acute respiratory failure, its definition and classification, and then present the incidence and outcomes of specific forms of acute respiratory failure from epidemiologic studies.

Definition and Classification

Normal respiration requires the integrated function of several components of the respiratory system (Fig. 1). Dysfunction of any component results in the impairment of normal gas exchange and may lead to acute respiratory failure and the need for mechanical ventilation. According to the underlying pathophysiologic mechanism, acute respiratory failure is usually divided into four patterns: Types I–IV (Table 1). Type I and type II respiratory failure are also referred to as hypoxemic and hyper-

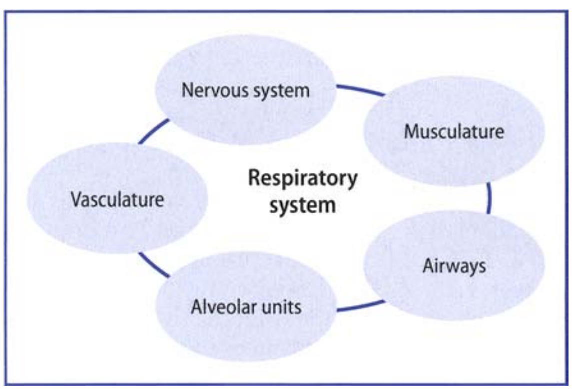

Fig. 1. Vital components of the respiratory system

Table 1. Pathophysiological classification of acute respiratory failure with corresponding clinical syndromes.

	Type I	Type II	Type III	Type IV
Mechanism	V/Q mismatch Shunt (Qs/Qt)	Alveolar hypoventilation	Atelectasis Shunt (Qs/Qt)	Hypoperfusion Metabolic acidosis
Anatomic components	Alveolar unit failure Pulmonary vascular failure	CNS dysfunction Neuromuscular failure Airway dysfunction	Regional alveolar unit collapse	All tissues Respiratory muscles
Clinical syndromes	Pulmonary edema ALI, CPE Pneumonia Trauma ILD*	Coma NMD* COPD*,** Asthma	Perioperative	Shock

* may occur as acute exacerbations – acute on chronic respiratory failure;

** type I and type II respiratory failure frequently co-exist; ILD: interstitial lung disease; NMD: neuromuscular disorder; COPD: chronic obstructive pulmonary disease; ALI: acute lung injury; CPE: cardiogenic pulmonary edema; CNS: central nervous system

capnic respiratory failure, based on a predominant gas exchange abnormality. In many disease states however, more than one pathophysiologic mechanism is operational and clinical criteria that incorporate setting, acuity, and severity are used more often (Table 1). Acute episodes (exacerbations) of respiratory failure in patients with chronic compensated respiratory insufficiency are usually referred to as 'acute on chronic' respiratory failure.

A consensus definition of acute respiratory failure is not available and most studies have used the combination of mechanical ventilation (of variable duration) with or without evidence of severe hypoxemia on arterial blood gas analysis. While some studies utilized a more strict definition than others, the essential component in all has been the need for mechanical ventilation. The indications for mechanical ventilation, however, are mostly based on clinical observations (increased respiratory rate, use of accessory muscles, paradoxical chest wall movements, changes in mental state), none of which has sufficient accuracy or precision. Therefore, the epidemiology of acute respiratory failure has so far been restricted to 'treated' acute respiratory failure, possibly explaining the wide variations in the reported incidence and outcomes of acute respiratory failure and associated clinical syndromes. Since the availability of intensive care and mechanical ventilation vary greatly in different parts of the world, the burden of acute respiratory failure may be severely underestimated depending on the access to ICU services.

Incidence and Outcome of Acute Respiratory Failure

The incidence of acute respiratory failure varies according to the definition used and the population studied (Table 2). Two European studies, one conducted in Germany [1] and the other in Sweden, Denmark, and Iceland [2], estimated very similar incidences, 88.6 and 77.6 cases per 100,000 person-years. Both studies used an identical definition (intubation and mechanical ventilation for > 24 h regardless of arterial blood gas findings) and employed a multicenter approach with large patient cohorts over a short period (8 weeks). On the other hand, Behrendt reported a much higher

Table 2. Comparison of selected epidemiological studies of acute respiratory failure

Study	Design	Definition of ARF	Age of population	Setting, duration and year of study	Incidence	Mortality %
Esteban [4]	Prospective observational	Need of mechanical ventilation > 12 hours	Adult	361 International ICUs, 1 month, 1998	33 % of ICU admissions	30.7 %
Vincent [7]	Prospective observational	PaO_2 /FiO_2 ratio < 200 and the need of mechanical respiratory support	> 12 years	40 International ICUs, 1 month, 1995	56 % of ICU admissions	31 %
Luhr [2]	Prospective observational	Intubation and mechanical ventilation ≥ 4 hours regardless of FiO_2	> 15 years	Sweden, Denmark Iceland & Norway, 8 weeks, 1997	77.6 per 100,000 person-years	41 %
Vasilyev [38]	Prospective observational	Mechanical ventilation > 24 hours and FiO_2 > 0.5 for at least 24 hours.	All ages	Multicenter, 2 months 1991–1992	Not studied	44.4 %
Lewandowski [1]	Prospective Observational	Intubation and mechanical ventilation ≥ 24 hours regardless of FiO_2	> 14 years	Berlin (Germany), 8 weeks, 1991	88.6 per 100,000 person-years	42.7 %
Behrendt [3]	Retrospective	ICD-9-CM for respiratory failure and mechanical ventilation	> 5 years	United States, 1 year 1994	137.1 per 100,000 person-years	35.9 %

incidence of acute respiratory failure in the USA, 137.1 per 100,000 patient-years. This incidence was estimated based on the ICD-9-CM disease codes for diagnoses and treatment in patients > 5 yrs old observed over a 1-year period [3]. The significant variation between the US and European incidences may in part be explained by the differences in study design (Table 2) and in part by inconsistent indications and access to mechanical ventilation in different countries.

Acute respiratory failure is often accompanied or followed by a failure of other vital organs, and death most often occurs because of multiorgan failure (MOF) and the withdrawal of mechanical ventilation when the chances for a meaningful recovery of the patient's quality of life are deemed to be exceedingly low. Imprecision of clinical prognostic criteria, variations in available resources, and patient and provider preferences limit the interpretation of mortality data from different epidemiologic studies.

Reported mortality rates for acute respiratory failure from the 1990s are remarkably similar, approximately 40 % in spite of differences in study designs and the definitions applied (Table 2). Lewandowski and coworkers [1] studied 476 patients from 72 ICUs in Berlin, Germany and reported mortality rates of 36–58 % depending on the lung injury score (LIS). In a large prospective study from Scandinavia, Luhr and coworkers reported an all-cause 90-day mortality of 41 % [2]. In a large, prospective international cohort involving 361 ICUs, Esteban and coworkers reported an ICU mortality of 30.7 %. Mortality increased significantly in patients with sepsis, shock, ARDS, or liver failure [4]. Vincent and coworkers used sequential organ failure assessment (SOFA) score criteria and the need for mechanical ventilation to define acute respiratory failure and estimated an overall ICU mortality of 31 %. The mortality was much lower (7 %) when the lung was the only organ involved [5]. Recently, Flaatten and coworkers reported the mortality from acute respiratory failure at different time points after disease onset. Mortality was again the lowest in single organ acute respiratory failure and rose with each additional organ failure. Higher mortality rates were found 90 days after the onset compared to at ICU or hospital discharge [6]. MOF following an ICU admission, presence of circulatory shock on ICU admission, older age, and pre-existing comorbidities (cirrhosis, malignancy and chronic renal failure) were independent risk factors for the mortality rate reported in several studies [4, 7–9].

Epidemiology of Specific Clinical Syndromes

Acute Lung Injury (ALI)

ALI and its more severe form, ARDS, are clinical syndromes defined as an acute onset of hypoxemic respiratory failure with diffuse pulmonary infiltrates in the absence of left atrial hypertension as the principal cause of acute pulmonary edema. ALI is a major cause of acute respiratory failure in the ICU and is associated with high morbidity and mortality. Since it was first described by Ashbaugh and colleagues [10] and than redefined in 1994 [11], there have been significant advances in the understanding of etiology, pathophysiology, and the epidemiology of ALI. Clinical risk factors for ALI are usually divided into direct (pulmonary) and indirect (extrapulmonary). Pneumonia, aspiration, lung contusion; and inhalation injury are the principal pulmonary risk factors, while sepsis, shock, trauma, pancreatitis, and multiple transfusions represent the most important extrapulmonary risk factors. In recent years, transfusion-related ALI (TRALI) and novel viral pathogens (severe acute respiratory syndrome [SARS]) have emerged as important risk factors for ALI.

The reported incidence of ALI has varied significantly. The 1972 report of the National Heart and Lung Institute Task Force on Respiratory Diseases, estimated 150,000 cases of ARDS per year yielding the annual incidence of 75 per 100,000 person-years. Subsequent studies reported an incidence of ALI ranging from 16 to 34 cases per 100,000 person-years in European countries [2, 12] and Australia [13], and a much higher incidences of ALI in the USA, 78 per 100,000 persons-years (190,600 cases per year) [13–15]. While a significant minority of patients with ALI is treated with non-invasive ventilation (NIV), the majority of studies included only patients treated with invasive ventilation. A recently completed, retrospective, community cohort study in Olmsted County, Minnesota included patients treated with NIV and found an even higher incidence of ALI, 156 per 100,000 person-years (personal communication, Rodrigo Cartin-Ceba).

Mortality from ALI varies greatly depending upon the age of the patient, underlying chronic illnesses, ALI risk factors, and non-pulmonary organ dysfunctions [15]. Two decades ago, the mortality rate from ALI ranged from 50–70 % [4, 8, 16, 17], but has since declined and more recently has been estimated to be about 30–50 % [2, 13, 15, 23]. Advances in general supportive care [9] and the use of new mechanical ventilation strategies [16] may account for most of the change.

Both the incidence of and mortality from ALI increase exponentially with age [1–3, 15, 18]. MOF [7, 19, 20], liver failure, severe sepsis [8, 9, 15, 17], aspiration [15], presence of infection and neurological failure on ICU admission [7], and preexisting cirrhosis [2, 8, 17, 21], bone marrow transplantation, human immunodeficiency virus (HIV) [17], hematologic [7, 22] or active malignancy [17, 22], and Charlson comorbidity score [23] have been associated with a higher mortality. Persistent severe hypoxemia and cardiovascular failure also predict poor outcomes [21, 23].

Non-survivors of ALI die predominantly of MOF. A landmark study published in 1985 reported that only 16 % of deaths were caused by respiratory failure [24]. Similar results (16 % and 9 %) were reported by two studies conducted in recent years [13, 25]. MOF, septic shock, and underlying comorbidities are the most common causes of death in patients with ALI.

Survivors of ALI often have a prolonged recovery and significant short and long-term disability. While lung function usually returns to normal within several months [9], neuromuscular and neurocognitive sequelae may persist much longer [26, 27]. The most important predictors of prolonged disability are the use of systemic steroids during the ICU stay, presence of a complicating illness acquired during the ICU stay, and the rate of resolution of ALI and MOF [27]. Neuropsychological sequelae are also common and about 27 % of long-term survivors develop post-traumatic stress disorder [28]. With a decline in mortality from ALI, more survivors are at risk of prolonged morbidity ('chronic critical illness') contributing to substantial increases in the utilization of health care resources.

Cardiogenic Pulmonary Edema

Cardiogenic pulmonary edema is a common cause of acute respiratory failure. In about 10 % of the mechanically ventilated patients in an international cohort study, cardiogenic pulmonary edema was the principal reason for instituting mechanical ventilation [4]. Other epidemiologic studies reported similar rates of cardiogenic pulmonary edema [2, 29] with mortality ranging from 28–48 % [1, 4]. In the past two decades, NIV, both continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) ventilation, have received a great deal of interest in the management of patients presenting with acute cardiogenic pulmonary edema. Randomized trials comparing either CPAP or BiPAP with standard medical therapy, found similar improvements in arterial blood gases and breathing rates, reduced need for intubation, and improved outcome [30].

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

According to the World Health Organization, chronic obstructive pulmonary disease (COPD) ranks fourth among all causes of death with an age-adjusted mortality rate of 39.9 per 100,000 person-years. The 20th century pandemic of cigarette smoking is taking its toll, evident by the increase in the annual hospitalization rate for acute exacerbation of COPD from 9.7 in 1988 to 24.4 % in 2005. Moreover, about 10 % of all hospitalizations are directly or indirectly attributable to COPD [31]. Many patients with acute exacerbation of COPD require admission to the ICU for acute respiratory failure. In an international cohort study [4], acute exacerbation of COPD was a principal indication for initiating mechanical ventilation in 13 % of patients with acute respiratory failure.

The hospital mortality rate of COPD patients admitted with acute exacerbation varies between 2.5–30 %, depending on the methodology of the data collection and the patient population. Seneff et al. [32] reported a hospital mortality rate of 24 %

in 362 admissions for acute exacerbation of COPD selected from the acute physiology chronic health evaluation (APACHE) III database of 17,440 admissions in a prospective multicenter trial. Mortalities rose to 30 % at hospital discharge and doubled to 59 % at the 1-year follow-up. Invasive mechanical ventilation was instituted in 170 of 362 patients with a mortality rate of 47 %. After controlling for the severity of illness, mechanical ventilation at ICU admission was not associated with either hospital mortality or subsequent survival. Development of non-respiratory organ dysfunction was the most important predictor of hospital mortality, while the abnormalities in gas exchange ($PaCO_2$, pH, PaO_2) indicative of advanced dysfunction were strongly associated with six month mortality.

Esteban et al. [4] reported a hospital mortality of 28 % in patients receiving mechanical ventilation for acute exacerbation of COPD. Liu et al. [33] retrospectively studied a cohort of 138 patients with COPD requiring invasive mechanical ventilation for acute respiratory failure. The cause of acute respiratory failure was acute exacerbation of COPD in 55 % and pneumonia in 44 % of patients. The hospital mortality rate was 39.9 % in all patients and 31.1 % in the acute exacerbation of COPD subgroup. Respiratory acidosis was corrected (pH > 7.30) in 69.9 % of survivors but only in 21.8 % of non-survivors.

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In a recent study, 205 consecutive patients hospitalized with acute exacerbation of COPD were followed prospectively for 3 years [31]. The in-hospital mortality rate was 8.3 %. The overall 6-month mortality was 24 %, with 1-, 2-, and 3-year mortality rates of 33 %, 39 %, and 49 %, respectively. More severe gas exchange abnormalities and longer hospital stays were associated with the hospital mortalities. Long-term mortality was associated with longer disease duration, lower serum albumin, low body mass index, and lower PaO_2. MOF and sepsis were the most common immediate causes of death in patients with acute exacerbation of COPD admitted to the ICU. In another prospective study of 250 patients with acute exacerbation of COPD [34], invasive mechanical ventilation was started in 60 % and NIV was tried in 40 % of patients and was successful in 54 % of them. Median duration of ventilation was 6 days. After several clinical trials reported improved outcomes [35], NIV has become the principal initial mode for providing mechanical ventilation to patients with acute exacerbation of COPD [36]. Since the indications for NIV are more liberal than those of invasive ventilation, it is difficult to directly compare the outcomes of mechanically ventilated patients treated with the two modes. In a study by Girou et al., however, adjusted odds of death (0.37; 95 % confidence interval [CI], 0.18–0.78) suggested that the mortality in patients with similar severity of illness treated with NIV was significantly lower.

Asthma

Severe status asthmaticus is a rare cause of acute respiratory failure requiring mechanical ventilation (1.5 % of patients in the international cohort study) [4]. Patients in status asthmaticus who require invasive mechanical ventilation are at high risk of severe complications (pneumothorax, cardiopulmonary arrest) and mortality. Afessa et al. reported the incidence and outcomes of status asthmaticus in a US inner city hospital, from 1995 to 1998 [37]. Forty-eight out of 132 hospital admissions required mechanical ventilation (36 %). Mechanically ventilated patients had significant mortality (21 %) and high complication rates. Sixteen patients developed non-pulmonary organ failure and four developed pneumothorax requiring chest tube drainage. Interestingly, all patients who died in this study were female.

Pneumonia

Pneumonia is a common cause of hypoxemic acute respiratory failure. Approximately 14–23 % of acute respiratory failure episodes requiring mechanical ventilation are due to pneumonia. ICU mortality rates from acute respiratory failure due to pneumonia range from 37–44 % [1, 2, 4, 38]. In many patients with pneumonia, however, complications such as septic shock and ALI, or acute worsening of underlying chronic lung disease (COPD) are the principal reasons for instituting mechanical ventilation. Compared to other ALI risk factors, pneumonia is associated with higher mortality (see ALI paragraph above).

Interstitial Lung Diseases

The majority of patients with interstitial lung disease and acute respiratory failure admitted to the ICU require invasive mechanical ventilation. Interstitial lung disease is, however, an uncommon cause of acute respiratory failure (less than 2 % of patients in the international cohort study [4]). In a retrospective review [39] of 75 patients with interstitial lung disease who were mechanically ventilated at Mayo Clinic from 2003 to 2005, acute respiratory failure was the most common cause of ICU admission (77 %), followed by sepsis (11 %) and cardiopulmonary arrest (4 %). Seventeen patients were initially treated with NIV but eventually all patients required invasive mechanical ventilation. Hospital mortality was 49 %. Patients with idiopathic pulmonary fibrosis tended to have a higher mortality rate than non-idiopathic pulmonary fibrosis forms of interstitial lung disease. Conventional lung protective mechanical ventilation was not associated with improved outcome. Worsening hypoxemia and higher positive end-expiratory pressure (PEEP) settings were associated with increased mortality. In an earlier study, Saydain and coworkers observed the clinical course of 38 patients with idiopathic pulmonary fibrosis admitted to the ICU. Acute respiratory failure was the most common reason for ICU admission. While 49 % of the patients survived to hospital discharge, 12 of 13 survivors (92 %) died within 2 months after hospital discharge [40].

Neuromuscular Diseases

Patients with neuromuscular disease are frequently treated with both acute and chronic mechanical ventilation. Neuromuscular disease accounted for 2 % of patients receiving mechanical ventilation in the international cohort study [4]. Compared to other causes of acute respiratory failure, patients with neuromuscular disease had higher costs and length of ICU stay and 68 % required tracheostomy [4]. Hospital mortality was 15 %. Epidemiologic studies looking at the outcomes of acute respiratory failure due to specific forms of neuromuscular disease are scarce. Recently, Ali et al. [41] reported on the outcomes of 54 patients with Guillain-Barré syndrome who required mechanical ventilation. All but six patients (89 %) required tracheostomy. Forty-six patients (85 %) survived to hospital discharge, and 39 (72 %) were alive at the 1-year follow-up

Trauma

According to the international cohort study [4], in 7.3 % of patients mechanical ventilation was employed because of trauma. Hospital mortality for these patients was

20 %. In a retrospective incident study of acute respiratory failure in the USA [3], acute respiratory failure related to trauma was more common in the younger age group and trauma without MOF was associated with a very low mortality rate. In a Scandinavian study, approximately 9 % of cases of acute respiratory failure were caused by trauma [2]. Of the 508 cases of acute respiratory failure in the Berlin study, 19 were due to trauma with mortality of 20 % [1]. Complicating coma, shock, and ALI are common indications for mechanical ventilation in patients with trauma. About 8 – 15 % of cases of ALI are related to trauma [2, 4, 15] with mortality lower than that for other ALI risk factors (24 %, see above) [15].

Shock

Shock is characterized by global hypoperfusion leading to lactic acidosis, hyperventilation and hypoperfusion of respiratory muscles, resulting in type IV respiratory failure. Up to 30 % of oxygen consumption in shock may be used by the respiratory muscles contributing to a global imbalance between oxygen delivery and consumption. Pulmonary edema, ALI, and anemia often contribute towards respiratory distress. Work of breathing may ultimately overcome respiratory reserve leading to the development of acute respiratory failure. Early use of mechanical ventilation in severe shock may be justified to limit the work of breathing and decrease oxygen consumption by respiratory muscles. Septic shock, in particular, is commonly associated with acute respiratory failure and ALI. In the international cohort study, septic shock was a primary indication for mechanical ventilation in 9 % of patients with mortality of 55 % [4].

Coma

Coma is a non-specific syndrome of widespread central nervous system impairment resulting from various metabolic and structural etiologies. It usually results in type II respiratory failure due to upper airway dysfunction and hypoventilation. Intubation and invasive mechanical ventilation are usually required to protect the airway and maintain gas exchange. In the study by Esteban et al. [4], 16 % of patients required mechanical ventilation because of coma. Reported ICU mortality was 36 % in patients with coma who received mechanical ventilation.

Conclusion and Future Considerations

Advances in mechanical ventilation have dramatically changed the management and outcome of patients with acute respiratory failure. With increased access to mechanical ventilation, the burden of acute respiratory failure may grow beyond the health care budget of even the richest societies. Inconsistent use of standardized definitions for acute respiratory failure and, in particular, indications for mechanical ventilation, present the major impediment to the meaningful understanding of clinical research results and will have to be overcome in future studies. Population studies are needed to determine the risk factors, prevalence, and the attributable outcomes of various forms of acute respiratory failure in the community. Such studies will help identify the best strategies for the prevention and treatment of acute respiratory failure, will pinpoint important uncertainties that need to be tested in clinical trials, and will allow informed decisions regarding allocation of scarce resources so that bedside practitioners may best improve the quality-adjusted survival of their patients.

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