The Importance of Acute Respiratory Failure in the ICU

Y. Sakr and J.L. Vincent

Introduction

Acute respiratory failure (ARF) results from a disorder in which lung function is inadequate for the metabolic requirements of the individual. ARF in critically ill patients is associated with mortality rates of between 40 and 65 % [1–13], and represents a wide spectrum of syndromes with different severities, which should be viewed in the context of the underlying pathology and associated organ dysfunction. Most of the published literature has focused on the severest forms of ARF, namely acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

Mechanical ventilation is imperative in many forms of ARF, with additional concerns about associated complications, e.g., hazards related to endotracheal intubation [14], ventilator induced lung injury (VILI) [15, 16] and ventilator associated pneumonia (VAP) [17]. Clinical and experimental evidence [15, 16, 18–20] suggest that mechanical ventilation may influence end organ function, a major determinant of outcome in this population.

The Spectrum of ARF

Failure of the respiratory system represents the final common pathway for a wide range of respiratory disorders. The spectrum of ARF varies widely (Fig. 1) from the severest form, namely ARDS, with severely impaired oxygenation ($PaO_2/FiO_2 \leq$ 200 mmHg, regardless of the level of positive end-expiratory pressure [PEEP]), bilateral pulmonary infiltrates on chest radiograph, and pulmonary-artery occlusion pressure (PAOP) ≤ 18 mmHg or no evidence of elevated left atrial pressure on the basis of chest radiograph and other clinical data [21]. ALI is a broader category that involves patients with a less severe form of impaired oxygenation (PaO_2/FiO_2 ≤ 300 mmHg) but presenting other clinical and radiographic features of ARDS [21]. Other forms of ARF are not uncommon, as for patients with respiratory failure with atypical radiographic changes requiring respiratory support. While these patients are not included in the ALI/ARDS definitions, they represent an important source of concern for intensive care unit (ICU) practitioners.

Few studies have reported the incidence of ARDS in a general ICU population. Knaus et al. [22] reported that only 2.4 % (423/17,440) of all ICU admissions met the diagnostic criteria for ARDS. However, the diagnosis was not based on respi-

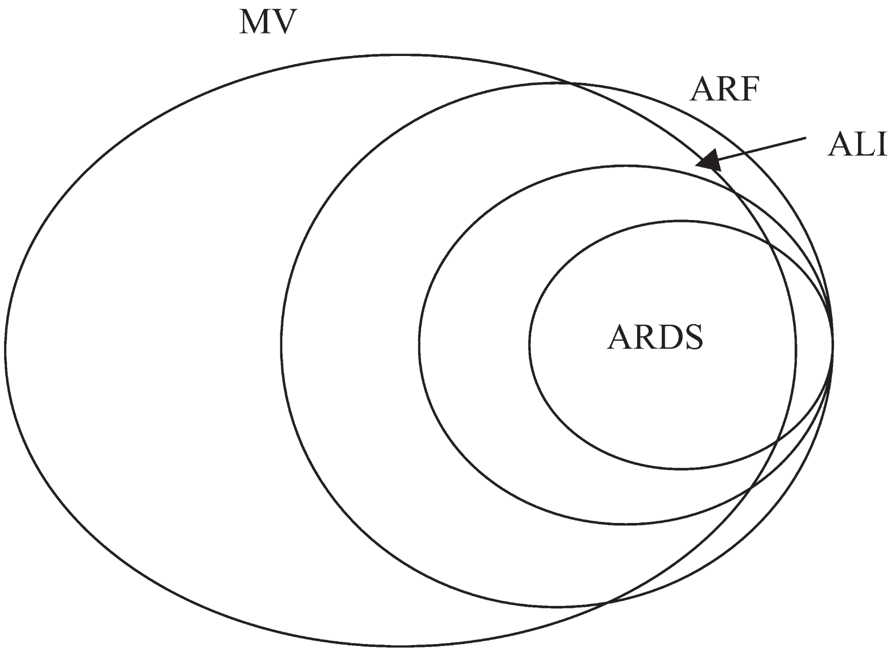

Fig. 1. Schematic representation of various ARF subpopulations and their relation to mechanical ventilation (MV mechanical ventilation, ALI acute lung injury, ARDS acute respiratory distress syndrome)

ratory variables, so this incidence is probably an underestimate. Other studies have reported an incidence of around 7 % [9, 11, 23, 24]. A cohort multicenter European study (ALIVE) reported that 7.4 % (2.8 % ALI and 5.3 % ARDS) of ICU patients were admitted with ALI/ARDS, or developed it during their stay [25], with considerable variations among countries, ranging from 1.7 % in Switzerland to 19.5 % in Portugal, although the criteria used to define ALI/ARDS were the same for all countries. Higher incidences of ARDS have been reported (11–23 %) in mechanically ventilated patients [13, 26–28].

The epidemiology of ARF in the ICU has been studied less. Lewandowski et al. [3] reported that ARF, defined as the need for intubation and mechanical ventilation > 24 hours, accounted for 69 % of all ICU bed usage in an urban population. The severity of lung disease was evaluated using the lung injury score (LIS); 3.6 % of evaluated patients had severe lung injury after 24 hours of intubation and mechanical ventilation, only 2.8 % had severe injury after 48 hours. The sequential organ failure assessment (SOFA) database of 1449 patients, excluding patients with routine postoperative surveillance, showed ARF to be present in 32 % of patients on ICU admission, with a further 24 % of patients developing ARF during their ICU stay (Fig. 2) [29]. ARF was defined as $PaO_2/FiO_2 < 200$ mmHg and the need for respiratory support, denoting a severe form of respiratory failure, and addressing the magnitude of this problem in a heterogeneous ICU population. Recently, Esteban et al. [28], reported that 33 % (5183/15,757) of patients admitted to the participating centers received mechanical ventilation for more than 12 hours; ARDS was the cause of ARF in only 4.5% of ventilated patients.

In the recent sepsis occurrence in acutely ill patients (SOAP) study (unpublished observations) including a total of 3147 ICU patients, excluding uncomplicated postoperative patients, 58.8 % received mechanical ventilation on admission (2.6 % non-invasive ventilation), and another 5.5 % later during the ICU stay for a median of 3 days. Ventilatory days accounted for 55.6 % of total ICU days. Three hundred ninety three patients (12.5 %) had ALI/ARDS as defined by hypoxemia (PaO_2/ FiO_2 < 300 mm Hg), bilateral chest infiltrates, and the need for mechanical ventilation in the absence of a history of chronic obstructive pulmonary disease (COPD) or manifestations of left ventricular failure.

Mortality from ARF

Reported mortality rates from ARF, ALI, and ARDS are largely influenced by the definitions used and by differences in the populations studied. The ALI and ARDS definitions proposed by the American-European Consensus Conference are widely accepted and used, but no universal definitions exist to describe the remaining part of the ARF spectrum (Fig 1).

Mortality rates from ARDS are cited within the range 40–60 % [2, 5, 6, 9–11, 13, 23, 27, 28, 30–43]. Only Ullrich et al. [35] reported a very low mortality rate of 20 %. In the SOAP study (unpublished observations), the ICU mortality of patients with ALI/ARDS was 38.9 % versus 15.6 % for patients without ALI or ARDS. The ICU mortality rate for patients with ARDS was 42.2 %. Luhr et al. [13] reported a 90 day mortality rate of 41 % in 1231 patients mechanically ventilated > 24 hours. Two other large studies reported similar mortality rates of around 40 % [4, 44]. In 615 patients mechanically ventilated > 24 hrs, Luhr et al [13] showed that mortality rates were comparable among patients who had ARDS and those who did not (44 vs. 41 %), underlining ARF as an entity with an outcome as bad as ARDS. The SOFA database [29] (Fig 2) showed a mortality rate of 31 % in patients with a severe form of ARF, an observation confirmed recently by Esteban et al. [28], although in a different population of patients with less severe ARF.

Despite increased understanding of the pathophysiology ARF related syndromes and apparent advances in respiratory support technology, there has been no clear decrease in mortality rates from ARDS over time [45]. However, there may have been changes in the case-mix of the ARDS population, with sicker patients being treated in our ICUs.

Factors Influencing Outcome from ARF

Preexisting comorbid diseases can be associated with increased mortality in ARF. In a multivariate analysis, Luhr et al. [13] reported that immunosuppression was associated with mortality in ARF patients. The SOFA database [29] identified a history of hematologic or chronic renal or liver failure as independent risk factors

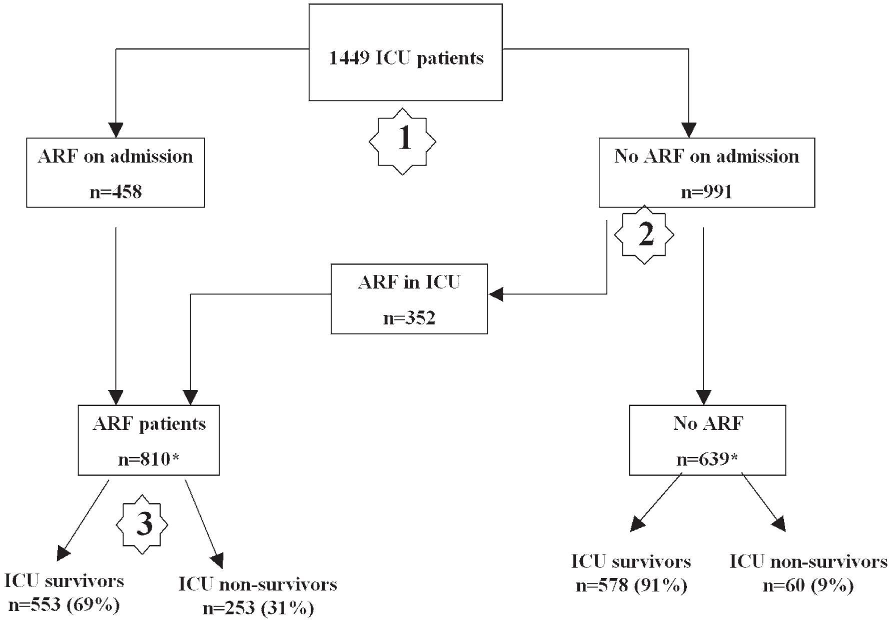

Fig. 2. Flow chart of the study and different subgroups [29]. 1 = description of the differences between ARF and non-ARF patients on ICU admission; 2 = study of risk factors for the development of ARF in the ICU; and 3 = study of the risk factors for death in the ARF patients; *outcome was undefined in four ARF patients and in one non-ARF patient. From [29] with permission

for death from ARF. Chronic liver disease has been associated with mortality from ARDS in several studies [2, 9, 13]. Zilberberg and Epstein [10] identified organ transplantation, human immunodeficiency virus (HIV) infection, cirrhosis, active malignancy, and sepsis as independent factors for hospital mortality in patients with ALI. Monchi et al. [9] reported that the length of mechanical ventilation prior to ARDS, cirrhosis, and the occurrence of right ventricular failure were associated with an increased risk of death.

Many investigators have found death from ARDS to be primarily related to the degree of organ dysfunction [24, 29, 46]. Doyle et al. [2] found that multiple organ failure (MOF), liver disease, and sepsis were the main factors contributing to death. Other important prognostic factors include age [28, 29, 47] and the development of acute renal failure [48]. The prognostic value of the degree of hypoxemia is not well established. Luhr et al. [37] emphasized that the degree of hypoxemia was unimportant in terms of mortality prediction. Likewise, Valta et al. [36] reported that the PaO_2/FiO_2 ratio at the onset of ARDS was similar in survivors and nonsurvivors.

The cause of death in ARDS patients is usually nonrespiratory, i.e., they die with, rather than from ARDS. Montgomery et al. [49] showed that only 16 % of deaths were due to refractory respiratory failure; early death (within 72 hours) was due to the underlying illness or injury whereas late death (beyond 72 hours) was due to sepsis. Ferring and Vincent [5] reported similar findings in 129 patients with ARDS of whom 67 (25 %) died: 50 % from sepsis/MOF, 16 % from respiratory failure, 15 % from cardiac failure/arrhythmia, 10 % from neurologic failure, and 8 % from other causes. Bersten et al. [23] reported that respiratory failure was the only cause of death in 9 % of patients with ARDS and contributed to death in just 24 % of ARDS patients. Recently Estenssoro and colleagues [24] noted in 217 patients with ARDS that MOF was the major cause of death in 88 patients, sepsis in 84, and refractory hypoxemia in 19; 56% of patients had more than one cause of death with 17 of the 19 patients with refractory hypoxemia also having sepsis or MOF.

The Time Course of Acute Respiratory Failure

Despite its limited prognostic value, the degree of hypoxemia can be an important predictor of disease progression in patients with ARF. As early as 1989, Bone et al [50] emphasized that survivors and nonsurvivors differed in the early response of the PaO_2/FiO_2 ratio to conventional therapy. Likewise, higher degrees of organ failure are likely to be present in nonsurvivors than in survivors, as MOF is the cause of death in the majority of patients; however, the time course of organ failure can follow different patterns before reaching this final stage.

In a prospective study of 182 patients with ARF in our institution (unpublished observations), we separated 133 patients who had early ARF (an onset < 48 hours after ICU admission) and 49 with late ARF (an onset <48 hours after ICU admission). On admission, the cardiovascular SOFA score was higher in early than in late ARF, whereas the neurologic score was higher in late than in early ARF. In early ARF, a high SOFA score and low Glasgow Coma Score were predictors of mortality, and in late ARF, a low Glasgow Coma Score at 48 hours predicted mortality. These findings suggest that there may be important differences in the epidemiology and outcome of ARF that are dependent on the time of onset.

Conclusion

ARF comprises a spectrum of diseases that includes ALI and ARDS, and importantly is a valid entity in its own right. Indeed, the severity of ARF is similar to that of ALI/ARDS and it is more easily defined. ARF is common in ICU patients and associated with considerable mortality and morbidity.

References

1. Milberg JA, Davis DR, Steinberg KP, Hudson LD (1995) Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983–1993. JAMA 273:306–309
2. Doyle LA, Szaflarski N, Modin GW, Wiener-Kronish J, Matthay MA (1995) Identification of patients with acute lung injury. Predictors of mortality. Am J Respir Crit Care Med 152:1818–1824

3. Lewandowski K, Metz J, Deutschmann C, et al (1995) Incidence, severity, and mortality of acute respiratory failure in Berlin, Germany. Am J Respir Crit Care Med 151:1121–1125
4. Vasilyev S, Schaap RN, Mortensen JD (1995) Hospital survival rates of patients with acute respiratory failure in modern respiratory intensive care units. An international, multicenter, prospective survey. Chest 107:1083–1088
5. Ferring M, Vincent JL (1997) Is outcome from ARDS related to the severity of respiratory failure? Eur Respir J 10:1297–1300
6. Suchyta MR, Clemmer TP, Elliott CG, et al (1997) Increased mortality of older patients with acute respiratory distress syndrome. Chest 111:1334–1339
7. Nolan S, Burgess K, Hopper L, Braude S (1997) Acute respiratory distress syndrome in a community hospital ICU. Intensive Care Med 23:530–538
8. Squara P, Dhainaut JF, Artigas A, Carlet J (1998) Hemodynamic profile in severe ARDS: results of the European Collaborative ARDS Study. Intensive Care Med 24:1018–1028
9. Monchi M, Bellenfant F, Cariou A, et al (1998) Early predictive factors of survival in the acute respiratory distress syndrome. Am J Respir Crit Care Med 158:1076–1081
10. Zilberberg MD, Epstein SK (1998) Acute lung injury in the medical ICU: comorbid conditions, age, etiology, and hospital outcome. Am J Respir Crit Care Med 157:1159–1164
11. Roupie E, Lepage E, Wysocki M, et al (1999) Prevalence, etiologies and outcome of the acute respiratory distress syndrome among hypoxemic ventilated patients. Intensive Care Med 25:920–929
12. Garcia-Garmendia JL, Ortiz-Leyba C, Garnacho-Montero J, Jimenez-Jimenez FJ, Monterrubio-Villar J, Gili-Miner M (1999) Mortality and the increase in length of stay attributable to the acquisition of Acinetobacter in critically ill patients. Crit Care Med 27:1794–1799
13. Luhr OR, Antonsen K, Karlsson M, et al (1999) Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. The ARF Study Group. Am J Respir Crit Care Med 159:1849–1861
14. Troche G, Moine P (1997) Is the duration of mechanical ventilation predictable? Chest 112:745–751
15. Dreyfuss D, Saumon G (1993) Role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation. Am Rev Respir Dis 148:1194–1203
16. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS (1997) Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 99:944–952
17. Rello J, Ollendorf DA, Oster G, et al (2002) Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 122:2115–2121
18. Ranieri VM, Suter PM, Tortorella C, et al (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54–61
19. Ranieri VM, Giunta F, Suter PM, Slutsky AS (2000) Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 284:43–44
20. Imai Y, Kajikawa O, Frevert C, et al (2001) Injurious ventilatory strategies enhance organ apoptosis in rabbits. Am J Respir Crit Care Med 163:A677 (Abst)
21. Bernard GR, Artigas A, Brigham KL, et al (1994) The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824
22. Knaus WA, Sun X, Hakim RB, Wagner DP (1994) Evaluation of definitions for adult respiratory distress syndrome. Am J Respir Crit Care Med 150:311–317
23. Bersten AD, Edibam C, Hunt T, Moran J (2002) Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. Am J Respir Crit Care Med 165:443–448
24. Estenssoro E, Dubin A, Laffaire E, et al (2002) Incidence, clinical course, and outcome in 217 patients with acute respiratory distress syndrome. Crit Care Med 30:2450–2456

25. Brun-Buisson C, Minelli C, Brazzi L, et al (2000) The European Survey of acute lung injury and ARDS: Preliminary results of the ALIVE study. Intensive Care Med 26 (suppl 3):617 (Abst)
26. Trouillet JL, Chastre J, Vuagnat A, et al (1998) Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 157:531–539
27. Markowicz P, Wolff M, Djedaini K, et al (2000) Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. ARDS Study Group. Am J Respir Crit Care Med 161:1942–1948
28. Esteban A, Anzueto A, Frutos F, et al (2002) Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 287:345–355
29. Vincent JL, Akca S, de Mendonca A, et al (2002) The epidemiology of acute respiratory failure in critically ill patients. Chest 121:1602–1609
30. Hudson LD, Milberg JA, Anardi D, Maunder RJ (1995) Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 151:293–301
31. Chastre J, Trouillet JL, Vuagnat A, et al (1998) Nosocomial pneumonia in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 157:1165–1172
32. Brochard L, Roudot-Thoraval F, Roupie E, et al (1998) Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med 158:1831–1838
33. Weg JG, Anzueto A, Balk RA, et al (1998) The relation of pneumothorax and other air leaks to mortality in the acute respiratory distress syndrome. N Engl J Med 338:341–346
34. Stewart TE, Meade MO, Cook DJ, et al (1998) Evaluation of a ventilation strategy to prevent borotrauma in patients at high risk for acute respiratory distress syndrome. N Engl J Med 338:355–361
35. Ullrich R, Lorber C, Roder G, et al (1999) Controlled airway pressure therapy, nitric oxide inhalation, prone position, and extracorporeal membrane oxygenation (ECMO) as components of an integrated approach to ARDS. Anesthesiology 91:1577–1586
36. Valta P, Uusaro A, Nunes S, Ruokonen E, Takala J (1999) Acute respiratory distress syndrome: frequency, clinical course, and costs of care. Crit Care Med 27:2367–2374
37. Luhr OR, Karlsson M, Thorsteinsson A, Rylander R, Frostell CG (2000) the impact of respiratory variables on mortality in non-ARDS and ARDS patients requiring mechanical ventilation. Intensive Care Med 26:508–517
38. The ARDS Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
39. Esteban A, Alia I, Gordo F, et al (2000) Prospective randomized trial comparing pressure-controlled ventilation and volume-controlled ventilation in ARDS. For the Spanish Lung Failure Collaborative Group. Chest 117:1690-1696
40. Rocco Jr TR, Reinert SE, Cioffi W, Harrington D, Buczko G, Simms HH (2001) A 9-year, single-institution, retrospective review of death rate and prognostic factors in adult respiratory distress syndrome. Ann Surg 233:414–422
41. Gattinoni L, Tognoni G, Pesenti A, et al (2001) Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 345:568–573
42. Nuckton TJ, Alonso JA, Kallet RH, et al (2002) Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 346:1281–1286
43. Derdak S, Mehta S, Stewart TE, et al (2002) High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 166:801–808
44. Kurek CJ, Dewar D, Lambrinos J, Booth FV, Cohen IL (1998) Clinical and economic outcome of mechanically ventilated patients in New York State during 1993: analysis of 10,473 cases under DRG 475. Chest 114:214–222
45. Pola MD, Navarrete-Navarro P, Rivera R, Fernandez-Mondejar E, Hurtado B, Vazquez-Mata G (2000) Acute respiratory distress syndrome: resource use and outcomes in 1985 and 1995, trends in mortality and comorbidities. J Crit Care 15:91–96

46. Gowda MS, Klocke RA (1997) Variability of indices of hypoxemia in adult respiratory distress syndrome. Crit Care Med 25:41–45
47. Dellinger RP, Zimmerman JL, Taylor RW, et al (1998) Effets of inhaled nitric oxide in patients with acute respiratory distress syndrome: Results of a randomized phase II trial. Crit Care Med 26:15–23
48. Rogers RM, Weiler C, Ruppenthal B (1972) Impact of respiratory intensive care unit on survival of patients with acute respiratory failure. Chest 62:94–97
49. Montgomery BA, Stager MA, Carrico J, et al (1985) Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 132:485–491
50. Bone RC, Maunder R, Slotman G, et al (1989) An early test of survival in patients with the adult respiratory distress syndrome. The PaO2/FiO2 ratio and its differential response to conventional therapy. Chest 96:849–851