HISTORY OF MEDICINE

Acute Lung Failure — Our Evolving Understanding of ARDS

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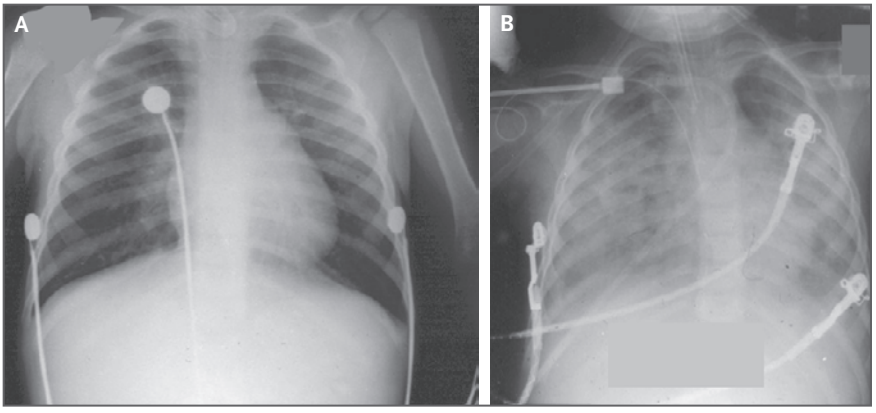
Though what we now call the acute respiratory distress syndrome (ARDS) has almost certainly plagued humans since the beginning of our species, one of the best-known early descriptions of the problem came from René Laennec, who, after inventing the stethoscope in 1816, described the gross pathology of idiopathic anasarca of the lungs (pulmonary edema without heart failure) in 1821. At the time, such anasarca, characterized by severe shortness of breath and cyanosis, was nearly universally fatal.

It took until the 1920s for physicians to gain the capacity to visualize the lungs of patients with the condition. Although W.C. Roentgen had described x-rays that could reveal abnormalities of the lungs in 1896, the first chest radiographs required exposure times of more than 20 minutes; for this and other reasons, routine chest radiographs did not become available for another generation (see images).

In 1929, Drinker and Shaw invented the iron lung, which would be put to the test during a polio epidemic in the early 1950s. Recognizing that many patients with polio required the constant ventilation that had recently been established by anesthesiologist Peter Safar as a core practice of "intensive care," Bjørn Aage Ibsen created the first intensive care unit in Copenhagen and provided patients with negative pressure ventilation using the iron lung. It worked well for patients with normally compliant lungs — but not so well in those whose lungs were "stiff" because of edema, inflammation, and greatly reduced surfactant function. So in 1954, Ibsen became the first to routinely make use of an ICU environment where such patients could be treated with positive pressure ventilation delivered through a cuffed endotracheal tube.

Taken together, these innovations turned the fatal lung disease described by Laennec into a potentially survivable condition. It was variously called double pneumonia, because it involved both lungs; shock lung, because of association with septic and other forms of shock; post-traumatic lung; respirator lung, be-



Normal Chest Radiograph and Radiograph Showing ARDS.

The image in Panel A is from a young patient shortly after admission for near-drowning; it is essentially normal. The image in Panel B is from the same patient and was taken approximately 12 hours after admission; it shows bilateral diffuse infiltrates consistent with ARDS.

cause it was thought to actually be caused by mechanical ventilation; and eventually Da Nang lung, named for the Vietnamese city where many U.S. soldiers were transported for care during the Vietnam War. Then, in a landmark 1967 article, Ashbaugh and colleagues referred to a condition of "acute respiratory distress" associated with "a clinical, physiological, and pathological course of events that was remarkably similar to the infantile respiratory distress syndrome (hyaline membrane disease)." Even though the cases they studied stemmed from diverse causes, including pancreatitis, pneumonia, and multiple trauma, these investigators described similar pathophysiology, radiographic changes, alterations in surfactant, and clinical course. They also described the potential value of treatment with positive end-expiratory pressure (PEEP) and glucocorticoids, each of which has subsequently been the focus of dozens of clinical trials.

In 1956, Avery and Mead had found that premature babies dying of infant respiratory distress syndrome (IRDS) lacked surfactant and had surmised that that was why these babies were able to take their first few breaths but were progressively unable to reinflate their lungs after exhaling. Ashbaugh and Petty now recognized a similar defect in adults, and in 1971 they began to refer to ARDS as "adult respiratory distress syndrome" to differentiate it from IRDS. Unlike IRDS, however, ARDS has not been shown to respond to surfactant replacement, though the reason for that failure is uncertain.

In a prospective, randomized clinical trial in patients with ARDS that my colleagues and I reported on in 1987, we tested methylprednisolone, as suggested by Ashbaugh and Petty, and found no benefit to such treatment. Studies in animals and small observational studies in humans have supported the concepts of continuous positive airway pressure (CPAP) and PEEP. But the proper application and optimal level of PEEP remain controversial.

Meanwhile, the nomenclature of ARDS continued to evolve, and in 1994, the American–European Consensus Conference (AECC) published specific criteria for diagnosing ARDS that were designed to aid and help standardize clinical and epidemiologic research. The term "acute lung injury" could be applied to a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic (bilateral infiltrates consistent with pulmonary edema), and physiological abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension. The syndrome was further described as "most often associated with sepsis syndrome, aspiration, primary pneumonia, or multiple trauma." Acute (now rather than "adult") respiratory distress syndrome was defined as a subtype of acute lung injury associated with worse hypoxemia — that is, a ratio of arterial oxygen tension (Pao_2) to inspired oxygen fraction (FIO_2) of 200 or lower, whereas the threshold for acute lung injury was a Pao_2:FIO_2 of 300.[1]

In 2012, a panel of experts revisited the criteria for the ARDS diagnosis. The result, known as the Berlin definition, is very similar to the AECC definition except that the concept of acute lung injury has been dropped, and all patients with a Pao_2:FIO_2 of 300 or lower are considered to have ARDS, but of varying severity (severe, Pao_2:FIO_2 ≤100; moderate, >100 to 200; mild, >200 to 300). These modifications may make the syndrome easier to describe and the definition more precise.[2]

Over the past quarter century, mortality among patients with ARDS in clinical trials has decreased from approximately 60% to 25%. Perhaps only a third of this 35-percentage-point improvement can be accounted for by the

consistent application of low airway pressure and low tidal volume ventilation (a lung-protective strategy). Some trials, the largest of which was the lower tidal volume trial conducted by the ARDS Clinical Trials Network,[3] revealed that reducing tidal volume from a typical traditional size of 12 ml per kilogram of *actual* body weight to 6 ml per kilogram of *predicted* body weight reduced mortality by 9%.[3] The remainder of the reduction in overall mortality in modern ICUs has not been clearly explained, but it appears to be attributable to better training of physicians, nurses, respiratory therapy staff, and others involved in the routine care of patients with ARDS. Improved alarm systems, ventilator equipment, and radiologic and laboratory evaluation — the availability of magnetic resonance imaging and computed tomography, for example, as well as point-of-care testing with rapid return of results — have undoubtedly also contributed.

Though the vast improvement in ICU and hospital mortality from ARDS is heartening, the poor subsequent condition of the growing number of survivors is showing us that much more needs to be done. Full recovery in patients who have been hospitalized with ARDS happens very slowly, if at all. At 1 year after discharge, vital capacity and 6-minute walk distance remain significantly reduced from patients' pre-ARDS status. Furthermore, less than half of such patients have been able to return to work.[4] Perhaps most worrisome, as many as 50% of patients who have received mechanical ventilation in an ICU — commonly but not always because of ARDS — have cognitive impairment as long as a year after hospital discharge.[5]

We have come a long way since the middle of the last century with regard to recognition, evaluation, treatment, and long-term follow-up of patients with ARDS. Related mortality has fallen so far that it may be reaching a floor rate dictated more by the underlying diseases associated with ARDS — such as sepsis, severe trauma, or pancreatitis — than by either the syndrome itself or other associated organ dysfunction. Fortunately, such progress allows us to turn a much larger portion of our research and clinical attention to the rapidly growing population of ICU survivors.

Disclosure forms provided by the author are available at NEJM.org.

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