Fifty Years of Research in ARDS
ARDS: How It All Began

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Looking back, years later, Dr. Thomas Petty would say that luck was a major factor in the recognition of acute respiratory distress syndrome and the discovery of the therapeutic value of positive end-expiratory pressure (PEEP) (1). There is no question that we were lucky, but the most significant key to these discoveries was the establishment of an interdisciplinary critical care team for the assessment and management of all patients requiring respiratory support at Colorado General Hospital. This team, conceived by Drs. Tom Petty and David Ashbaugh, rounded together daily in the intensive care unit. The unit became a clinical laboratory for understanding and innovation in critical care medicine. Guided by an important discovery in basic pulmonary physiology, the applications of that discovery in clinical neonatology, and a critical pathophysiologic correlation, this team was able to define a new clinical entity and, with a little luck, suggest a unique treatment approach.

The advance in pulmonary physiology was made in the late l950s by Dr. John Clements at the Army Chemical Center in Edgewood, Maryland (2). Using a surface tension balance and static pressure volume measurements in isolated rabbit lungs, Clements discovered the presence of pulmonary surfactant and defined its role in maintaining alveolar volume stability.

At nearby Johns Hopkins Hospital, Drs. Mary Ellen Avery and Jere Mead proposed—on the basis of Clements's studies—that the diffuse alveolar collapse found in neonatal hyaline membrane disease (infantile respiratory distress syndrome) was caused by a lack of surfactant activity (3).

In 1962, Dr. Clements left the Army Chemical Center. At that time, I was drafted from my medical residency and by incredible chance was sent to run his laboratory, where I spent two years continuing studies of the correlation between pressure–volume relationships and surfactant activity. After those years of research, I applied for a pulmonary fellowship in Denver.

In 1964, Dr. Tom Petty and Dr. David Ashbaugh, a thoracic surgeon, had both finished their respective chief residencies and had become faculty members at Colorado General Hospital. They were assigned the task of creating a respiratory care service at the hospital. Such a service was novel then, as pulmonary critical care medicine did not really exist. Pulmonologists had extensive skills, but few were intensivists, and the idea of rounding as a respiratory critical care team was unique.

Despite their charge, very few resources were available. For example, arterial blood gas measurements were not available for clinical use, and the only ventilators at Colorado General Hospital were a few Bennett pressure-cycled devices and one old iron lung. Given the situation, Tom obtained funding for arterial blood gas electrodes and taught himself how to run them. The pulmonary fellows, Dr. Boyd Bigelow and I, would draw the blood samples using sterile techniques and bring them to Tom's office for analysis. If we had a severely ill patient at night, Tom was called in to run the blood gases! We began daily rounds as a team on all respirator patients, trying to learn as much as possible from each patient encounter. Over time, our team grew to include a respiratory nurse (Louise Nett), a blood gas technician (Susan Tyler), and new fellows and house staff.

One of the respiratory team's first projects was to characterize our potential patient population. We performed a retrospective study of 272 patients at Colorado General Hospital who required ventilator support. We found that a small number of the patients reviewed presented with diffuse infiltrates and marked hypoxemia. Those patients could not be ventilated by the available pressure-cycled respirators. Mortality rates were very high. At autopsy, the lungs of these patients showed marked alveolar collapse and hyaline membranes.

Tom Petty made the critical observation that the pathologic findings in the lungs of this patient group closely resembled those described by Avery and Mead in the neonates with hyaline membrane disease. He suggested that a loss of surfactant activity also led to the mechanical dysfunction in the lungs of patients in our study.

Based on that insight, Tom proposed a prospective study to analyze the clinical and pathologic findings as well as the surfactant activity in patients presenting with diffuse infiltrates, who were also very difficult to ventilate. At the outset of this study, it became apparent that our pressure-cycled ventilators were inadequate for this particular patient group. Searching for a better treatment option, Dave Ashbaugh

(Received in original form June 29, 2017; accepted in final form July 11, 2017)

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Am J Respir Crit Care Med Vol 196, Iss 10, pp 1247–1248, Nov 15, 2017

Originally Published in Press as DOI: 10.1164/rccm.201706-1281ED on July 21, 2017
Internet address: www.atsjournals.org

found and borrowed an old volume-cycled Engstrom anesthesia ventilator from the anesthesia department's storage. He first used it to treat a young trauma victim with diffuse infiltrates and poor compliance. He found that although tidal volumes were improved with this device, little change in blood gases or clinical course occurred. Shortly after that experience, the Engstrom was tried on a patient with diffuse pulmonary infiltrates complicating acute hemorrhagic pancreatitis. Again, tidal volumes improved somewhat, but severe hypoxemia persisted. While the team was rounding on this patient, one of our new fellows, Dr. Michael Finnegan, noted a knob on the Engstrom labeled "expiratory retard." He asked what that knob did, and because no one knew, a decision was made to push it. Shortly after the knob was pushed, the patient's oxygenation improved and maximum inspiratory pressures decreased. "Expiratory retard" was, of course, PEEP.

Based on this finding, all subsequent study patients were treated with the Engstrom and the use of PEEP. We noted an improvement in our ability to successfully ventilate them, and survival rates improved significantly.

In 1967, the findings from 12 of these patients were summarized for publication. After some debate, the disorder was named "adult respiratory distress syndrome." We proudly submitted the manuscript to *The New England Journal of Medicine*. The paper was quickly rejected. The reviewers commented that PEEP was contraindicated because it would decrease cardiac output due to decreased venous return. The paper was then sent to two other U.S. journals: *The Journal of the American Medical Association* and *The Annals of Thoracic Surgery*. Both of these journals also promptly rejected the paper. Convinced that our observations were of value, Dave Ashbaugh submitted the article to *The Lancet*. The editors at *The Lancet* believed the article was of great importance and accepted the paper for rapid publication as a lead article. The major change they advised was that we change the name of the disorder to "acute respiratory distress in adults" (4).

And that is how it all began. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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