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From Continuous Positive-pressure Breathing to Ventilator-induced Lung Injury

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Continuous positive-pressure ventilation in acute respiratory failure. By Kumar A, Falke KJ, Geffin B, Aldredge CF, Laver MB, Lowentein E, Pontoppidan H. N Engl J Med 1970; 283:1430–6. Reprinted with permission.

Continuous positive-pressure ventilation was used in eight patients with severe acute respiratory failure. Cardiac output and lung function were studied during continuous positive-pressure ventilation (mean end-expiratory pressure, 13 cm H_2O) and a 30-min interval of intermittent positive-pressure ventilation. Although the mean cardiac index increased from 3.6 to 4.5 l/min per square meter of body surface area, the mean intrapulmonary shunt increased by 9% with changeover to intermittent positive-pressure ventilation. Satisfactory oxygenation was maintained in all patients during continuous positive-pressure ventilation with 50% inspired oxygen or less. With intermittent positive-pressure ventilation, arterial oxygen tension promptly fell by 161 mm of mercury, 79% occurring within 1 min. Prevention of air-space collapse during expiration and an increase in functional residual capacity probably explain improved oxygenation with continuous positive-pressure ventilation. In four patients, subcutaneous emphysema or pneumothorax developed. Weighed against the effects of prolonged hypoxemia, these complications were not severe enough to warrant cessation of continuous positive-pressure ventilation.

IN 1970, Kumar *et al.*[1] published the first in a series of studies from the Respiratory Unit and the Anesthesia Laboratories of Massachusetts General Hospital (Boston, MA) defining the physiologic effects of positive end-expiratory pressure (PEEP) in humans with acute respiratory failure (at the time, Anil Kumar, M.D. was a Clinical and Research Fellow in the Department of Anesthesia at the Massachusetts General Hospital). Previously in 1967, Ashbaugh *et al.*[2] had reported in *The Lancet* their results of continuous positive pressure ventilation in patients with acute respiratory distress syndrome (ARDS), a term that they coined. At the time, David G. Ashbaugh, M.D. was Chief Surgical Resident at the Colorado General Hospital, Denver, Colorado.In May 1968, a National Research Conference on the "The Pulmonary Effects of Nonthoracic Trauma"[3] took place in Washington, DC. The conference was sponsored by the National Science Foundation (Arlington, VA) and the National Research Council (Washington, DC) and generated widespread interest in this area. The conference was stimulated by the interest of military surgeons well acquainted with respiratory complications in battle casualties during the Vietnam War. Drs. Ashbaugh, Petty, and I were among the few civilians present (at the time Thomas L. Petty, M.D. was Assistant Professor of Medicine at the Colorado General Hospital, Denver, CO). Conference attendees agreed that continuous positive-pressure ventilation was a relatively simple and apparently safe new method that might improve the dismal prognosis of patients with ARDS. This prompted a search for the mechanisms of, indications for, and possible complications of this unconventional mode of ventilation. During the next three decades, a wealth of publications, probably numbering in the thousands, appeared, and investigators promoted numerous new approaches, some of which endured while others were discarded. The syndrome of ARDS is difficult to treat and an increased ARDS patient survival has only been documented in large, controlled trials within the past decade.

Most of the early studies, like that of Kumar *et al.*,[1] focused on measuring the effect of a PEEP of 10–15 cm H_2O on circulation, blood gas exchange, and lung mechanics. The reason for the interest in circulatory effects was partly historic. Andre F. Cournand, M.D.,[4] a famous cardiologist and Nobel Laureate (1895–1988 Professor of Medicine at Columbia University, New York, NY) had observed that end-expiratory pressure with its resultant increase in mean airway pressure impaired venous re-

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turn and depressed cardiac output during positive-pressure breathing. Most mechanical ventilators then produced in the United States were therefore not designed to produce reliable PEEP, although some offered an optional, variable expiratory flow resistor. Ashbaugh *et al.* used a Swedish Engstrom ventilator (Datex-Ohmeda, Stockholm, Sweden) with a calibrated PEEP device. At Massachusetts General Hospital we used the Emerson piston-driven volume-controlled ventilator with expiratory flow retard, individually calibrated to give the desired PEEP (Emerson Respirator Company, Cambridge, MA). With expiratory flow retard, expiratory flow is interrupted by the next inflation before airway flow and pressure reach zero. This equipment has long since been replaced by diverse plateau-pressure methods, in which expiratory pressure is kept constant. Some clinicians, however, still use the simple but effective method of immersing the exhalation tube under water. For the Kumar study, we set the tidal volumes at approximately 12 ml/kg predicted weight, as was the practice at the time. We already had gained extensive anecdotal evidence of the benign effects of continuous positive-pressure ventilation 12–13 cm H_2O on cardiac output in ARDS, but we could not identify the responsible compensatory mechanisms in patients.

Abrupt application of 12 cm H_2O PEEP in healthy normovolemic dogs severely depresses cardiac output secondary to a decrease in pulmonary and cardiac transpulmonary transvascular pressure. Transfusion restores baseline output.[5] It is important to note that, in most clinical studies, ventilation with PEEP was the control state and was instituted in a graded manner to gauge the effect on circulation of each increment of PEEP. In a follow-up study to the Kumar study, Falke *et al.*[6] (at the time, Konrad J. Falke, M.D. was a Clinical and Research Fellow in the Department of Anesthesia at the Massachusetts General Hospital) observed no significant changes in cardiac output with random order imposition of 5, 10, and 15 cm H_2O PEEP using a threshold PEEP valve. It is possible that these patients had more severe ARDS than those studied by Kumar *et al.* All but one patient in the two studies, however, met the oxygenation criteria for entry into the recent ARDS Network study of ventilation with low tidal volumes in ARDS ($Pa_{O_2}/F_{I_{O_2}}$ less than 200).[7] These two clinical studies convincingly demonstrated the tolerance of the circulation to high PEEP and mean airway pressures in ARDS.

Kumar *et al.*[1] produced a PEEP of 12–13 cm H_2O by applying a variable orifice expiratory flow impedance. Flow impedance must have raised the mean airway pressure more than the equivalent plateau PEEP. More importantly, the end-expiratory small airway pressure presumably was greater. We did not recognize or attempt to measure this "intrinsic PEEP" until years later.

To intensive care unit clinicians, an equally important finding of our study was the rapidity of decline in Pa_{O_2} after cessation of PEEP; 79% of the change had taken place when the first sample of arterial blood was collected after 1 min. Rapid derecruitment of airspaces was presumably the cause. Kumar *et al.* did not obtain airway pressure-volume loops, but considering the high PEEP level (13 cm H_2O) applied, it seemed reasonable to assume that he was ventilating the patients above what is now referred to as the lower inflection point of the inspiratory pressure-volume curve, presumably keeping airspaces open throughout the respiratory cycle. Most likely peek inspiratory airway pressure exceeded the upper inspiratory inflection point of that curve, overdistending open airspaces.

In a follow-up study by Falke *et al.*[6] Pa_{O_2} increased after augmenting PEEP levels and this correlated with the increase of the functional residual capacity. Static lung compliance was greater during ventilation at high as compared with low levels of PEEP. Oxygen transport was unchanged. I believe that these two studies from our intensive care unit were the first to correlate varying PEEP levels and associated changes in functional residual capacity with arterial oxygen tension in patients with severe ARDS and to show that the average functional residual capacity without PEEP was only 50% or less of normal.

In 1967,[8] Nash *et al.* (at the time Gerald Nash, M.D. was a teaching fellow in the Department of Pathology, Harvard Medical School and First Assistant Resident in Pathology, Massachusetts General Hospital, Boston, MA) described the now well-known stages of lung pathology in ARDS (exudative, proliferative/fibrotic) and attributed them to pulmonary oxygen toxicity. Although an author of that study, I now lack the original data on modes of mechanical ventilation in these 70 patients. I doubt that PEEP was used at the time, as the study period preceded the "PEEP Era." Most, if not all, patients were ventilated with Bennett (Puritan Bennett Company/TYCO, Carlsbad CA) or Bird (VIASYS, Palm Springs, CA) pneumatically operated ventilators, providing tidal volumes of 12–15 ml/kg body weight. Thus, volume trauma may well have occurred. The end-expiratory pressures probably were near zero, with the resultant consequences for small airway patency, as discussed in the following paragraphs.

By the mid-seventies, we had a fairly complete picture of the malfunction and pathology of the lung in ARDS. However, we did not know the causes of lung damage and assumed this was triggered by the initial disease process and perhaps aggravated by oxygen toxicity. Only the presence of extra-airway air was then defined as pulmonary barotrauma. Nothing alerted us to the possibility of other, additive, ventilator-induced lung injury from "volotrauma," the term that is now used. We did not make the probable connection until 10 or 15 yr later when relevant laboratory studies were published.[9] Instead, we focused on maintenance of normal arterial carbon dioxide and the use of

PEEP of sufficient magnitude to allow reduction of F_{IO_2} to presumed nontoxic levels.

During the past decade or so, it has been shown that these classic ventilation patterns may contribute to lung damage in ARDS. Both repetitive opening and closing and severe overstretching of alveoli can cause rapid and severe lung injury. The first occurs if end-expiratory pressure is smaller than the inflection-point pressure of the pressure-volume plot. Air spaces then collapse during expiration and are reopened at some point during inflation. Alveolar over-distension is probably inevitable if "traditional" tidal volumes (*i.e.*, 12 ml/kg or larger) are applied to a lung with a functional residual capacity of less than 50% of normal. The demonstration of these sequences, usually referred to as "volotrauma" or ventilator-induced lung injury, has led to a new approach to mechanical ventilation in lung injury: tidal volume is now maintained at 50% of the previous "standard" or approximately 6 ml/kg body weight. Hypercapnia may either be accepted ("permissive hypercapnia") as long as pH is maintained in an acceptable range or is corrected by raising respiratory frequency. A multicenter trial (under the auspices of the ARDS Network)[7] provided the first convincing evidence of a significant reduction in mortality. Refinements continue to be introduced, such as the addition of an intermittent ventilator-delivered sigh.[10] It seems that we may finally have good news about ventilator therapy for ARDS.

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