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EDITORIAL

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Evidence-based medicine or fuzzy logic: what is best for ARDS management?

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Questions and proposals

Treatment of acute respiratory distress syndrome (ARDS) is a challenge for most ICU physicians. Independently of the severity of the patient's condition, the difficulty stems from our uncertainty on two important points: (a) Has ARDS prognosis improved over the years? (b) Have enough studies of sufficient quality been carried out to know what is the best (or the least deleterious) way of managing such patients? Laudable efforts have been made to clarify these questions. In this issue of *Intensive Care Medicine*, Rossaint and colleagues [1] present an overview of the available science on the symptomatic management of ARDS. The value of this review does not disspell some frustration about ARDS management. This is for two reasons. First, what are the respective roles of randomized controlled studies (the gold standard for proponents of evidence-based medicine) and of the rest of scientific litterature, i.e., clinical physiological studies, historical clinical series, clinical case series, and physiological studies (modeling and animal studies) in improving symptomatic treatment? Second, does considering ARDS as a syndrome and not a variety of diseases direct enough attention to causal treatment? Our opinion about these questions we express in terms of two questions and three propositions:

- Questions

- What has contributed most to improve the symptomatic treatment of ARDS – a report on physiology [2] published only 3 years after the original description of ARDS description [3], which forms the rationale of an intense experimental and clinical research effort, or randomized controlled studies [4, 5, 6, 7]?
- What would a patient prefer (if he had to choose) in a case of severe, worsening of oxygenation during ARDS treatment: a recruitment maneuver or the diagnosis and treatment of a complication (e.g., ventilator-associated pneumonia, fat embolism, peritonitis etc.).

- Proposals

- ARDS is so complicated and multifactorial that symptomatic management is unavoidable. This approach should be guided by ample physiological and clinical knowledge rather than by excessive reliance on cookbook-based medicine.
- Causal treatment should be preferred to symptomatic treatment, except in cases of vital symptomatic emergency.
- Given the complexity of ARDS, the uncertainties on many treatment aspects and the contradictions between goals (a simple example: transporting patients to the computed tomography suite to try to optimize their symptomatic management [8], is a risk factor for ventilator-associated pneumonia [9]), we should use our intellect and limited knowledge and, as humans have done since the beginning of civilization, reason with our natural "fuzzy logic," the only way to approach the solving of an equation with so many ill-defined variables.

Improving the ARDS prognosis over time: a (likely) reality

At least two studies suggest that improvement is real (it is beyond the scope of this contribution to review the extensive literature on the subject). Milberg et al. [10] observed a decrease in mortality of their sepsis-related ARDS patients from 1983 to 1993. Intriguingly, fatality rates improved the most dramatically during the last 3 years of the survey (from 67% to 40%). During the same period physicians markedly reduced the tidal volume that they used for mechanical ventilation of ARDS patients [11]. Jardin and colleagues [12] recently published a provocative study reporting a decrease in mortality from 64% in a historical control group (1978–1981) to 32% in a recent group (1993–1996). They ascribed this reduction in mortality to the implementation of a low-stretch mechanical ventilation approach. Do these reports qualify as examples of evidence-based medicine"? Certainly not. Did they influence the way we care for patients? Certainly yes.

The role of a physiological approach in this (putative) improvement

Mead et al. [2] conducted a physiological low-tech high-mind experiment using springs and condoms to model lung elasticity and simulate lung heterogeneity. They concluded with the visionary statement that, "Mechanical ventilators, by applying high transpulmonary pressure to the nonuniformly expanded lungs of some patients who would otherwise die of respiratory insufficiency, may cause the hemorrhage and hyaline membranes found in such patients' lungs at death." As mentioned above, this conclusion was reached soon after the initial description of ARDS [3] and is a shining affirmation of the importance of physiological concepts in the progress of patient care. Although ignored for many years, this concept has formed the basis for considerable experimental work on ventilator-induced lung injury that led to clinical reflection on ventilator-associated lung injury and lung-protective strategies [13].

Did we wait for randomized controlled trials to change our (patients') lives?

This seemingly iconoclast question is worth considering. Close examination of the tidal volumes used in ARDS patients during the 1970s and early 1980s shows that they were in the 12–20 ml/kg range [14, 15, 16]. Based on the physiological concepts explained above and on a non-evidence-based medicine clinical report [17], clinicians reduced tidal volumes well before any randomized controlled trial (RCT) of lower tidal volume was undertaken. These famous trials provided a clear demonstration of clinical wisdom. Two studies [5, 6] using rather small tidal volumes in the "control group" (which resulted in moderate differences in plateau pressure in the "protective group") failed to demonstrate a difference in mortality with a "protective strategy." Two other studies in which higher tidal volumes were used in the "control group" (which resulted in notable differences in plateau pressure in the "protective group") reported a significant difference in mortality between the groups [4, 7].

Two different interpretations of these findings can be proposed: Either these trials demonstrate that a complex lung protective strategy (requiring determination of pressure-volume curves and the use of high positive end-expiratory pressure, PEEP, levels [4] or the use of very low tidal volumes and an important increase in respiratory rate [7]) reduces mortality, or they confirm that excessively high tidal volumes are unsafe. These studies do not tell us whether ARDS patients should be ventilated with a tidal volume of 6 ml/kg body weight or simply only less than 12 ml/kg, as previously suggested on physiological grounds [12, 17, 18, 19]. A recent paper [11] informs us that the mean tidal volume was 10.3±2 ml/kg predicted body weight (or 8.6±2 ml/kg measured weight) in patients enrolled in the ARDS Network trial [7], *before randomization.* Then the patients assigned to the "conventional" arm of this trial received a tidal volume higher than that selected by the clinician caring for them before they were included in the study.

Further, it is noteworthy that many physicians are reluctant to implement the guidelines for lung-protective ventilation derived from the ARDS Network study [20, 21]. Does this mean that clinicians resist evidence-based medicine or anticipate it because they have heard of Claude Bernard and physiology-based medicine? Indeed, one may hypothesize that, given the above physiological and clinical data, physicians may not be convinced of the need for a very large reduction in tidal volume and increased respiratory rate [12]. More importantly, the ARDS Network trial [7] included only 10% of patients (861/7456) admitted with ARDS in the participating centers [11]. It would not be fair to conclude that the results of this outstanding study constitute a 10% evidence-based medicine. In fact, this reflects the unavoidable contradiction between evidence-based medicine and a comprehensive medicine that does not ignore the complexity of the clinical reality [22]. In an editorial entitled "Medicine-based evidence, a prerequisite for evidence based medicine," Knottnerus and Dinant [22] wrote:

We face the problem that criteria for internal and external validity (that is, clinical applicability) may conflict. Clinical studies are usually performed on a homogeneous study population and exclude clinically complex cases for the sake of internal validity. Such selection may not, however, match the type of patients for whom the

studied intervention will be considered. Medical practice is often confronted with patients presenting several problems.

The complexity of comprehensive care of ARDS patients

The importance of causal treatment of ARDS is not a trivial issue: the appropriateness of surgical management of trauma or abdominal emergencies, or of the antibiotic choice for pneumonia is probably (at least in the early stage) more important than the titration of PEEP. Similarly, the prevention and detection of complications during treatment is fundamental. The incidence of ventilator-associated pneumonia (VAP) is probably much higher during ARDS than initially thought [23]. Given the potential for morbidity and mortality of VAP [24], adequate diagnosis and treatment of this condition is not less important than recruitment maneuvers. As discussed above, the optimal ventilatory strategy is still unknown. Reduction in tidal volume is mandatory, but no one knows whether reducing it to 8–9 ml/kg body weight is sufficient, or whether a goal of 6 ml/kg is desirable. If 6 ml/kg is adopted, no one knows whether PCO_2 should be allowed to rise, which may be protective by itself [25], or should be avoided by an increase in respiratory rate [7]. The level of PEEP that should be applied is also unknown. Would any ethics committee accept a RCT on zero end-expiratory pressure in ARDS only because nice evidence-based data are lacking? Then PEEP would be applied.

High PEEP or low PEEP? The ARDS Network study clearly shows that simple tidal volume reduction with PEEP levels below 10 cmH_2O reduces mortality [7]. However, can auto-PEEP always be avoided when the respiratory rate is 30/min [26]? Jardin et al. [12] found a 32% mortality with moderate tidal volume reduction (9 ml/kg) and a PEEP set at 6 cmH_2O only. Amato and coworkers [4] observed the same mortality rate in patients ventilated with a markedly reduced tidal volume (6 ml/kg) and a PEEP of 13 cmH2O. However, as mentioned above, was tidal volume reduction plus high PEEP responsible for a decrease in mortality or ventilation with a higher than usual tidal volume responsible for an increased mortality (mortality was surprisingly high, 71%, and associated with high incidence of barotrauma, 42%) in the Amato et al. study[4]?

Finally, high PEEP may prove deleterious, as suggested by an abstract from the ARDS Network study group. The authors found that higher PEEP levels were associated with a greater risk of incident barotrauma [27]. The problem of the level of PEEP is made even more complicated by the lack of certainty on the importance, if any, of oxygen toxicity during ARDS when antioxidant defenses of the lung may be upregulated [28]. If high FIO_2 is not very toxic, why use high PEEP levels simply in order to reduce it? Finally, there is no objective indicator of the appropriateness of a peculiar ventilatory strategy. Monitoring mechanics is probably worthwhile. For instance, plateau pressures should obviously be monitored [13], but they may be biased by the parietal component, which may be nonnegligible [29]. The value of pressure-volume curves remains debated. They were not used in the only large-scale study showing a reduction in mortality according to ventilatory mode [7]. Arterial oxygenation is certainly not a good indicator of lung protection. First, its physiological meaning is unclear if mixed venous oxygenation is unknown, which is rather usual. Second, the ARDS Network [7] study clearly shows complete dissociation between arterial oxygenation and survival: the high tidal volume group had a higher PaO_2/FIO_2 ratio.

Prone positioning may have dramatic effects on oxygenation. Should we abandon it simply because no RCT has shown a reduction in mortality with this maneuver [30]? Perhaps, as suggested by the authors, this may nevertheless benefit the most severe patients. However, what is the impact of prone position on VAP, compared with semirecumbent position [31]?

The optimal hemodynamic support is also unknown. Whether the lung should be kept wet or dry has not received a satisfactory answer. Some have found a benefit with fluid restriction [32, 33]. This is consistent with the demonstration of the lack of benefit, and even the deleterious effect, of "optimization" of oxygen transport in critically ill patients [34, 35]. However, a recent report suggests that optimizing this transport at a very early stage of sepsis saves lives [36].

So many variables, so little "evidence": a plea for the integration of complexity

Such complexity may discourage some physicians. Two approaches are possible. First, one may wish to perform RCTs on each of all the parameters listed above (and on the many that are not). We fear that this is neither possible nor desirable. Not possible for obvious logistic reasons. Not desirable, because it looks like an obsessive quest of the objective truth, which may be an illusive goal. If we admit the premises of this editorial perspective, that is, that many variables should be included, we must examine whether these variables interact. If they interact, it makes no sense to test one intervention alone. If we look at the (nonexhaustive number of) parameters listed in the previous paragraph, it is clear that most of them are linked. A strategy of high PEEP would likely require a more marked reduction in tidal volume than a low PEEP strategy to keep plateau pressure at the same level. Then, a discussion on the appropriate $PaCO_2$ will ensue. Moreover, the hemodynamic status may be more

affected in a high PEEP strategy [37], leading to increased need of fluids and vasopressors whose safety is not well known. Obviating the need of high PEEP by placing patients in the prone position has unknown effects of the occurrence of VAP. Finally, there is substantial controversy over the incidence, appropriateness of diagnostic procedures, and influence on outcome [24, 38] of VAP.

The second approach begins with the modest acknowledgement of the lack of omnipotence of the methodological "objectivity." It would be as counterproductive not to take into account the present evidence obtained from RCTs as to believe that they will solve all problems. A reasoned approach should include clinical physiology to take into account the complexity of the ARDS patient. Expert decision is obtained by fuzzy logic.

References

1. Kopp R, Kuhlen R, Max M, Rossaint R (2002) Evidence based medicine in the therapy of acute respiratory distress syndrome. Intensive Care Med http://dx.doi.org/10.1007/s00134-002-1232
2. Mead J, Takishima T, Leith D (1970) Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol 28:596–608
3. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults. Lancet II:319–323
4. Amato M, Barbas C, Medeiros D, Magaldi R, Schettino G, Lorenzi-Filho G, Kairalla R, Deheinzelin D, Munoz C, Oliveira R, Takagaki T, Ribeiro Carvalho C (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347–354
5. Stewart T, Meade M, Cook D, Granton J, Meade M, Hodder R, Lapinsky S, Mazer C, McLean R, Rogovein T, Schouten B, Todd T, Slutsky A, and the Pressure- and Volume-Limited Ventilation Strategy Group (1998) Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. N Engl J Med 338:355–361
6. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondéjar E, Clémenti E, Mancebo J, Factor P, Matamis D, Ranieri M, Blanch L, Rodi G, Ferrer M, Dreyfuss D, Mentec H, Brun-Buisson C, Tobin M, Lemaire F, and the multicenter trial group on tidal volume reduction in ARDS (1998) Tidal volume reduction for prevention of ventilator-induced lung injury in the acute respiratory distress syndrome. Am J Respir Crit Care Med 158:1831–1838
7. Network ARDS (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratoire distress syndrome. N Engl J Med 342:1301–1308
8. Puybasset L, Gusman P, Muller J, Cluzel P, Coriat P, Rouby J-J (2000) Regional distribution of gas and tissue in ARDS. III consequences for the effects of positive end-expiratory pressure. Intensive Care Med 26:1215–1227
9. Kollef M, Von Harz B, Prentice D, Shapiro SD, Silver P, St John R, Trovillion E (1997) Patient transport from intensive care increases the risk of developing ventilator-associated pneumonia. Chest 112:765–773
10. 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
11. Thompson B, Hayden D, Matthay MA, Brower R, Parsons P (2001) Clinicians' Approaches to Mechanical Ventilation in Acute Lung Injury and ARDS. Chest 120:1622–1627
12. Jardin F, Fellahi J, Beauchet A, Vieillard-Baron A, Loubieres Y, Page B (1999) Improved prognosis of acute respiratory distress syndrome 15 years on. Intensive Care Med 25:936–941
13. International consensus conferences in intensive care medicine (1999) Ventilator-associated lung injury in ARDS. Am J Respir Crit Care Med 160:2118–2124
14. Falke KJ, Pontoppidan H, Kumar A, Leith DE, Geffin B, Laver HB (1972) Ventilation with positive end-expiratory pressure in acute lung disease. J Clin Invest 51:2315–2323
15. Suter PM, Fairley HB, Isenberg MD (1975) Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292:284–289
16. Jardin R, Farcot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP (1981) Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 304:387–392
17. Hickling KG, Henderson SJ, Jackson R (1990) Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 16:372–377
18. Slutsky A (Chair), Brochard L, Dellinger P, Downs J, Gallagher T, Gattinoni L, Hickling K, Kackmarek R, MacIntyre N, Marini J, Morris A, Pierson D, Rouby J, Tobin M, Younes M (1994) Mechanical Ventilation (Consensus Conference). Intensive Care Med 20:150–162
19. Kollef MH, Schuster DP (1995) The acute respiratory distress syndrome. N Engl J Med 332:27–37
20. Rubenfeld G, Cooper C, Carter G, Thompson T, Hudson L (2001) Barriers to providing lung protective ventilation to patients with acute lung injury and acute respiratory distress syndrome (ALI/ARDS). Am J Respir Crit Care Med 163:A766
21. Rubenfeld G, Caldwell E, Hudson L (2001) Publication of results does not increase use of lung protective ventilation to patients with acute lung injury. Am J Respir Crit Care Med 163:A295
22. Knottnerus JA, Dinant GJ (1997) Medicine based evidence, a prerequisite for evidence based medicine. BMJ 315:1109–1110
23. Markowicz P, Wolff M, Djedaini K, Cohen Y, Chastre J, Delclaux C, Merrer J, Herman B, Veber B, Fontaine A, Dreyfuss D (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
24. Fagon JY, Chastre J, Vuagnat A, Trouillet JL, Novara A, Gibert C (1996) Nosocomial pneumonia and mortality among patients in intensive care units. JAMA 275:866–869
25. Laffey JG, Kavanagh BP (1999) Carbon dioxide and the critically ill–too little of a good thing? Lancet 354:1283–1286

26. Koutsoukou A, Armaganidis A, Stavrakaki-Kallergi C, Vassilakopoulos T, Lymberis A, Roussos C, Milic-Emili J (2000) Expiratory flow limitation and intrinsic positive end-expiratory pressure at zero positive end-expiratory pressure in patients with adult respiratory distress syndrome. Am J Respir Crit Care Med 161:1590–1596
27. Eisner M, Thompson T, Hayden D, Mattahy M (2001) Airway pressue and the risk of early barotrauma in ALI/ARDS. Am J Respir Crit Care Med 163:A803
28. Capellier G, Beuret P, Clement G, Depardieu F, Ract C, Regnard J, Robert D, Barale F (1998) Oxygen tolerance in patients with acute respiratory failure. Intensive Care Med 24:422–428
29. Ranieri VM, Brienza N, Santostasi S, Puntillo F, Mascia L, Vitale N, Giuliani R, Memeo V, Bruno F, Fiore T, Brienza A, Slutsky A (1997) Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. Am J Respir Crit Care Med 156:1082–1091
30. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, Malacrida R, Di Giulio P, Fumagalli R, Pelosi P, Brazzi L, Latini R, Group P-SS (2001) Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 345:568–573
31. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M (1999) Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet 354:1851–1858
32. Humphrey H, Hall J, Sznajder I, Silverstein M, Wood L (1990) Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. Chest 97:1176–1180
33. Simmons RS, Berdine GG, Seidenfeld JJ, Prihoda TJ, Harris GD, Smith J, Gilbert TJ, Mota E, Johanson WGJ (1987) Fluid balance and the adult respiratory distress syndrome. 135:924–929
34. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 330:1717–1722
35. Gattinoni L, Brazzi L, Pelosi P, et al. (1995) A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. N Engl J Med 333:1025–1032
36. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. Early Goal-Directed Therapy Collaborative Group. N Engl J Med 345:1368–1377
37. Schmitt JM, Vieillard-Baron A, Augarde R, Prin S, Page B, Jardin F (2001) Positive end-expiratory pressure titration in acute respiratory distress syndrome patients: impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements. Crit Care Med 29:1154–1158
38. Papazian L, Bregeon F, Thirion X, Gregoire R, Saux P, Denis JP, Perin G, Charrel J, Dumon JF, Affray JP, Gouin F (1996) Effect of ventilator-associated pneumonia on mortality and morbidity. Am J Respir Crit Care Med 154:91–97