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EDITORIAL

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Small tidal volumes – large benefit?

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Within the last few decades, it has become evident from laboratory and clinical research that in patients with acute lung injury (ALI), mechanical ventilation (MV) contributes to the progression of the disease. To describe the nonspecific radiographic, physiologic, and pathologic manifestations of ALI and its complications, the term "respirator lung" was used for some years during the 1970s and 1980s until Nash et al. drew their historical conclusion that "respirator lung" was a misnomer [1]. They attributed the observed lung lesions mainly to oxygen toxicity rather than to MV. Recent studies, however, confirmed that MV with too low or too high positive end-expiratory pressure (PEEP) levels, high airway pressures, and large tidal volumes (V_T) can further damage the injured lung. In the aftermath of these insights, a new term was made out of the old: "ventilator-induced lung injury" (VILI) [2]. VILI – for years used synonymously with barotrauma of the lung – is currently viewed as a systemic disease which closely resembles the symptoms and the macro- and microscopical features of experimental ALI and is not markedly different from the diffuse alveolar damage present in human acute respiratory distress syndrome (ARDS). It may be associated with pulmonary and systemic infections, multisystem organ dysfunction, volutrauma, barotrauma, and increased mortality. High shear forces taking effect on healthy or diseased lungs ventilated with inappropriate respirator settings can increase capillary permeability, promote gas leaks and edema, and initiate inflammation [3, 4]. The latest reports suggest that MV can induce activation and influx of neutrophil granulocytes and liberation of cytokines leading to local and systemic inflammatory reactions [5]. These findings were paralleled by implementation of the "protective-ventilation strategy" into the critical care of patients with severe acute respiratory failure [6]. This therapeutic concept intends to shield the diseased, ventilated lung by applying only small V_T.

The present state of knowledge on lung protective MV has been reached due to numerous experimental and clinical studies which paved the way for the subsequent randomized controlled trials (RCTs) described here. First, Macklin and Macklin should be recognized for their fundamental experimental studies on the development of tension pneumothorax [7], and then Webb and Tierney [4] are to be honored for their outstanding study in animals which clearly showed that MV can generate/produce pulmonary edema. Dreyfuss and Saumon, in 1992, published an editorial in this journal, the important message of which was that mainly a large V_T and not a high airway pressure is responsible for ventilator-induced lung injury. They suggested a change in terminology: volutrauma should be used instead of barotrauma [8]. The fruitful cooperation between T. Kolobow and L. Gattinoni led to the development of the "baby lung model" [9] and the strategy of resting the injured lung by means of low-frequency MV and extracorporeal CO_2 removal. The impressively high survival rate of 49% in their ARDS patients reported in 1986 [10] was later corroborated by others [11, 12]. Hickling and coworkers introduced accepting elevated arterial carbon dioxide tension ($PaCO_2$)-levels into intensive care practice for ARDS patients to accomplish lung-protective MV [13, 14], and last, but not least, Amato and colleagues, for the first time, showed that a lung protective approach with moderate to high

PEEP levels can indeed reduce mortality in ARDS [6]. The reader will excuse the incompleteness of this list. There were many more researchers who contributed to the knowledge that MV with a large V_T and high positive inspiratory pessure (PIP) worsens ALI and that a lung-protective strategy may minimize the risk of further lung damage.

The impact on mortality rates has been tested, first in uncontrolled clinical studies [11, 13, 14], later on in small [6] or large scale RCT [15–19]. In two uncontrolled, non-randomized, single-center studies, Hickling and coworkers noticed a significant reduction in APACHE II-predicted hospital mortality rates from 39.6 to 16 % in their retrospective analysis [13] and from 53.3 to 26.4 % in their prospective trial [14]. They deliberately restricted peak airway pressures (PIP) to 30–40 cmH_2O, which resulted in mean maximum $PaCO_2$-levels of 62 mmHg and V_T of approximately 7 ml/kg body weight (BW). Lewandowski et al. applied an algorithm controlled, lung protective treatment concept to 122 ARDS patients. Therapeutic measures incorporated in the algorithm were pressure controlled mechanical ventilation with PEEP and permissive hypercapnia, positional maneuvers, differential lung ventilation, dehydration for reduction of pulmonary edema, inhalation of nitric oxide and extracorporeal membrane oxygenation. The mean PIP limit was set to 35 cmH_2O which resulted in mean V_T of 10 ml/kg BW. The 75 % intensive care unit (ICU)-survival rate markedly exceeded those from historical controls [11]. Favorable results from a lung protective approach were also reported by Amato et al. in a two-center RCT, testing V_T of 6 versus 12 ml/kg BW in 53 ARDS patients applying PIP of < 40 cmH_2O, which resulted in $PaCO_2$-levels of 50–55 mmHg in the protective-ventilation group [6]. 28-day mortality rate in the latter group was 38 %, while it was 71 % in the conventional-ventilation group ($p < 0.001$). The difference in mortality at hospital discharge, however, was not significant. Two large scale RCT did not find significant differences regarding mortality rates when V_T of 7.2 versus 10.8 [15] and 7.1 versus 10.3 ml/kg BW [17] were evaluated: The hospital mortality rates were 50 versus 47 % ($p = 0.72$) in Stewart's et al. study [15], and the 60-day mortality rates in the Brochard et al. study [17] were 46.6 versus 37.9 % ($p = 0.38$). Analyzing 725 patients with sepsis-induced ARDS, Weg and colleagues could not detect significant differences in 30-day mortality rates among patients with no air leaks, those with any air leak, and those with specifically pneumothorax, V_T were 11.4, 11.7, and 11.7 ml/kg BW in the respective groups [16]. Finally, very recently, the National Heart, Blood and Lung Institute of the USA stopped the "The ARDS Network Study of Ventilator Management in ARDS" on recommendation of the study's Data Safety and Monitoring Board because an interim analysis on data on the first 847 patients had shown approximately 25 percent fewer deaths among patients receiving V_T of 6, rather than 12 ml/kg BW [18, 19].

How shall the humble intensivist handle these seemingly contradictory data? Is it a "good move" to limit V_T in diseased lungs and if so, to what extent, or does the almost regularly accompanying hypercapnia harm the patient. A closer look at some of the above mentioned studies may help to unveil the right answer.

The studies under discussion have been criticized for their retrospective or uncontrolled nature, for the heterogeneous definitions used, for their lack of exactly reporting various pressures, volumes or $PaCO_2$-levels at different time points, or for their varying outcome end points (28-day-, 30-day-, 60-day-, hospital mortality). Furthermore, different modes of MV and titration of PEEP levels were used. Obviously, comparisons between studies are hampered by these differences. One could also argue that the adverse effects of elevated $PaCO_2$-levels resulting from V_T reduction antagonize the benefits from avoiding alveolar overstretching. However, in Hickling's et al. retrospective and prospective studies [13, 14], there was no significant difference between survivors and nonsurvivors regarding their $PaCO_2$-levels. In all other studies the resulting mean $PaCO_2$-levels were in the moderate range of 50–60 mmHg. It is of far more importance to notice that in those studies where the difference between the tested V_T was rather small, i. e., "reasonable" volumes were applied in the protective ventilation as well as in the control group, no significant differences in mortality rates became apparent [15–17]. Interestingly, in the limited ventilation and control groups of both, Stewart's et al. study [15] and Brochard's et al. study [17], peak inspiratory and plateau pressures were below 35 cmH_2O. Most likely, the transpulmonary pressure limit of 35 cmH_2O, viewed as safe on the basis of animal studies and recommended by the "Consensus Conference on Mechanical ventilation" [20], had not been violated in both these studies. On the contrary, studies investigating largely different V_T documented significantly reduced mortality rates [6, 13, 14, 18, 19]. To put it in a nutshell, a given study will likely detect significant differences in mortality rates if the V_T used in the control group is of sufficient magnitude to induce damage to the ventilated lungs. In the cited studies, the V_T was related to "kg actual body weight" [6, 11, 13, 14, 16], "kg actual body weight minus the estimated weight gain due to water and salt retention" [17], or "kg ideal body weight" [15, 19]. Unfortunately, Brochard et al. [17] and Stewart et al. [15] have not yet reported their exact formulas for calculation of body weight and therefore comparison between studies is hampered. This problem raises the issue of what is the appropriate body weight, -mass, or volume to relate the V_T to, or whether it should be related to measures of body mass at all. The V_T of a sponta-

neously breathing adult at rest is approximately 500 ml [21]. Assuming a weight of 70 kg, the V_T would be 7 ml/kg BW. As suggested by work from comparative mammal physiology, body volume instead of body weight may be a more appropriate parameter for estimation of the "real" lung volume [22]. This information, however, is useless when it comes to ventilating injured lungs. In injured lungs, the amount of aerated lung volume is of concern for selection of safe V_T. In 1972, Falke et al. [23] performed first measurements of functional residual capacity (FRC) in ARDS patients. Mean FRC, a marker for aerated lung volume, was as low as 1.48 L. This is in line with Gattinoni's et al. baby lung concept which postulates that the acute respiratory failure (ARF)- or ARDS lung is rather small than stiff [9]. To get an impression of how small the lung volume is which is available for gas exchange, gas dilution, plethysmographic and radiographic techniques are at our hand. Unfortunately, most of them are technically demanding and impractical to perform at the bedside. A more feasible approach to search for the optimal V_T is the recording of pressure volume curves (P-V curve) which has become current practice in specialized centers [6, 11, 23, 24]. Analysis of the P-V curve reveals the lower and upper inflection point indicating alveolar collapse and overdistension of lung units. A PEEP level above the lower inflection point, and a V_T between the lower and upper inflection point is viewed as safe for patients with lung injury. Minute ventilation can then be manipulated by altering the size of the V_T within the safety limits of the lower and upper inflection point, by in- or decreasing the respiratory rate and the inspiratory time, and by varying the flow characteristics. With this approach the physician does not need to know the patient's actual weight, the height, or the lean body mass to set the respirator in a lung-protective fashion. Just setting pressures or V_T according to experts' advice or to fixed formulas may result in overdistension of the lung in as much as 80% of ARDS patients [24]. It should, however, be mentioned that setting the respirator according to P-V curves is currently a matter of controversy [25]. Only one of the discussed studies set V_T and PIP according to analysis of individual P-V curves [11]. We do therefore have no information on presence or absence of lung overdistension either in the limited ventilation or control groups. As has been shown in our study [11], analysis of P-V curves in ARDS patients revealed "safe" mean V_T of 10 ml/kg BW. Currently, the differences in survival rates in the studies discussed cannot be fully explained by the reduction of V_T, however, a certain impact can be assumed.

Lung protective MV alone, however, is and never will be a panacea that guarantees improved survival rates in acute respiratory failure. As has repeatedly been shown, survival from acute respiratory failure depends on numerous factors the most important of which probably are multiple organ dysfunction, HIV infection, active malignancy, organ transplantation, age, and presence of a septic state [26, 27]. There exist patient populations such as those with acute myelogenous leukemia and respiratory failure in whom survival virtually is zero [28]. These patients are very unlikely to benefit much from lung protective MV in terms of survival. Their survival rate much more depends on the clinicians' ability to impact on the underlying disease process. Modern medicine demands that the benefit of a therapeutic option is reflected in decreased mortality rates. ICU patient populations with life-threatening organ failures, e.g. those with ARDS, however, largely benefit from improvement of important physiological parameters (e.g. indices of oxygenation) and avoidance of additional iatrogenic damage. Not all of the discussed studies have revealed significantly higher survival rates when a lung protective strategy was applied, but some documented significant improvements of several important physiological or clinical parameters. For my part, I put a sticker on my favorite respirator: Small tidal volumes – large benefit!

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