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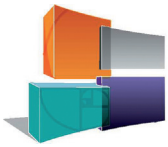

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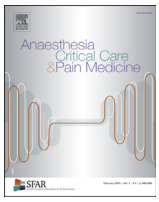

Editorial

Ventilatory setting in Adult Respiratory Distress Syndrome: Don't listen the sound of Sirens! But keep some dreams in your mind...

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How to set the "best" positive end-expiratory pressure (PEEP) in acute respiratory distress syndrome (ARDS) is a non-ending story born the same day than ARDS itself [1]. Is PEEP angel or devil, should we look at the oxygenation, the lung mechanics, the haemodynamic or all of them together?

Physicians routinely manage mechanical ventilation by controlling pressures measured at the airway as a surrogate of transpulmonary pressure. This would be a satisfactory strategy if pleural pressure values were predictable or restricted to a narrow range, when the chest wall elastance is within normal ranges. However, pleural pressure varies widely and unpredictably especially among patients with ARDS, likely due to higher intra-abdominal pressure, obesity, abdominal fluid accumulation and oedema, which influence the mechanical properties of the chest wall. In these cases, transpulmonary pressure should be estimated by the airway pressure minus the oesophageal pressure (Pes), the surrogate of pleural pressure. To obtain reliable Pes measurements, the oesophageal balloon must be placed in an appropriate position and the balloon inflated with an adequate volume of air. An under-filled balloon does not properly transmit the Pes, whereas an over-filled balloon can overestimate the pressure. Thus, oesophageal pressure is not so easy to be currently measured and appropriately interpreted at the bedside.

In 2008, Talmor and colleagues have published a single centre randomised control trial (RCT) of a mechanical-ventilation strategy in which PEEP was adjusted according to end-expiratory transpulmonary pressures [2]. Transpulmonary pressure was measured as the difference between the airway opening pressure and the pleural pressure; pleural pressure was estimated from Pes. PEEP was then adjusted to produce an estimated transpulmonary pressure at end expiration of 0 to 10 cm of water, according to PaO_2/FiO_2. Initially designed to enroll 200 subjects, the trial was stopped after only 61 subjects were enrolled based on an a priori stopping rule requiring a predefined difference in PaO_2/FiO_2 between groups. Based on this trial, the authors designed a larger, multicentre RCT to evaluate the impact on 90 days mortality of PEEP setting based on transpulmonary pressure. The results have just been published in the JAMA, and are negative [3]. Why are these results negative? Because the PEEP-FiO_2 table was the high one, because the study was underpowered, because Pes based PEEP did not result in the same difference of transpulmonary pressure than in the first study, because ARDS patients were not the same, because it was a multicentre study, because some patients were outliers? This paper shows that multicentric RCT often does not confirm the positive findings from single centre RCT, at least in critical care!

Team leaders are motivated to perform and publish a single centre randomised controlled trial, because the study is their idea, their project, because many authors from their institution will be listed for one paper. In multicentric RCT, on the contrary, very few investigators (if any) from each institution will be co-authors, the decision to participate comes from one person, not from the team and even if physicians may be more motivated in a multicentric randomised controlled trial because they perceive that they are involved in an important project that may change practice, they will be less motivated in the absence of a personal scientific reward or the perspective of highlighting their team. This is particularly true in this trial, where they required up to 5 years with 14 hospitals to include 200 patients when they planned to include the same numbers of patients in the initial monocentric trial.

It is intuitive that, in Intensive Care Medicine, if the control group is in line with current practices, interventions will show at best a modest effect size. Single drugs, techniques, or strategies are unlikely to deliver major outcome benefits in heterogeneous populations as ARDS patients are. Nevertheless, in this trial, the sample size was calculated according to the optimistic results of the single centre RCT and with a power of only 0.85. Even if it has probably changed nothing in the primary outcome, it could have given the opportunity to reach statistical significance for secondary outcomes as kidney injury.

The "expert centre" versus the "non-trained centre" effect. Most single centre RCT are performed by expert team in the field, which is obviously not the case of multicentre RCT, this have been published for non invasive respiratory support, glycaemic control and other therapeutic regimens in critical care. The strategy for training teams involved in large RCT and the evaluation of the training is a major point when we design RCT and should be

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published, as least as part of the protocol. In this case, this is probably a major issue. Oesophageal manometry is a smart but difficult technique to be applied and interpreted at bedside. A small error in Pes measurement can generate large changes in transpulmonary pressure and setting PEEP according to a wrong transpulmonary pressure may generate extreme values of airway pressure. If we look at the results, some patients have a really high plateau pressure and driving pressure. Even if it is only 10 or 20 patients, it may change the results of the study. Moreover, each work team follows internal dynamics, beliefs, that are never exactly the same in different work contexts: if such dynamics can influence the outcomes of the performance of a group (measured as patient outcomes), they may naturally also lead to the failure of multicentre RCT to confirm preliminary findings; this is the "nocebo" concept applied to the interventional arm when the team do not trust the evaluated strategy or have not choose to participate to the trial.

On the other hand, the present study compared a higher PEEP strategy with an individually titrated PEEP by using transpulmonary pressure. In other words, the study did not compare the new technique with a lower PEEP strategy. Lower PEEP (between 8 to 12 cmH_2O) was found comparable with higher PEEP (between 12 to 16 cmH_2O) strategy on outcome in ARDS patients [4]. Thus, the consequence is that a individualised PEEP strategy based on transpulmonary pressure is equivalent to lower PEEP in moderate to severe ARDS. But this was not proven on the study. The concept of avoiding higher (>15 cmH_2O) of PEEP in ARDS, to minimise static and end inflation overdistension, associated with protective tidal volumes, driving and inspiratory plateau pressures has been recently reconsidered [5]. More recently, the concept of minimising mechanical power has been suggested to optimise ventilatory setting in ARDS. The impact of PEEP in the amount of energy delivered to the lung remains questionable.

Should we stop trying to personalise mechanical ventilation? Personalisation of mechanical ventilation is the holy grail of intensivists involved in mechanical ventilation [6]. Nevertheless, looking to the last papers published, at the best there is no effect, for the worst it may kill patients [7]. We initiated personalisation of mechanical ventilation with Peter Suter at the beginning of the 70s [1], and now we are half across a ford, we should move on and look not only at oxygenation, lung mechanics, haemodynamic, but also to lung imaging, to inflammation, genetics, to characterise different ARDS phenotypes with different responses to therapeutic strategies [8]. We have some post-hoc analysis of large trials in line with this hypothesis and at least one ongoing trial [9], are we at the beginning of a new paradigm?

Should we stop multicentre RCTs in critically ill patients? The question has been raised by some of the most influent academic intensivists [10]. With all limitations and bias of multicentre RCT, we may look carefully to well-designed and well-conduced observational studies. If they are often criticised, they have many advantages, one of the majors being that the entire patient population can be enrolled; there are no exclusion criteria, making the study results more relevant to actual clinical practice. A second advantage is that informed consent is not needed, enabling larger patient populations to be enrolled, without needing to wait for consent, thus, reducing the need to enroll non-trained centres. If they are known to overestimate the beneficial effects of treatments, it seems that it is no longer true [11]. Further, the inclusion of a large number of patients makes the results more solid and applicable in different clinical situations. Otherwise it is possible that positive results from single centre randomised controlled trials may result in harm to our patients when adopted in other clinical and organisational contexts. Thus, we would be extremely careful in adopting any clinical strategy if not clearly shown effective in a sample of at least minimum 1000 to 1200 patients, depending on the primary outcome. Information from observational studies is increasingly used to support changes in therapeutic management, due to associations between different variables and outcome. We put a word of caution to translate findings from observational trials and adoption of clinical strategies. In our opinion, large observational studies are helpful for epidemiological description and generating hypothesis, before planning a large powered RCT. Thus, we should not absolutely abandon multicentre RCT, which also provide the advantage to perform subsequent individual data meta-analysis, which may provide further important information, but we may not summarise medicine to results of RCT.

At the end of the day, how should clinicians apply the results of the trial by Beitler and co-workers in clinical practice? As usual, the pragmatic answer depends! For the more enthusiastic, who furthermore work in centres with considerable expertise with ARDS, they may continue to use oesophageal pressure in obese patients, in patients with stiff chest wall, in really severe ARDS and try to find the best algorithm based on transpulmonary pressure. Alternatively, based on these data and others, for moderate to severe ARDS patients, the optimal mechanical ventilation setting simply includes a low V_T (4–6 mL/kg Predicted Body Weight), a plateau pressure below 30 cmH_2O, a driving pressure below 15 cmH_2O, with minimal respiratory rate to avoid a pHa less than 7.25 and PEEP set according to the lower PEEP-FiO_2 Table. This is probably the easier, cheaper, fastest and safest way to set PEEP in ARDS.

Disclosure of interest

The authors declare that they have no competing interest.

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