Letter to the Editor

Should the ART trial change our practice?

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The optimal level of positive end-expiratory pressure (PEEP) in ARDS has been discussed for more than 50 years (1). The concept of using recruitment maneuvers to open collapsed lung units in association with optimal PEEP was also proposed many years ago (2). A large body of animal studies and small mechanistic studies suggest that the open lung strategy might be beneficial to prevent ventilator-induced lung injury in patients with ARDS. Furthermore, systematic reviews of randomized trials assessing the effect of lung recruitment maneuvers for patients with ARDS suggest that this procedure can decrease mortality without substantial adverse events, however the quality of evidence is low due to risk of bias and variable use of co-interventions (3,4).

The Alveolar Recruitment for ARDS Trial (ART) was planned along many months with the aim to provide a reliable answer regarding the clinical effects of the open lung strategy compared to a low-PEEP strategy in moderate-to-severe ARDS patients (5). A total of 1,010 patients were enrolled in 120 sites. Contrary to most expectations, the results showed that open lung strategy increased 28-day mortality (6). It also resulted in a higher risk of barotrauma in 7 days and hypotension or need to start or increase vasopressors in 1 hour.

Are the results of ART reliable? We strongly believe they are. We conducted ART with a solid focus on delivering adequate training and guaranteeing adherence to study protocol. Several actions were deployed with those aims. Multiprofessional ICU teams of all sites were trained in loco before enrolling the first patient (except for Malaysia trained with web conference). All sites received several copies of didactic bedside manuals of operations (available with the main paper supplement) (6). We held annual investigators meetings and formal teleconferences 3 times per year. We communicated with site intensivists by WhatsApp soon after every patient was randomized and a 24/7 phone line was available for support. We also put a lot of effort on measuring and reporting adherence. Use of low tidal volumes, with mean values just below 6mL/kg of predicted body weight, nicely exemplifies the commitment of investigators with protocol adherence.

Dr. Villar and colleagues wrote an editorial raising several concerns regarding the ART and cautioning against application of its results to clinical practice (6). First is the 28-day mortality observed in the control group of the trial (49.3%), higher than most recent randomized trials. We believe there are some explanations for this. Initially are our eligibility criteria. Before assessing eligibility, all patients were ventilated with a standardized mechanical ventilation for at least 3 hours and arterial blood gases were collected with an FIO_2 of 100%. Only patients who persisted with PaO_2:FIO_2 ratio equal or lower than 200 were eligible. The ICU mortality in this subset of moderate-to-severe ARDS patients exceeds 50% compared to 20% in those that improve PaO_2:FIO_2 (7). Second, most patients were enrolled in Brazil. Critically ill patients tend to have higher mortality in Brazil and other middle-income countries than in Europe, North America or Australia (8,9). Third, our eligibility criteria were pragmatic allowing inclusion of patients with co-morbidities and other organ dysfunctions which is so

typical of patients with moderate-to-severe ARDS.

Dr Villar and colleagues argue that differences between the ART settings with those in higher income countries and the limited number of exclusion criteria limits generalizability of study findings. This interpretation assumes that relative treatment effect is modified according to baseline mortality. This assumption is hardly supported by evidence. Furthermore, even if it was the case, because 85% of the burden of critically illness is in low- and middle-income countries, generalizability could only be larger. Conversely, their suggestion to exclude the majority of ARDS patients with comorbidities or other organ dysfunctions would only decrease generalizability.

The second critic raised by Dr Villar and colleagues is the fact that although our main results (using Cox proportional hazards model) showed significant harm, P values are slightly higher than 0.05 using other statistical tests. We defined a priori in our SAP that the main analysis would be a Cox proportional hazards model (5,10). Therefore, the best approach to avoid multiple hypothesis testing error is to stick with the pre-specified analysis. Nevertheless, results of ART showed that the recruitment maneuver associated with titrated PEEP is definitely not beneficial and likely harmful for moderate-to-severe ARDS patients.

A third critic raised by Villar and colleagues is the use of PEEP 10 cmH_2O and FIO_2=100% to select patients for the ART trial. Our method was based on a study that suggested this strategy strongly discriminates mortality (7).

In their fourth critic, Villar and colleagues suggest that the use of high pressures and time might had led to seven cases of pneumothorax and three cases of cardiac arrest occurred during the recruitment maneuver. This is incorrect. No case of pneumothorax was detected during the recruitment maneuver. Although, three cases of cardiac arrest were temporally associated with the recruitment maneuver, the overall risk of cardiac arrest on day 1 was similar (1.0% and 0.4%; P=0.28). They further suggest that investigators lacked experience and training. We think this statement is unfair and not based on any objective fact. As pointed out above, several measures were deployed to ensure proper protocol delivery. Furthermore, we have shown that treatment effects on mortality were neither dependent on the volume of cases included in each site (treatment effects were homogeneous across sites) nor on the results of initial versus later cases in each site (6).

Fifth, Villar and colleagues argue that the volume-controlled mode and use of low tidal volumes may have led to frequent double-stacking and flow asynchrony in the experimental group. Apart from the recruitment maneuver and titrated PEEP, our ventilation strategy for the treatment group was the same as for the control group (ARDSNet protocol) (11). Hence, we agree with Villar and colleagues that asynchronies may be an issue with these ventilation settings, although their frequencies were likely similar between treatment groups. This point certainly requires further research, but it represents a general limitation of any protective strategy aiming the use of tidal volumes <6–7 mL/kg, especially when not using dedicated software for monitoring dysynchronies.

Should the ART change our practice? Use of open lung approach, with recruitment maneuvers and decremental PEEP titration, for moderate-to-severe ARDS patients has been debated fiercely along decades and many have adopted it to care for ARDS patients. However, besides some intriguing physiological benefits, there has never been adequate evidence showing benefits of this strategy on hard outcomes, except for the particular population of patients with hypoxemia after cardiac surgery. The results of ART showed that the general use of recruitment maneuvers, followed by decremental PEEP titration, is likely harmful for moderate-to-severe ARDS patients. Particularly in this trial, the amount of patients presenting large lung recruitability was low, not exceeding one third of patients. Moreover, the observed harm of the ART strategy seemed to be concentrated in those with null or negative "recruitability" (i.e., those presenting increased driving pressures after randomization to ART). It is always possible to hypothesize that the particular maneuver performed in the ART trial had low efficacy, presenting limited room for individualization. But without more intensive monitoring, it is hard to point out how it could be easily improved. Thus, apart for the rare patient with refractory hypoxemia (PaO_2 <55 mmHg with FIO_2 =100%), there is no basis for routine use of the ART strategy in clinical practice. Conversely, whether the open lung approach may be beneficial for specific subsets of ARDS patients, especially in those with highest lung recruitability, merits further research.

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Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

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