Editorial

The 25th birthday and premature death of the open lung approach?—from science, through art, towards precision medicine

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Mechanical ventilation is a challenging intervention applied on a complex and very sensitive organ—the lung. The coexistence of open and collapse units in the lungs of patients with acute respiratory distress syndrome (ARDS) make this intervention even more challenging, as this dramatically increases the risk of harm caused by positive pressure ventilation. Indeed, this intervention, per se, has been identified as one of the most harmful intrusions in ARDS patients. From a physiologic standpoint it may seem attractive to open the collapsed lung units and to keep them open during the whole breath cycle. This 'treats' the at times life-threatening hypoxemia, consequently preventing a further deterioration of the other organs.

While this year ARDS celebrates its 50th birthday, the adage *'open up the lung and keep the lung open'* celebrates its 25th birthday. Indeed, it was 25 years ago that Burkhard Lachmann wrote these legendary words (1). Since them this 'battle cry' could be heard in many intensive care units worldwide. Many research articles were published on this 'life–saving' strategy, also called the 'open lung approach' (OLA) (2), mainly showing that it worked nicely in animals, and even in humans for as long as physiologic endpoints were used. OLA found a solid place in clinical practice (3), simply 'because it worked', and because it was a costless and above all simple intervention. Yes, the least experienced residents could do this magic trick.

For a long time, however, we remained uncertain about the effects of OLA on clinical endpoints. We neglected the casuistic reports on severe adverse effects of OLA, and even the results of three adequately performed large randomized controlled trials were set aside as 'not true' (*Table 1*) (4-6). How happy we were when an individual patient data meta-analysis, using data from these three trials, showed OLA to improve survival (8). Well, it was only in patients with moderate or severe ARDS were OLA was beneficial—in our enthusiasm we all may have missed that the same meta-analysis suggested harm of OLA in patients with mild ARDS. One recent investigation started to bring more doubt about OLA (9). A computer tomography study in ARDS patients nicely demonstrated that some patients responded beneficially to OLA with recruitment of lung tissue, while in other patients OLA seemed to harm as it caused hyperinflation of lung tissue. If we do not know how a patient responds to OLA, how then to apply this intervention (5)?

The recently published 'Alveolar Recruitment for ARDS' (ART) put us at more doubt of unselected use OLA (7). The ART trial, performed in 1,010 patients with moderate or severe ARDS, compared OLA using intensive, or aggressive, recruitment maneuvers and decremental positive end-expiratory pressure (PEEP) to achieve the best compliance with a ventilation strategy in which PEEP

Table 1 Sufficiently-sized randomized controlled trials of OLA in patients with ARDS

Study	No. of patients	PaO_2/FiO_2 cut-of for inclusion	Intervention	Outcome
Brower *et al.* [2004] (4)	549	PaO_2/FiO_2 <300	PEEP/FiO_2-chart: Study: high PEEP Control: low PEEP	No significant difference in hospital mortality
Meade *et al.* [2008] (5)	983	PaO_2/FiO_2 <300	Study: high PEEP/FiO_2-chart + Pplat <40 cmH_2O + RM Control: lower PEEP/FiO_2-chart + Pplat <30 cmH_2O	No significant difference in 75-day mortality
Mercat *et al.* [2008] (6)	767	PaO_2/FiO_2 <300	Study: PEEP titrated to Pplat 30 cmH_2O Control: PEEP 5–9 $cmH_2O \rightarrow O_2$ goals	No significant difference in 28-day mortality
Cavalcanti *et al.* [2017] (7)	1,010	PaO_2/FiO_2 <150	Study: recruitment maneuvers + PEEP titrations (compliance-titrated) Control: PEEP according to PEEP/FiO_2-chart	Significantly increased 28-day mortality and 6-month mortality in the study group

OLA, open lung approach; PEEP, positive end-expiratory pressure; RM, recruitment maneuver.

and FiO_2 were titrated according to the ARDS Network tables. Surprisingly, OLA was associated with a significantly higher 28-day and 6-month mortality and resulted in more barotraumas (5.6% *vs.* 1.6%).

Why did ART fail to confirm what we all believed in? Of course, we could consider that the trial failed, and not OLA? Was the sample size too small for the effect size (decreases in driving pressure from the control to the OLA group were limited to less than 2 cmH_2O from day 1 through day 7)? Was the control group treated too well? Was OLA really individualized or was the protocol for OLA too pragmatic? And finally, were all investigators, at all sites, familiar with the protocol and experienced to perform the complex and potentially harmful intervention (enrolment of 1,010 patients in 120 units worldwide probably means that some centers may have enrolled low numbers of patients)?

But what if we believe the results of ART? In the end, this was a well-performed trial by a highly experienced group of trialists. Let's consider again the effect of OLA on the driving pressure: the decrease in driving pressure from the control to the OLA group were very limited indeed. But let's not forget that we are looking here at averaged data: could it be that there were patients in whom OLA did not decrease, but instead increase the driving pressure? And if so, was the change in driving pressure associated with outcome? This calls for an additional analysis to better understand what happened in ART.

Should we accept a premature death of OLA, or should we resuscitate? Maybe we should do the latter. It is alike with treatments we give for other diseases we deal with in critically ill patients, like '*sepsis*', and diseases outside the intensive care arena, like *multiple myeloma* and *colitis ulcerosa*: patients are probably seldom, if not never alike, and there is no one size fits all. The ARDS of *Mr. X.* may not be comparable to the ARDS of *Ms. Y.* There is increased interest in personalized, or precision medicine, also amongst critical care physicians (10). We may want to 'phenotype' our patients, probably based on a combination of clinical, radiographic, physiologic, and biologic characteristics to choose the best therapy for each individual, in this case the individual patient with ARDS (11). It is since short that we start to realize that certain therapeutic strategies can have opposite effects in individual ARDS patients and that we need personalized therapies in intensive care (12-14).

ART was a piece of art, alike the three previous trials of OLA (4-6). But we need even better trials, trials enrolling patients that could truly benefit from an intervention. Precision medicine for ARDS is the one and single goal, allowing us to decide that *Mr. X.* must receive OLA, while the lungs of *Ms. Y.* should stay rested.

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Footnote

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

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