Editorial

Respiratory rate and peak inspiratory pressure, new targets from the LUNG SAFE study analysis or physiopathological artifacts?

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Introduction

Acute respiratory distress syndrome (ARDS) will celebrate in 2017, his golden fiftieth anniversary since his first description by Ashbaugh and colleagues in 1967 (1). This long period of time has permitted many advances in pathophysiological concepts as the emerging role of ventilator-induced lung injury (VILI) (2). Unfortunately, relevant interventions allowing a better outcome are still scarce and include the use of low tidal volume (TV) ventilation (3) for all ARDS patients and the use of systematic prone positioning (4) and early short term neuromuscular blocking agents (5) for the most severe forms of ARDS. To better classify, to design high quality clinical trials and in order to stratify treatments and outcomes, a new definition so called the Berlin definition was published in 2012 (6). The LUNG SAFE study (7) is a global word wide epidemiological study of the burden of ARDS across the five continents. Beside the still crude 40% in hospital mortality of the disease, the LUNG SAFE study has under lightened the misrecognition and under recognition of the syndrome leading to potential inadequate treatments. Therefore, Dr. Laffey and colleagues performed a secondary analysis (8) of potentially modifiable factors contributing to outcome from the LUNG SAFE study whose aims were, first to identify management's factors associated such as ventilator-related parameters and second to investigate the role of non modifiable factors such as demographic characteristics, severity of illness and the variables associated with decisions of withholding or withdrawing treatments.

Methodology and mains results of the study

Methods

From the whole data base of the LUNG SAFE study including 3,022 patients fulfilled ARDS criteria according the Berlin definition, this study have enrolled a subset of 2,377 patients with persistent ARDS criteria during at least 48 h and invasively ventilated. ARDS severity was classified as mild (200< PaO_2/FiO_2 ≤300), moderate (100< PaO_2/FiO_2 ≤200) and severe (PaO_2/FiO_2 <100), all for a minimal level of PEEP of 5 cmH_2O. The weight of the following variables according to a predefined stratification was assessed for the relative risk of ICU and hospital mortality for the following variables, namely TV (<8, ≥8 mL/kg) and PEEP (<12, ≥12 cmH_2O) measured at ARDS onset. Among these patients, another subset of 742 patients with no evidence of spontaneous ventilation i.e., with equal set and measured respiratory rate (RR) were investigated for plateau pressure (Pplat) (<25, ≥25 cmH_2O) and driving pressure (DP) as defined by Pplat minus PEEP (<14, ≥14 cmH_2O). ICU organizational factors such beds per nurse ratio, beds per physician ratio and number of beds per ICU were also tested.

After bivariable analysis to identify factors associated either with ICU and hospital mortality either with a

limitation of life-sustaining therapies, a stepwise regression analysis including all variables with P value <0.05 in bivariable analysis was conducted. For respiratory variables at day 1 potentially associated with ICU and hospital mortality, a robust locally weighted regression and smoothing plot (LOWESS) method was performed.

Mains results

Concerning potentials modifiable respiratory variables, high (≥8 mL/kg) or low (<8 mL/kg) TVs did not discriminate the outcome (either ICU mortality, either hospital mortality) in each severity of ARDS group. Remarkably, ranges of TV were relatively narrow. The predefined PEEP level (<12, ≥12 cmH_2O) was only different in the moderate ARDS group with a significant greater percentage of PEEP ≥12 cmH_2O in the hospital survivors at ARDS onset but not in the ICU survivors. However, a high PEEP level was associated with a protector odds ratio (OR) of 0.95, 95% confidence interval (CI) (0.92–0.98), P=0.001 in the cohort of 2,091 patients included in the multivariate model analysis of factors associated with hospital mortality. Conversely, in the multivariate analysis, RR and peak inspiratory pressure (PIP) were higher in the non survivors. The predefined thresholds of Pplat of 25 cmH_2O discriminated severe ARDS patients with higher hospital and ICU mortalities rates in patients with Pplat ≥25 cmH_2O. Similarly, high (≥14 cmH_2O) DP were associated with higher fatality rates in both moderate and severe groups. The analysis of the LOWESS plots showed curvi-linear increases of hospital mortality rates for Pplat >20 cmH_2O and DP >10 cmH_2O. Below theses cut-offs, slop of the curves were flat. Concerning PIP, there was a constant increase in mortality with increase in PIP notably with a maximal bend of the curve for PIP above 40 cmH_2O. PaO_2/FiO_2 curve was flat between 300 and 150 mmHg and curved for the values below 100 mmHg.

Modifiable organizational factors founded that hospital mortality was inversely associated with ICU number of beds [OR, 0.99, 99%CI (0.99–1.00), P=0.035]. However, ICU mortality was not associated with ICU number of beds suggesting that in ICU with less number of beds or a high bed occupancy rate, patients were discharged earlier and sicker than in bigger ICUs.

Concerning non modifiable factors associated with hospital mortality in the invasively ventilated LUNG SAFE cohort, Dr. Laffey and colleagues identified older age, presence of active solid or hematologic malignancy, immunosuppression and chronic liver failure as factors independently associated with hospital mortality. Severity of illness regarding lower pH values, PaO_2/FiO_2 and higher non pulmonary SOFA score were also associated with worse prognosis.

Concerning the analysis of the factors associated with limitation of life-sustaining therapies or measures concerning 24% of the 2,377 invasively ventilated patients; overall mortality was 81% in this subset of population and we observed an overlap with non modifiable factors associated with hospital mortality reflecting that decisions of limitation of life-sustaining therapies or measures were probably the result of perceived futility.

Strengths and limitations of the study

Strengths of the study

The second analysis of the LUNG SAFE study reinforces some clinical message leading to potential substantial therapeutic modifications. If the main article focused on misrecognition, underutilization and lack of stratification of proven efficient therapy such as low TV ventilation, prone positioning and NMBA use at the onset of ARDS in "a real-life clinical setting", this second analysis highlights some possible changes in the ventilatory settings. TV, RR, DP, PEEP level and PIP are all components derived from the classical equation of motion and are either dynamic, static or resistive parts of the mechanical power delivered during invasive ventilation to the injured lungs (9). As a concept, the less you transfer energy to the injured lungs, the better it is. Even if this concept is mainly established in animal model (10), there are some arguments in a recent second analysis of the two randomized clinical trials PROSEVA and ACURASY of the impact of mechanical power on prognosis (11).

The study also empathizes the concept of threshold value of ventilator-related variables such as Pplat >20 cmH_2O and DP >10 cmH_2O and outcome in the era of low TV ventilation. Theses thresholds may help for designing futures randomized clinical trials or to more accurately estimate the risk of death.

Limitations of the study

Besides some limitations due to the design of the LUNG SAFE study (enrollment during winter, possible under-enrollment by centers, assumption of day 90 survival for

the patients discharged from the hospital before day 28 and potential bias due to quality data control), the study is still robust and points some potentially modifiable ventilator-related variables. However, if DP, PIP, RR and PEEP can be in some cases differently settled, in the same time they also reflect the severity of the disease by itself.

Conclusions

In a large, observational worldwide cohort study of mechanically invasively ventilated ARDS patients, RR and PIP are potential targets for improvement of outcomes. Furthers prospective interventional studies are warranted.

Acknowledgements

None.

Footnote

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

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