



Interpretation or misinterpretation of clinical trials on septic shock: about the ANDROMEDA-SHOCK trial

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In the ANDROMEDA study, Hernandez and colleagues evaluated whether a resuscitation strategy targeting the capillary refill time (CRT) normalization (CRT strategy) could be more effective to decrease 28-day mortality than a resuscitation strategy aiming at normalizing or decreasing lactate levels by 20% every 2 h (lactate strategy), in the first 8 h of septic shock (1). Resuscitation protocol was standardized in three successive steps: if the goal was not reached at the end of a step, the investigator had to go forward to the next step until the goal was reached. On the first step, the investigators had to test fluid responsiveness. The second step was a vasopressor test in order to increase mean arterial pressure (MAP) from 65 to 80–85 mmHg. The third step consisted in an inodilator test (low dose of dobutamine or milrinone, depending on the center). The authors made the hypothesis that the CRT strategy would decrease the mortality rate by 15% (from 45% to 30%) compared to the lactate strategy.

However, they observed a reduction of 8.5% in 28-day mortality in the CRT group, that did not reach “statistical significance” [hazard ratio, 0.75 (95% CI, 0.55 to 1.02); $P=0.06$; risk difference, -8.5% (95% CI, -18.2% to 1.2%)]. However, at day 3, the CRT strategy group had significantly less organ dysfunctions, assessed with Sepsis-related Organ failure Assessment (SOFA score) (2) [mean SOFA score, 5.6 (SD, 4.3) *vs.* 6.6 (SD, 4.7); mean difference, -1.00 (95% CI,

-1.97 to -0.02); $P=0.045$] suggesting a beneficial effect of the CRT strategy on organ dysfunction.

Despite the fact that the main outcome did not reach the statistical significance, clinician could consider that a reduction of 20% of the relative risk of mortality is clinically relevant. Furthermore, many reasons require us to be careful with interpretation of P values and confidence intervals (3,4). Indeed, all experimental and clinical studies are considered “positive” or “negative” according to an arbitrary p value cut-off of 0.05. One should remind that this only means that the study is considered as positive if the observed statistical difference between groups is less than 5% due to hazard. However, P value is today seriously challenged (5). In 2016, the American Statistician Association (ASA) made a statement on P values, the third statement was that “*scientific conclusions decisions should not be based only whether a p-value passes a specific threshold*” (6). In 2019, the same authors published an editorial entitled “*Moving to a World Beyond $P<0.05$* ” where they provide advice to use alternatives statistical methods to synthesize evidence across studies (i.e., meta-analysis, evidence reviews and Bayesian methods) (7). Other large trials, “negative on P value”, have also been subject to Bayesian approach (8). Hence, if a strict p-value cut-off aims to assess rigorously clinical trials with statistical significance, it is also the best way to misinterpret trials data. For all these reasons, the authors of this study

decided to test different analytic methods including post-hoc Bayesian and mixed logistic regression approaches to help the interpretation of the study (9).

Bayesian approach consists on a posteriori evaluation of the credibility of an event knowing new data (4). It is a mathematical way to reallocate credibility of an event or for some data to be explained.

The primary endpoint of the new analysis was 28-day mortality, and secondary endpoints were 90-day mortality and changes in SOFA score between groups at different time points (8, 24, 48 and 72 h). The analysis has been performed using different degrees of skepticism concerning the efficacy of the CRT-based resuscitation strategy (optimistic, neutral, null or pessimistic). The authors built a Bayesian hierarchical Bernoulli regression model for the primary endpoint adjusted for 6 variables: Acute Physiology And Chronic Health Evaluation 2 (APACHE2) score (10), admission SOFA score, baseline lactate level, baseline CRT, source of infection and admission center).

Concerning the primary endpoint (28-day mortality), they observed a beneficial effect of the strategy based on CRT normalization, compared to the strategy based on lactate clearance for all hypothesis but the pessimistic one [OR =0.62 (0.38–0.92) for the null hypothesis, OR =0.63 (0.41–0.9) for the optimistic hypothesis, OR =0.67 (0.43–0.96) for the neutral, OR =0.76 (0.5–1.09) for the pessimistic one, respectively]. When looking at the 90-day mortality, no beneficial effect of resuscitation based on CRT normalization was observed in all hypothesis. Patients treated in the CRT based resuscitation group had a higher probability to have a SOFA between 0–7 at 48 and 72 h [OR =1.55 (1.02–2.37) and OR =1.52 (1.00–2.24), respectively] compared to the lactate strategy group. However, the potential beneficial effect on organ dysfunction in the CRT strategy group is possibly due to the fact that patients in the lactate strategy had a higher MAP at 72 h (85 ± 13 vs. 80 ± 12 mmHg, $P < 0.01$) possibly requiring higher doses of norepinephrine [0.10 (0.06–0.21) vs. 0.1 (0.03–0.18) mcg/K/min, $P < 0.01$] which may have artificially increased the SOFA score.

Despite some limitations that can be avoided by standardizing the measurement method of CRT (11,12) a resuscitation based on CRT target is seducing and present many advantages (e.g., non-invasive, easily performed at the bedside, a rapid recovery with patient's improvement and is available even in resource limited-setting). Therefore, the authors have concluded from this Bayesian analysis of ANDROMEDA study that "*Peripheral perfusion-targeted resuscitation may result in lower mortality and faster resolution*

of organ dysfunction when compared to a lactated-targeted resuscitation strategy". However, they could also have concluded that a resuscitation protocol based on lactate clearance may result in higher mortality.

The strategy based on lactate decrease emerges from the surviving sepsis campaign's recommendations that suggests "*guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion*" (13). Nevertheless, the grade of this recommendation is weak, with a low quality of evidence. The goal of this strategy is to normalize or decrease lactate levels by 20% every 2 h by increasing arterial oxygen transport. To increase the arterial oxygen transport, the first line therapy is commonly intravascular volume expansion using crystalloids. This approach involves at least two wrong assumptions.

First, this strategy assumes the hypothesis that hyperlactatemia in septic shock is mainly due to tissue hypoperfusion with an imbalance between organ oxygen demand and blood oxygen supply. As recently recalled by Hernandez *et al.* there is few evidence that hyperlactatemia in septic shock is secondary to tissue hypoxia (14). Almost 15 years ago, Levy *et al.* elegantly showed by using microdialysis in the muscle of septic shock patients that hyperlactataemia was essentially due to exaggerated aerobic glycolysis through Na^+/K^+ -ATPase stimulation (15). Indeed, patients in septic shock have increased beta adrenergic stimulation, with increased glycogenolysis, resulting in glucose metabolization into pyruvate. This large amount of pyruvate exceeds the capacity of Krebs cycle leading to lactate production (16). In ANDROMEDA study, significantly more patients in the lactate strategy group received epinephrine infusion compared to CRT strategy group [35 (16.5%) vs. 21 (9.9%), respectively, $P < 0.01$]. Similarly, epinephrine increases lactate production through Na^+/K^+ -ATPase activation (17). This could explain in part that patients who did not reach the therapeutic goal in the lactate strategy (decrease in lactate level by 20% every 2 h) could have received unnecessary therapeutics (e.g., fluid infusion, increasing vasopressor or inodilator) leading to worst outcome.

The second assumption is that septic shock is associated with volume loss and that optimizing arterial oxygen transport would improve the outcome. Gattinoni *et al.* showed almost 25 years ago that increasing cardiac index at a supra-normal level did not improve outcome among critically ill patients (18). More recently, 3 multicentric studies evaluating the effect of the early goal directed therapy have failed to show a beneficial effect of this strategy (19). In a recent post-hoc analysis of patient from ALBIOS

study, Gattinoni *et al.* observed a U shape relationship between ScVO₂ and lactatemia, with two types of patients with hyperlactatemia at each extremity of the U curve: patients with high lactate level and a low ScVO₂ (24–62%) (supposing a deficit in oxygen delivery) and patients with high lactate level and a high ScVO₂ (82–98%) (suggesting a deficit in oxygen consumption). In this study, only one third of patient had a ScVO₂ below 70%, suggesting that patients with impaired tissue oxygenation are more common in septic shock (20). Therefore, trying to optimize oxygen transport with fluid bolus in this population seems illogical and potentially harmful. We know from cohort studies that a positive fluid balance and a high central venous pressure (CVP) are associated with organ dysfunction (i.e., acute kidney injury, acute respiratory distress syndrome) and mortality (21–25). Indeed, fluid overload leads to high CVP, which is opposed to venous return. Fluid overload, by increasing more CVP than mean systemic pressure (MSP) decreases organ perfusion pressure by decreasing driving pressure gradient (MSP–CVP) (26).

Septic shock can no longer be today a single “package” that would be the same for all patients. As well as targeted therapies for onco-hematology patients, therapies in ICU should also be customized to various subgroups of septic patients. Since a few years, after the golden age of the “early-goal directed therapy”, several authors and data have highlighted the interest of microcirculation. However, the goals of the resuscitation are still today subjects to debate. Instead of guiding the resuscitation on microcirculation disorders using CRT or skin mottling, some authors suggest to target microcirculation disorders (27). More than 15 years ago, De Backer *et al.* observed that the administration of acetylcholine restored microcirculation in the sublingual territory (assessed using an orthogonal polarization spectral imaging technique) (28). This observation suggests that an inappropriate vasoconstriction could participate to microcirculation disorders and could be reversed using vasodilators. This concept has been illustrated by Legrand *et al.* (27) as the “bottleneck-like vascular barrier” where an inappropriate arteriolar vasoconstriction decreases microcirculation blood flow. Legrand *et al.* make the hypothesis that using drugs targeting this inappropriate vasoconstriction could improve microcirculation perfusion and then organ dysfunction. In order to test this theory, prostacyclin analogue administration has been tested in patient with septic shock with high dose of norepinephrine and persistent peripheral circulation disorders (29). This strategy showed promising results, however, the absence

of control group does not allow us to conclude on their effectiveness in this indication. This is actually tested in an ongoing multicentric randomized controlled clinical trial comparing ilomedin to placebo in patients with persistent peripheral circulation disorders (NCT03788837).

In summary, this post-hoc analysis of ANDROMEDA study suggests that CRT strategy compared to lactate strategy improves 28-day survival. To our opinion, this study highlights the fact that septic shock patient’s resuscitation should not be guided by serum lactate levels but by microcirculatory endpoints such as CRT. Further studies should focus on tailored resuscitation targeting microcirculation.

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