

## EDITORIAL



# SUPERNOVA: will its energy trigger the formation of a new therapeutic star?

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In 1983, Luciano Gattinoni had the vision of a ‘motionless lung’ [1] with the help of an extracorporeal carbon dioxide elimination concept. At that time the term VILI (ventilator induced lung injury) was still far beyond the horizon and no intensivist or respiratory therapist anticipated the consequences of the ARDS Network study from 2000 [2], which began to hold a mirror up to the intensive care community in terms of a protective approach to the injured lung. Did no intensivist or respiratory therapist really anticipate this? The answer is just a few around Gattinoni who stated in 1978 “that patients treated with mechanical ventilation ultimately die, either of the underlying disease process or of complications of pulmonary therapy with mechanical ventilation” [3]. In the late 1990s, a long and partly successful story began on lung protective strategies aimed at saving lives by preventing the deleterious effects of artificial ventilation. Why only partly successful? The answer seems simple, but it is not: the reduction of tidal volume and inspiratory pressure levels was helpful, but it was not the definitive solution to the dilemma between the necessity of mechanical ventilation (to guarantee a life-saving gas exchange) and the attenuation of its harmful effects. In other words, the low tidal volume strategy combined with a limitation of inspiratory pressures went in the right direction, but the clinical scientists continued to ask: “Is there a safe upper limit to inspiratory plateau pressure in patients with ALI/ARDS?” [4].

In 2009, stimulated by the CESAR trial [5], the technique of extracorporeal membrane oxygenation (ECMO) celebrated a triumph, which continues to this day [6]:

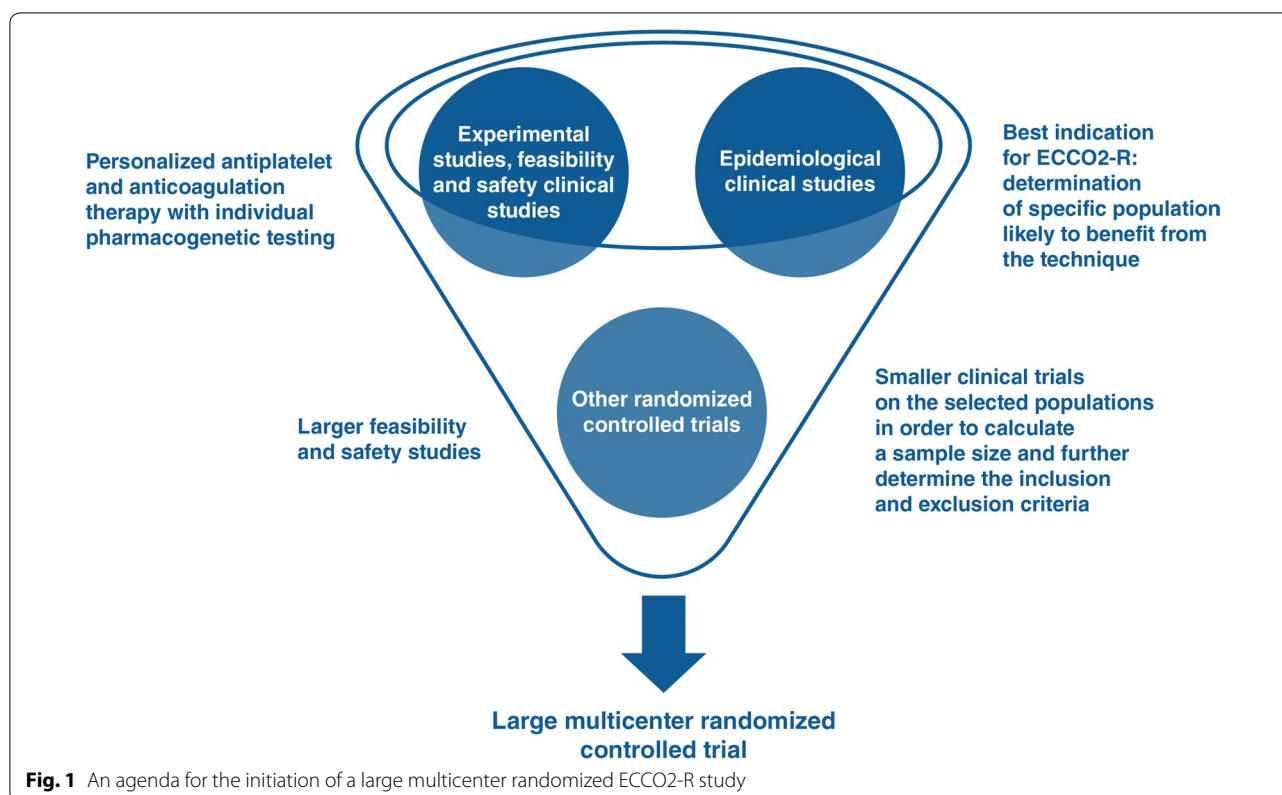
the concept of extracorporeal carbon dioxide removal (ECCO2-R), the little sister of ECMO, reanimated Gattinoni’s vision of ‘motionless lungs’. In contrast to full-blown ECMO, the ECCO2-R technique is characterized by lower extracorporeal blood flow rates between 400 and 1000 ml/min in combination with smaller cannulae promising less complications [7]. The effectiveness of such a strategy regarding carbon dioxide removal in substantial amounts has been demonstrated in several experimental studies [8, 9]; with this technique, Gattinoni’s vision was modified to the possibility of ‘super-protective’ [10] ventilation allowing ‘near-motionless’ lungs. The first controlled trial with the use of ECCO2-R combined with the concept of lung protection randomized 79 patients with ARDS to a very low tidal volume (VT) strategy [ $\approx 3$  ml/kg predicted body weight (PBW)] combined with pumpless arterio-venous ECCO2-R, or to lower ARDS Network standard VT ventilation ( $\approx 6$  ml/kg PBW) without the extracorporeal device [11]. In that trial, the concept of ventilation with very low VT appeared to work, but some adverse events were observed. Although the overall number of ventilator-free days and mortality rates were not different between the two intervention groups, a post hoc analysis suggested fewer ventilator-free days at 60 days with ECCO2-R in patients with severe hypoxemia ( $\text{PaO}_2/\text{FIO}_2$  ratio  $< 150$ ).

Another feasibility trial of ECCO2-R (SUPERNOVA) aiming at (ultra)-protective ventilation was recently published in *Intensive Care Medicine* [12]. This trial enrolled 95 patients with ARDS; the primary endpoint was the proportion of patients achieving an ultra-protective level of low VT ventilation (reduction of VT to 4 ml/kg and a target  $P_{\text{plat}}$  of  $\leq 25$  cmH<sub>2</sub>O) using various veno-venous ECCO2-R devices allowing extracorporeal blood flows between 300 ml/min (lower extraction) and 1000 ml/min (higher extraction). The primary endpoint was achieved within 8 h by 78% and within 24 h by 82% of

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the participants. Again, ECCO2-R-related adverse events were observed (catheter displacement or infectious complications in 2% and membrane lung clotting or bleeding in 14%, highlighting the coagulation/anticoagulation balance as most problematic).

Is evidence for feasibility (and safety!) of ECCO2-R provided with these results? Feasibility is defined as a “state or degree of being *easily* or *conveniently* done” [13]. It is debatable whether a substantial number of participants with coagulation problems—be it clotting or bleeding—allows a statement that ultra-protective ventilation using ECCO2-R devices is easily or conveniently applied. The unsolved problem of a targeted balance of anticoagulation—allowing low extracorporeal blood flow and simultaneously avoiding clotting or bleeding complications—requires further careful experimental and clinical studies before planning a “well-designed randomized clinical trial” (Fig. 1), as requested by the authors of the SUPERNOVA trial paper. It may be that a personalized antiplatelet and anticoagulation strategy is needed [14]. With the development of such newer strategies using individual pharmacogenetic and pharmacodynamic testing, important information could be provided to assist intensivists with the best antiplatelet and anticoagulation therapy, which could replace the ‘good old’ activated partial thromboplastin time (aPTT) as a non-specific and

insensitive marker for optimal coagulation balance in the individual ECCO2-R patient. Similarly, the selection of the population most likely to benefit from ECCO2-R therapy is crucial; from no-ARDS patients to mild or moderate or moderate to severe ARDS patients, further studies are still needed to inform about the better population.

SUPERNOVA is not yet ready to trigger a new star—a lot of work must be done before a next ‘feasibility and safety’ study. Supernovas can indicate the sudden gravitational collapse of a massive star’s core, or they can trigger the formation of a new star. We hope the latter will happen!

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#### Compliance with ethical standards

#### Conflicts of interest

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