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Improving donor management and transplantation success: more research is needed

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At the time of writing, million of patients worldwide are on a waiting list for a lifesaving organ transplant, 123,833 in the United States [1] and nearly 63,000 in the European Union [2]. However, the number of organs that become available each year falls far short of providing for those in need, and thousands die each year waiting for transplantation. There are clearly many missed opportunities in the severely brain-injured population, many patients dying without the care teams pursuing the chance to give life to others through donation [3, 4].

Donation after brain death (BD) still remains the main source for organs, and it carries the advantage of being performed in a relatively controlled setting with ongoing perfusion and oxygenation. Death as determined by neurological criteria has been accepted worldwide [5, 6], and strict criteria exist for proper determination [7]. However, delays in the diagnosis of BD have been associated with decreased rates of organ donation, as well as decreased

viability of organs transplanted [8]. One of the obstacles is the inherent difficulty that families have dealing with these highly stressful situations, in which they are trying to balance the desire to be altruistic with their need to grieve the often sudden loss of their loved one [9].

The reasons for decreased organ viability are multiple, likely related to secondary effects from the occurrence of BD itself. BD induces a pro-inflammatory state with a massive catecholamine release with ensuing hormonal, metabolic and hemodynamic effects. BD has been associated with renal injury [10]. Hormonal effects include decreases in serum cortisol, insulin, thyroid hormone and other pituitary hormone levels, and non-randomized studies have suggested an improvement in hemodynamic status with hormone replacement [11]. This has not been confirmed in randomized controlled trials (RCT), and the evidence for their use is poor.

Hand in hand with the hormonal alterations is the impairment in the hemodynamic system, affecting organ perfusion and sometimes even leading to cardiac arrest [12]. Hemodynamic instability following BD is frequent and can usually be attributed to multiple causes, as a sympathetic surge preceding medullary damage in BD leading to a cardiac damage, a spinal cord infarction resulting in loss of sympathetic tone and further hypotension, and pituitary dysfunction and consequent diabetes insipidus. Therefore, many guidelines and protocols aim at repairing hormonal imbalances and maintaining hemodynamic stability [13, 14], although strong data to support this practice are lacking. Physicians and organ procurement organizations (OPO) have thus based their practices on hypotheses and non-randomized clinical data. There has been a call to arms for improved donor management that will be evidence-based and effective [15].

In an article recently published in *Intensive Care Medicine*, Al-Khafaji et al. [16] reported the results of the Monitoring Organ Donors to Improve Transplantation

Fig. 1 Summary of the treatment aims in the potential organ donor and the evidence coming from RCT. For most of the targets, there is no available guidance or negative guidance from RCT, and most are small RCT

Results (MONITOR) trial, a protocolized fluid therapy in brain-dead organ donors in an effort to improve organ viability and survival in recipients. Using eight organ procurement organizations, they randomly assigned donors to either protocolized or usual care; the protocolized therapy algorithm targeted cardiac index (CI), mean arterial pressure (MAP) and pulse pressure variation (PPV) as variables reflective of the hemodynamic status of the donor, and whether fluid therapy was warranted. The protocol was ultimately implemented in 76 % of those randomized to the interventional arm. In the end, there was no statistically significant difference between the arms: 3.39 organs per donor with protocolized care, versus 3.29 with usual care. In a modified intention-to-treat analysis, there remained no significant difference between the groups. The mortality rate at 1 year was the same between the groups (7.8 vs. 7.9 %).

At first glance, there appears to be little positive that can be taken from this trial. But it is important to recognize the impacts of the trial, as well as its limitations, that may open the door for future trials. First and foremost, the trial confirms the possibility of conducting large, good RCT in the field of organ donation that so badly needs clinical data. Without such trials, we cannot truly know whether our current interventions actually

work, or might be detrimental to donor management and organ viability. Secondly, the authors performed a “responder analysis,” in which the donors in the protocolized arm were deemed to have responded to the fluid protocol and were analyzed separately; this subgroup analysis showed a nearly significant difference in the number of organs transplanted per donor, an increase of 0.58 ± 2.07 (95 % CI 0.02–1.19, $p = 0.059$). Although subgroup analyses are not “take-home messages,” they do give an indication for the right type of groups to study in the future as a priori hypotheses.

The limitations of the trial are notable. The choice of hemodynamic parameters was limited to only CI, MAP and PPV, and, although these are reasonable choices, there may be other factors that might guide fluid management more accurately or appropriately, such as the use of pulmonary arterial catheters with other hemodynamic markers. The device used to measure CI, MAP and PPV was complicated, requiring education and training at multiple sites. Obviously, critical care units are adept and comfortable adapting to new technology, but this device appears to have been particularly troublesome, with zero participants classifying the device as “easy” to use. The protocol was implemented in 76 % of the subjects randomized to intervention, meaning that 24 % never

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