Direct Peritoneal Resuscitation Improves Inflammation, Liver Blood Flow, and Pulmonary Edema in a Rat Model of Acute Brain Death

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BACKGROUND: Brain death in organ donors alters central hemodynamic performance, impairs physiology, exaggerates inflammation, and causes end-organ microcirculatory dysfunction and hypoxia. A new treatment, direct peritoneal resuscitation (DPR), might improve these derangements in acute brain death (ABD).

STUDY DESIGN: We studied a standardized rodent model of brain death with matched controls to assess the efficacy of DPR as a resuscitation strategy after ABD. Anesthetized Sprague-Dawley rats were randomized as follows: ABD (supradural balloon inflation) with minimal IV fluid (IVF; 2 mL/h, n = 12); ABD + adequate IVF (5 mL/h, n = 12); ABD with aggressive IVF (goal: mean arterial pressure [MAP] >80 mmHg, n = 15); or ABD + IVF + DPR (goal: MAP >80 mmHg, n = 12). Ventilation support, IVF, and DPR were started at loss of reflexes, and MAP, heart rate, and effective hepatic blood flow were recorded.

RESULTS: High IVF and DPR prevented mortality (0%) compared with low IVF (81.8%) or mid IVF (16.7%). Effective hepatic blood flow was decreased in low and mid IVF (2.8 ± 0.3 mL/min/g body weight and 4.0 ± 0.5 mL/min/g body weight, respectively) vs baseline, but was stable in high IVF (6.2 ± 0.5 mL/min/g body weight; NS) or improved with DPR (8.6 ± 0.7 mL/min/g body weight). The high-IVF group had significant organ edema, which was prevented in the DPR group. The mid-IVF and low-IVF groups had higher serum markers of organ injury compared with high-IVF or DPR groups. The high-IVF group had elevated inflammatory cytokines compared with the DPR group.

CONCLUSIONS: Direct peritoneal resuscitation improved survival and effective hepatic blood flow, required less IVF to stabilize blood pressure, prevented organ edema, and normalized fluid electrolyte balance compared with IVF-alone groups. Direct peritoneal resuscitation in animals reduced inflammatory response after ABD compared with IVF-alone controls. These data suggest a potential role for DPR in organ donors to stabilize donors and possibly increase the number of organs suitable for transplantation per donor. (J Am Coll Surg 2014;219:79–89. © 2014 by the American College of Surgeons)

Organ transplantation is the curative treatment for multiple end-stage diseases, unfortunately, the availability of organs for transplantation has not been sufficient to meet the high demand. Nationally, the number of patients waiting for a transplant is >100,000, and the number of organ donors is approximately 8,000. Problems with organ procurement include family refusal to donate, inability to recognize slowly evolving brain death, and physiologic instability after brain death.[1,2] This has led to strategies for expanding the limited deceased donor pool, increasing living organ donation, and pushing to increase organ donation after cardiac death.[1,2] Although these strategies expand the pool of potential organ donors, donation of thoracic organs and liver continue

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Abbreviations and Acronyms

ABD = acute brain death
ALT = alanine aminotransferase
DPR = direct peritoneal resuscitation
EHBF = effective hepatic blood flow
$[Gal]_{SS}$ = steady-state systemic galactose concentration
IL = interleukin
IVF = IV fluid
MAP = mean arterial pressure

to be a problem across the nation. Donor management goals, or the aggressive medical management of hemodynamic instability in the brain-dead donor before organ procurement, have been successful in increasing the number of organs donated per donor.[3] This simple idea has opened the realm of research into how manipulation of the brain-dead donors' physiology can increase or enhance the number and functions of the organs donated at time of procurement.

Brain death is associated with substantial hemodynamic and hormonal instability, as well as an increase in inflammatory processes throughout the body. After brainstem herniation, an autonomic storm occurs, lasting hours, which causes transient increases in systemic vascular resistance, cardiac force of contraction, and cardiac output.[4,5] After the catecholamine surge, sympathetic vascular tone decreases substantially, resulting in profound hypotension and organ hypoperfusion.[4] Unfortunately, conventional resuscitation with blood products, crystalloid, and vasopressors, although allowing a restoration of central hemodynamics, sacrifices peripheral organ perfusion.[3,6-9] This organ hypoperfusion can lead to tissue hypoxia, cellular necrosis, and inflammation, which can compromise graft viability and reduce function in the organ recipient.[4]

Additionally, changes in electrolyte composition in the serum and cells due to the initiation of hyperosmolar therapy before brain death and in response to physiologic derangements can have a profound effect on organ-specific blood flow. Endothelial and cellular edema can lead to reduced capillary diameter and a reduction in effective blood flow to the organs. Also, the hypernatremia in potential donor organs can cause intracellular water accumulation, cell lysis, and potential organ damage when the organs are transplanted in patients with normal sodium levels.

New and better treatment options for organ donors to preserve organ function are needed to increase the suitability of organs for donation. Direct peritoneal resuscitation (DPR) is a novel treatment for hypovolemic shock that reverses visceral organ hypoperfusion and dysfunction to prevent development of multiple organ failure in hemorrhagic and septic shock models. In resuscitated hemorrhagic shock, DPR prevents edema formation, prevents systemic inflammatory response syndrome, stabilizes intestinal and liver blood flow, and improves survival in animals. In a small nonrandomized clinical trial in trauma patients with hemorrhagic shock, DPR decreased time to primary wound closure and prevented septic complications.[10] Acute brain death (ABD) in trauma patients presents a similar low-flow condition in the visceral circulation, and we propose that DPR might provide stability to visceral blood flow in ABD with ventilator and IV fluid (IVF) support similar to that found in resuscitated hemorrhagic shock.

In the current study, we hypothesized that liver perfusion, organ function, inflammatory cytokine expression, and organ-specific edema are worsened in a slow-onset model of ABD, and that the addition of DPR using warm 2.5% Delflex solution (Fresenius) would reverse that event and minimize end-organ dysfunction. To test this hypothesis, we studied a rat model of ABD produced by supradural angioplasty balloon catheter inflation to increase intracranial pressure.

METHODS

Animals

Rats were maintained in the American Association for the Accreditation of Laboratory Animal Care—approved Veterinary Medical Unit of the Robley Rex Veterans Affairs Medical Center in Louisville, Kentucky. The research protocol was approved by the Institutional Animal Care and Use Committee and the Biohazard Safety Committee at the Robley Rex Veterans Affairs Medical Center. Fifty-one Sprague-Dawley rats (198 to 222 g) were acclimated for 2 weeks before experimental use, during which time the animals received standard rat chow (20 g/d) and water ad libitum. Rats were randomly assigned to one of the following groups: ABD plus minimal IVF resuscitation (low IVF, n = 12); ABD plus fixed IVF resuscitation (mid IVF, n = 12); ABD plus aggressive IVF to maintain blood pressure >80 mmHg (high IVF, n = 15); or ABD plus IVF management and DPR (IVF + DPR, n = 12). Direct peritoneal resuscitation was given as 30 mL warm (37.0°C) 2.5% Delflex solution by intraperitoneal injection at the time of the start of IVF and mechanical ventilation. The electrolyte composition per liter of the Delflex is as follows: dextrose 2.5 g, sodium chloride 576 mg, calcium chloride 26.1 mg, magnesium chloride 15.4 mg, sodium lactate 353 mg, and sodium bicarbonate 29.4 mg. This concentration was chosen based on earlier laboratory and clinical studies outlined in this article.