Critical Care Management of the Potential Organ Donor

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Organ donation and transplant rates vary widely across the globe, with the gap between requirements and available organs continuing to be a significant problem in many countries.[1–3] This ongoing shortage has driven the creation of numerous initiatives to educate the public of the need for organ donation and to attempt to dispel urban and religious concerns over the ethics and appropriateness of organ donation.[2,4] In the United States, the Revised Uniform Anatomical Gift Act requires organ procurement organizations (OPOs) and donor hospitals to have polices and guidelines in place to make sure all possible donors are appropriately evaluated and efforts are maximized to increase donation.[5] As a result of these initiatives, 95% of US citizens state they "support or strongly support" organ donation, yet only 60% of eligible donors are registered donors.[6] Internationally, the gap between organ supply and demand has been addressed through public outreach and education campaigns, incentives to encourage donation, enactment of presumed consent (opt-out) legislation, and other programs. Despite these nonclinical initiatives, an increased reliance on expanded or extended criteria donation (ECD), including donation after circulatory death (DCD), has been required to increase organ availability in many countries yet still falls short of the increasing demand.[2] For anesthesiologists who manage the organ donor in operating rooms and intensive care units (ICUs), it is critical to implement and monitor donor management programs that support

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improvement in the number of organs available for transplant per donor and subsequent graft function.

Currently, the majority of donated organs retrieved for transplantation continue to come from donors who have met criteria for donation after neurological determination of death (DNDD), although DCD has shown significant increases over the last decade. Recently, it has been shown that comanagement of potential donors using the expertise of the OPO, transplant team, and critical care practitioners can improve organ procurement rates and potentially impact graft function.[7–12] As anesthesiologists become increasingly involved in donor management, it is imperative that the same rigor that is applied to the care of living patients be employed in the care of organ donors. Standardized practices and guidelines addressing the management of potential organ donors are limited. A Canadian publication based on the 2004 forum, Medical Management to Optimize Donor Organ Potential, stands as one of the initial attempts to develop expert consensus recommendations on critical care management of the potential multiorgan donor. More recently, the Society of Critical Care Medicine (SCCM) and the American College of Chest Physicians (ACCP) established a working group of experts in critical care medicine, organ transplantation, and donor management to create a consensus document on management of the potential organ donor in the ICU.[13]

Given their pivotal role in family communications, donor management, and care coordination, anesthesiologists in the operating room and ICU have the potential to directly impact organ shortage and transplantation outcomes. This review will focus on aspects of perioperative donor management that have the potential to improve donation outcomes with an emphasis on DNDD. The process of determining death[14,15] and the DCD[16] process has been well described in recent reviews and will not be discussed in detail. In addition, given the increasing use of ECD organs, it is vital that physicians have an understanding of the extended criteria and contraindications to organ donation, many of which continue to evolve.

■ Critical Care Management and Donor Suitability

Donor organ availability in the United States has continued to worsen as noted in the 2012 Annual Report from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients.[17] This shortage has led many transplant programs toward the use of a donor pool previously considered to be unsuitable, including donors with known or potentially transmissible disease and malignancy. This pool also includes donors deemed to have higher-risk

organs based on marginal or extended selection criteria and those presenting for DCD.[18,19] The use of ECD requires an assessment of the potential risks and benefits of transplanting organs from marginal donors weighed against the urgency of transplantation for the candidate. In the United States, the overall quality of donated livers appears to be declining in the last decade with an increased prevalence of advanced donor age, elevated body mass index (BMI), diabetes, and DCD increasing the need for predonation optimization.[20] This optimization process includes intensive monitoring and guided resuscitation of the donor to maintain organ function and maximize the number of organs suitable for transplantation up through the point of procurement.

Extended Criteria Donation (ECD)

Efforts to address the critical shortage of organs required to meet increasing demand have led to the use of ECD as a more frequent source of organs for transplantation. (Table 1).[21,22] An ECD kidney is defined as one with a > 1.7 relative risk for allograft failure. Although the criteria for ECD kidneys have been standardized by the Unified Network for Organ Sharing (UNOS), a universal definition for an ECD liver has not been established. Advanced donor age (above 60 y), steatosis, and prolonged ICU stay appear to be the most important criteria defining ECD livers.[19] The presence of multiple criteria increases the likelihood of a poor outcome after transplantation and decreases the likelihood of an ECD organ being transplanted;[20,23] however, this must be weighed against risk in postponing transplantation for the failing candidate.

To address the need for aggressive management of ECD in the United States, many OPOs have developed donor management guidelines (DMGs) in an attempt to increase the number and quality of organs transplanted per donor. These DMGs are evidence-based or expert opinion-derived physiological and management parameters reflecting a targeted, normal hemodynamic, respiratory, acid-base, electrolyte, and renal status in the donor. An example of 1 organization's DMG targets is shown in Table 2 and others are discussed in more detail below. Taken as a package, achievement of these targets before DNDD has been associated with an increase in the number of organs transplanted per donor based on standard criteria for donation.[10,25,26] The use of these established DMGs in ECD also appears to improve organ procurement rates.[27] Patel and colleagues found that achieving 7 of 9 DMG endpoints in ECDs (excluding DCD), as defined by the UNOS kidney definition above, before organ recovery was an independent predictor of 3 or more organs transplanted per donor [odds ratio = 1.90 (95% confidence interval, 1.35-2.68)]. The percentage of ECD resulting in ≥ 3 organs

Table 1. *Extended Donation Criteria for Liver and Kidney Donors*[21,22]

Liver	Kidney
Age > 60 y	Age > 60 y
Serum sodium > 165 mmol/L	Age 50-59 with 2 of the following:
Intensive care unit stay with ventilation > 5-7 d	Serum creatinine > 1.5 mg/dL
Aspartate aminotransferase > 90 U/L	Cerebrovascular accident as cause of death
Alanine aminotransferase > 105 U/L	History of hypertension
Serum bilirubin > 3 mg/dL	
Body mass index > 30 kg/m^2	
Steatosis	

transplanted was found to increase from 35% to 54% in donors achieving the targeted bundle of DMGs.

The time point at which DMGs are achieved may also play an important role in improving organ procurement rates. In 2 studies looking at standard criteria for donation and ECD, respectively, only 15% of potential donors met a targeted DMG bundle at the time of authorization and 30% to 45% immediately before recovery.[25,27] Interestingly, meeting the DMG targets before authorization did not result in an increase in the number of organs transplanted per donation compared with meeting them at the time of recovery. In a study looking at ECD, donors who had a significant change in the number of individual DMGs met (from referral to organ recover) were more likely to yield >3 organs transplanted per donor. Although not specifically evaluated, it is possible that a modest delay in organ procurement to allow for aggressive resuscitation targeting a DMG bundle may be preferred to recovery at the earliest time, particularly when the donor does not meet multiple DMGs at the time of authorization. This, of course, must be balanced against other considerations for early versus delayed organ recovery since some of the improvement may be due to improvement in the donor's

Table 2. *Donor Management Goals*[24]

Goal	Target
Mean arterial pressure	60-100 mm Hg
Central venous pressure	4-10 mm Hg
Ejection fraction	> 50%
Vasoactive infusions	No more than 1 running at low dose
Arterial pH	7.3-7.45
P_aO_2/FiO_2	> 300 mm Hg
Serum sodium	135-155 mEq/L
Blood glucose	< 150 mg/dL
Urine output	1-3 mL/kg/h over 4 h

FiO_2 indicates fraction of inspired oxygen.

underlying condition rather than active management targeting predetermined critical care endpoints.

In addition to its impact on the number of organs available for transplantation, DMGs may also impact the quality of those transplanted organs. In 2013, 30% and 47% of deceased kidney donors were from ECD in Europe and France, respectively.[28,29] During that same time period, ECD accounted for 16.6% of US kidneys with many potentially harvested organs rejected likely because of concerns about allograft and recipient prognosis.[17,30,31] Malinoski et al[24] found that achieving 7 of 9 DMGs similar to those in Table 2 was associated with a 50% reduction in delayed graft function (DGF), a likely marker for graft survival and 1-year and 5-year mortality. The reduction in DGF was seen only in donors meeting DMG criteria at the time of consent. No difference was seen in donors meeting DMG criteria at the time of recovery, which may reflect the importance of meeting these criteria earlier in the management of the potential organ donor, unlike the impact of meeting DMG criteria at the time of recovery on the number of organs transplanted per donor. As there are multiple factors contributing to DGF, including donor tissue quality, brain death (BD) and related stress, preservation variables, immune factors, and recipient variables, not all of these are impacted by focusing on donor management. Nonetheless, ECD will continue to be an increasing part of the donor pool, and prerecovery optimization appears to be an additional target for improving subsequent graft function and number of organs transplanted per donor.

Donors With Documented Infection

Decisions regarding the use of organs from donors with active or suspected infections should take into account the urgency of transplantation for the candidate, laboratory data, and treatment options as well as the availability of alternatives. Any treatable, active infections in the donor or recipient should be addressed and, ideally, resolved before procurement where possible.[32–37] There are no universal guidelines for the management of ongoing infections such as bacteremia, meningitis, encephalitis, or pneumonia, although recent recommendations are beginning to address some of these considerations.[13] Bacteremia and/or bacterial sepsis should not be considered an absolute contraindication.[13] The finding of positive blood cultures in prospective organ donors is not unusual, and documented transmission to recipients is extremely rare,[35,38] with limited case reports of early posttransplant sepsis or mycotic aneurysm formation at the site of vascular anastomoses.[39–42] If bacteremia is documented in a donor, 48 hours of treatment with pathogen-specific antibiotics should be considered before organ recovery. Delaying the procurement process

to complete the full 48 hours should be considered where feasible.[13] In those cases where recipients received organs from donors whose blood culture positivity was not discovered until after procurement, mortality and graft dysfunction does not appear to be greater compared with that in recipients of noncontaminated organs, provided the recipients are treated with 7 to 14 days of antibiotics specific to the recovered pathogen.[35,43,44]

Another group of patients frequently presenting as potential organ donors are those with bacterial or viral meningitis. In the donor with documented or presumed bacterial meningitis, appropriate antibiotic therapy before procurement and continuation of antibiotics for the recipients has not been associated with cases of donor transmission of infection or compromised survival. Donors with bacterial meningitis should receive a course of appropriate antibiotic therapy for 24 to 48 hours before procurement and this should be continued in the recipient for 5 to 10 days.[13] With respect to viral meningitis, transmission of lymphocytic choriomeningitis virus and rabies virus has been reported from donors to solid-organ transplant recipients.[45,46] These viral infections were not detected in the donor before transplantation, and were only found on follow-up when multiple recipients became symptomatic. The current recommendation is that organs should not be procured from patients with undiagnosed febrile illnesses, encephalitis, viral meningitis, or flaccid paralysis of unknown etiology.[13]

For donors who are seropositive for hepatitis C virus (HCV+), there is no absolute contraindication to organ donation as these organs may be directed for use in HCV+ recipients. This applies to both liver and kidney transplantation. Liver transplantation from HCV+ donor to HCV+ recipient, when adjusted for donor and recipient characteristics, shows no difference in graft or recipient survival.[47] Although there is evidence that long-term outcomes of HCV+ recipients who receive kidneys from HCV+ donors are slightly worse than outcomes when receiving an HCV− donor kidney,[48] there does not appear to be a difference in short-term recipient survival or graft function.[48–53] In addition, wait times for these recipients are significantly shorter.[51] A different consideration arises when the recipient has been treated for HCV and is currently HCV RNA negative. Concerns for reintroducing HCV infection in this subpopulation may lead to not transplanting the organ from a HCV+ donor. From a donor management perspective, there are no specific therapies indicated before procurement.

Similarly, management of potential donors with prior hepatitis B virus (HBV) infection and no evidence of active disease should be no different than that for donors without prior exposure. These donors should be positive for HBV core antibody (anti-HBc+) but negative for HBV core antigen (HBcAg−) and surface antigen (HBsAg−). Recent

guidelines from the American Society of Transplantation and the Canadian Society of Transplantation for Management of Solid Organ Transplantation from HBV-Positive Donors state that, regardless of donor HBV surface antibody (anti-HBs) status, donors who are HBsAg− and anti-HBc+ should be considered for all adult transplant candidates after an individualized assessment of the risks and benefits and appropriate recipient consent.[54] Transmission of HBV in this setting continues to be reported (liver > kidney > cardiac), necessitating appropriate recipient management including HBV immunization and antiviral prophylaxis as indicated.[54] The use of organs from HBsAg+ donors is less well studied, and many OPOs and transplant centers continue to avoid their use.

Donors at High-risk of Infection

Although known human immunodeficiency virus (HIV) infection has been considered an absolute contraindication for donation,[55] concern exists regarding potential transmission through organ transplantation from donors with a history of high-risk behavioral criteria (as well as HBV and HCV) developed by the Public Health Service.[56] Potential donors in these high-risk behavior groups who test negative by enzyme-linked immunosorbent assay, with or without nucleic acid amplification testing (NAT), should not be excluded from consideration for donation. In a 2011 survey of US OPOs, 98% performed HIV NAT on high-risk donors and 68% on all potential donors.[57] Similar rates were reported for HBV and HCV NAT. When making a decision regarding the use of this donor pool (high-risk behaviors and negative NAT), transplant teams must weigh the urgency for transplantation against the very small risk for occult HIV. In addition, the transplant team should review their concerns and potential risk during the consent process with the prospective recipient.

In 2013, the HIV Organ Policy Equity Act was enacted in the United States to support research efforts in determining whether transplanting organs from HIV-positive donors into HIV-positive recipients could further expand the donor pool.[58] To date, this practice is not widely available, but may offer an additional source of donation for this subset of recipients on transplant waitlists. At least 1 US center is currently approved by UNOS to perform HIV-positive to HIV-positive organ transplants with the first kidney and liver transplants occurring in 2016.

Donors With History of Malignancy

Guidelines have been developed by multiple agencies for the use of organs from donors with a history of malignancy.[13,59,60] There is a small,

but real, risk of cancer transmission following transplantation of organs from a donor with a history of cancer that must be balanced against the risk of dying while awaiting transplant. For example, between 2001 and 2010 in the United Kingdom, 15 of 30,765 transplant recipients (0.05%) developed donor-transmitted cancers with 3 related deaths.[61] During the same time period, over 4000 patients died while awaiting transplantation.[62] Use of these organs assumes that the malignancy was treated correctly, appropriately followed up, and that a thorough evaluation for recurrence at the time of recovery through thoracotomy and laparotomy was performed.[63]

The type of cancer and disease-free period should be considered when making decisions regarding consideration for donation. The Israel Penn International Transplant Tumor Registry (IPITTR), an established and comprehensive registry of transplant-associated malignancies, has been used to identify tumors with high rates of transmission including choriocarcinoma and malignant melanoma.[64,65] As the registry is based on voluntary reporting of index cases and may fail to appreciate the entire at-risk population, the high rates have been suggested to reflect reporting bias and may be an overestimation of the true risk. In donors with an extended disease-free interval after curative surgery, donation may still be considered after review of prior pathology and thorough evaluation. More recently, a systematic review looking at donor cancer transmission in kidney transplant recipients identified renal cancer, melanoma, lymphoma, and lung cancer as the most commonly transmitted donor cancers, with melanoma and lung cancer having the worst overall survival.[66]

The SCCM/ACCP consensus statement does not consider prior malignancy an absolute contraindication.[13] Determination of donor suitability should be done in conjunction with the involved OPO and transplant centers. In the case of central nervous system malignancies, evidence supports the use of organs from donors with an established diagnosis and grading. As the malignancy is frequently active or recent and is often the cause of death, it is unlikely that there is extraneural spread. Current recommendations state that individuals with central nervous system tumors of low histologic grade (grades I-II) and no history of craniotomy, brain irradiation, or ventricular shunts can be considered suitable for organ donation. Potential donors with higher grade malignancies (grades III-IV) and/or those who have undergone craniotomy or placement of ventriculoatrial or ventriculoperitoneal shunt should be evaluated jointly with the involved OPO and transplant centers for suitability. In all cases, a careful, individualized risk-benefit assessment for use of organs from a donor with a history of malignancy should be done and presented to the candidate before transplantation with full, informed consent obtained before proceeding.[67]

■ General Considerations

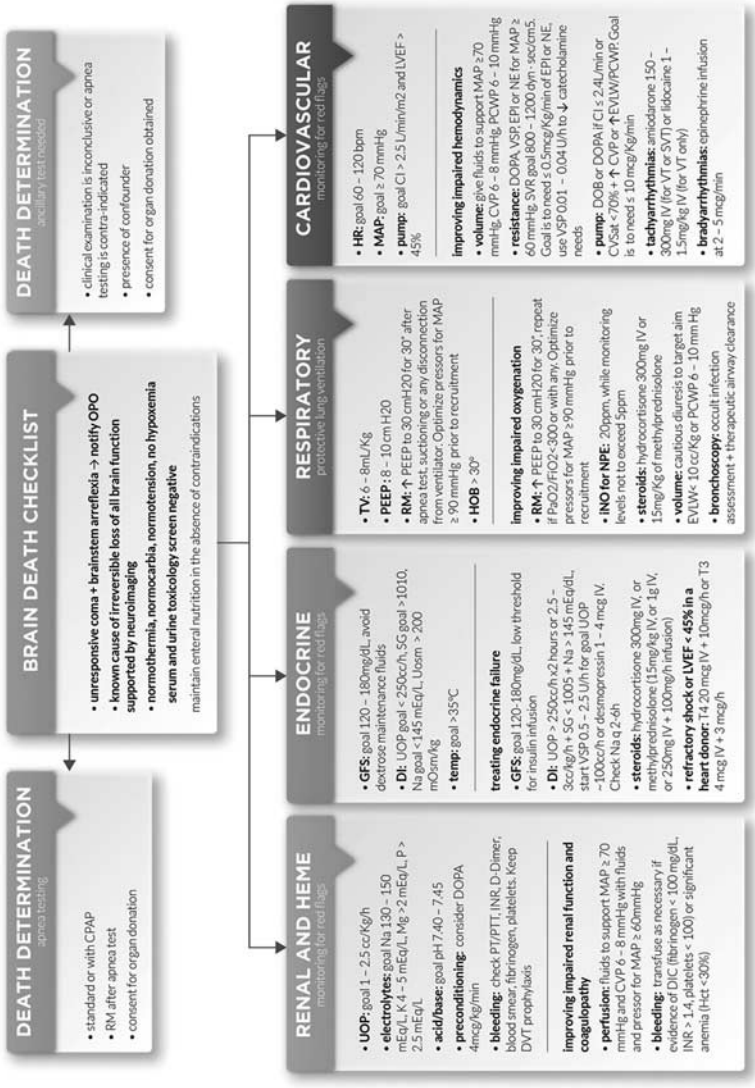
Organ preservation begins with the optimal management of the potential organ donor and continues during procurement, storage, and transport. Controversy remains regarding the most appropriate time from diagnosis to procurement for DNDD. There is increasing evidence that taking time to stabilize the donor and institute measures to optimize organ function before organ retrieval may be better than proceeding to procurement in the setting of ongoing inflammatory and hemodynamic compromise.[68] The cascade of multisystem dysfunction resulting from BD requires a systematic approach to the DNDD donor. Figure 1 provides a flowchart with key DMGs for DNDD.[69]

Ventilation Management

As noted in Table 2, DMGs include ventilation and oxygenation goals in the general management of the potential organ donor. For DNDD candidates, the potential for lung injury is very high because of pathophysiological changes related to BD and ICU-related complications. This places increased importance on donor lung preservation and optimization as part of the DMGs in an attempt to at least preserve, if not improve, the lung quality of potential donors. The inflammatory cascade associated with BD exposes donors to mediators that can exacerbate pulmonary inflammation contributing to neurogenic pulmonary edema.[70,71] Combined with ICU-related complications such as pneumonia, atelectasis, and adult respiratory distress syndrome, it becomes difficult to attain a PaO_2/fraction of inspired oxygen (FiO_2) ratio > 300 mm Hg, a standard criterion for lung donation.

The SCCM/ACCP consensus statement and other recommendations note there is evidence that lung donation rates can be improved through an aggressive ventilation management strategy up through the point of procurement.[13,72–75] Potential lung donors who do not meet the PaO_2/FiO_2 > 300 mm Hg criterion on initial assessment should be targeted to

Figure 1. *Clinical pathway and algorithm for the potential DNDD management. CPAP indicates continuous positive airway pressure; CVP, central venous pressure; DI, diabetes insipidus; DIC, disseminated intravascular coagulation; DOB, dobutamine; DOPA, dopamine; DVT, deep venous thrombosis; EVLW, extravascular lung water; EPI, epinephrine; GFS, glucose fingerstick; HOB, head of bed; HR, heart rate; iNO, inhaled nitric oxide; IV, intravenous; K, potassium; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; Mg, magnesium; Na, sodium; NE, norepinephrine; NPE, neurogenic pulmonary edema; P, phosphorous; PCWP, pulmonary capillary wedge pressure; PEEP, positive end-expiratory pressure; OPO, organ procurement organization; RM, recruitment maneuver; SG, specific gravity; SVR, systemic vascular resistance; SVT, supraventricular tachycardia; VSP, vasopressin; VT, ventricular tachycardia; TV, tidal volume; Temp, temperature; UOP, urinary output. Reproduced from Maciel and Greer[69] with permission from Springer.*



maintain euvolemia and undergo aggressive chest physiotherapy, therapeutic bronchoscopy, and recruitment maneuvers in an attempt to decrease atelectasis and improve the likelihood of meeting the DMG targets. This has led to work looking at the application of a lung protective ventilatory strategy similar to that used in patients with adult respiratory distress syndrome applied to the donor population. Mascia and colleagues compared a large tidal volume (10 to 12 mL/kg) and lower positive end expiratory pressure (3 to 5 cm H_2O) to a lung-protective protocol using a lower tidal volume (6 to 8 mL/kg) and higher positive end expiratory pressure (8 to 10 cm H_2O). Use of the lung protective strategy resulted in a 100% increase (27%→54%) in lung recovery.[76]

More recently, a multicenter trial comparing lung donation and primary graft dysfunction rates before and after use of a lung donor management protocol found that the lung donation rate almost doubled with no change in mortality or graft dysfunction in recipients.[73] The protocol included the following:

- apnea test performed with a ventilator on continuous positive pressure mode;
- a total of 6 to 8 mL/kg tidal volume based on predicted body weight; positive end-expiratory pressure 8 to 10 cmH_2O;
- recruitment maneuvers once per hour and after any disconnection from the ventilator;
- bronchoscopy with bilateral bronchoalveolar lavage immediately after BD; and
- semilateral decubitus position and recruitment maneuvers for $PaO_2/FiO_2 < 300$ mm Hg.

Alternative means of achieving an "open lung" condition that may improve donation outcomes include the use of airway pressure release ventilation (APRV). Although there are few data on this approach, the results of a small, retrospective, single-center trial found that implementation of APRV in potential donors resulted in marked improvement in the rate of lung donation (18%→84%) without an adverse impact on short-term recipient mortality or graft function.[77] When taking donors on APRV or other pressure modes of ventilation into the operating room, it is essential to convert to a volume mode of ventilation to avoid overinflation of the lungs after opening the thoracic cavity.

In addition to using a lung protective ventilatory strategy, potential lung donor management must also pay attention to overall fluid balance. Despite concerns of a restrictive fluid approach to optimize lung function leading to a negative impact on donor renal function, maintaining a goal central venous pressure (CVP) <8 to 10 mm Hg seems safe[72,73,78] and is a component of several DMGs.[10,13,24,26] Although randomized controlled trials are lacking, the use of inhaled

nitric oxide can be considered in the setting of neurogenic pulmonary edema for DNDD because of its impact on local vasodilatation and decreased vascular resistance with potential to improve perfusion.[79,80]

Hemodynamic Management

The goal of hemodynamic management in the donor is maintenance of optimal perfusion to all organs and, for the potential liver donor, avoidance of impaired venous drainage and congestion that may be detrimental. Liver function is susceptible to ischemic injury not only at the time of organ procurement but also during the progression to BD. Several pathophysiological processes occur during the progression of neurological death due to cerebral edema and/or brain stem herniation, making hemodynamic decompensation likely. Increasing intracranial pressure (ICP) and tentorial herniation is associated with neurohumoral inflammation and a release of proinflammatory cytokines that produce a noted cardiovascular response.[81,82] The final pathway of hemodynamic decompensation following neurological death is therefore manifested in a 2-phase process: progression of cerebral ischemia and completion of BD.

Progression of cerebral ischemia, including the pons and medulla, leads to profound hemodynamic alterations. Involvement of these structures results in the classic hypertensive response (Cushing reflex) associated with increasing ICP. A catecholamine surge and dysfunction of the parasympathetic centers of the brainstem cause unopposed sympathetic activity[82,83] with a concomitant and reflexive increase in mean arterial pressure. This compensatory mechanism, mediated by the sympathetic nervous system, serves to maintain cerebral perfusion pressure in the setting of intracranial hypertension due to worsening cerebral edema and ischemia from progressive BD. The loss of baroreceptor control may further cause deterioration in hemodynamic stability via arrhythmogenic processes and cardiac dysfunction.[84] Sympathetic activity and the release of vasoactive hormones, such as epinephrine, norepinephrine, and dopamine, leads to intense vasoconstriction and increased myocardial oxygen utilization. This may further result in an imbalance of myocardial oxygen delivery and consumption, with the end result of significant cardiac dysfunction, which may occur in up to 40% of BD donors.[85,86] Increasing myocardial oxygen demand and subendocardial ischemia can lead to a reduction in cardiac output (CO) and subsequent organ hypoperfusion.[87] Furthermore, with increases in ventricular filling pressures and CVP, there exists an increasing risk for hepatic venous congestion. Therefore, cardiac dysfunction as a result of cerebral ischemia presents numerous implications for potential donor organ function.

As cerebral edema and ischemia evolve to the phase of BD completion, there is a deactivation of sympathetic hyperactivity and loss of vasoregulatory tone, a decrease in catecholamine production, and loss of cardiac stimulation.[69] The overall hemodynamic profile transitions from one of vasoconstriction and hypertension to that of vasodilation, hypotension, and hypoperfusion. Relative hypovolemia occurs due to increased venous capacitance as a result of vasodilation leading to a reduction in cardiac preload. In conjunction with decreased afterload as a result of the loss of vasoconstriction, this relative hypovolemia contributes to a reduction in CO. Hypovolemia may be further exacerbated during the completion of BD by other pathologic processes. Diabetes insipidus (DI) is a well-documented occurrence associated with severe cerebral ischemia and neurological death.[88] Hyperosmolality and hypovolemia are cardinal features of DI that complicate the overall hemodynamic challenges of impending BD. In addition, medications used to treat elevated ICP, such as mannitol, can produce an osmotic diuresis contributing to further volume loss. In conjunction with vasodilation, hypovolemia, and decreased myocardial loading conditions, the previously described cardiac dysfunction that is manifested in the earlier phase of progressive cerebral edema and ischemia is additive to the detrimental hemodynamic conditions associated with completion of BD.

Hypotension specifically in liver donors is associated with reduced allograft function and prolonged recipient hospital length of stay.[89,90] Hepatic ischemia results in a release of inflammatory cytokines that is manifested by changes in organ-specific enzymatic function. Acute changes in aspartate amino transferase and alanine amino transferase levels, in addition to unconjugated bilirubin, may reflect alterations in intrinsic hepatic function related to organ perfusion. Similarly, values of hepatic synthetic function may be altered. Therefore, serial liver function laboratory values, such as aspartate amino transferase / alanine amino transferase, unconjugated bilirubin, and international normalized ratio, are recommended every 6 hours during ICU donor management.[91] Presently, there are no absolute limits or an upper threshold above which hepatic function enzymes preclude liver donation; however, restoration of adequate hepatic blood flow should be addressed in the period leading up to and following the determination of death.

Monitoring

Numerous approaches and measurements have been described to monitor blood flow and end-organ perfusion. Mean arterial pressure (MAP) is most commonly targeted as a surrogate parameter for end-organ perfusion; however, it is important to consider that other factors,

such as systemic vascular resistance, contribute to MAP and do not always necessarily imply adequate blood flow. Many organ procurement and donor management protocols recommend targeting a MAP of > 70 mm Hg and a systolic blood pressure > 100 mm Hg.[10,24,25,69,84,92] CVP is frequently included in DMGs to guide clinical decision making and resuscitation in the potential organ donor. CVP goals of 6 to 10 mm Hg, in conjunction with hormone replacement therapy (discussed below), have demonstrated significant improvement in viability of certain organs for transplant, such as the lungs and kidneys.[93] Unfortunately, there are few data to suggest the optimal CVP in potential liver donors. Considering the relationship of CVP and hepatic congestion in living-donor–related transplantation and partial hepatectomy, it may be prudent to consider a lower CVP target (ie, 6 mm Hg) in the isolated deceased liver donor with evidence of hepatic congestion, such as increasing portal venous stasis, increasing transaminases, and a dilated hepatic vein. However, further data are necessary to support this in routine practice. Other continuous indices of hemodynamics obtained through central monitoring devices, such as CO, cardiac index, and pulmonary artery occlusion pressure, have been targeted as potentially valuable tools to guide therapy.[69,91] Ultimately, there is substantial variability in practice and little data to support routine use of a pulmonary artery catheter in all potential donors. Selection of pulmonary artery catheter utilization should therefore depend on the donor's underlying cardiopulmonary condition.[13] Further clinical markers of end-organ perfusion and function should also be targeted, such as previously discussed hepatic function and monitoring of liver enzymes, in addition to maintenance of adequate urine output (eg, >1 ml/kg/h).[69,84] It is important to consider that adequacy of urine output may be seemingly present in the setting of DI, and therefore appropriate clinical suspicion should be present to thoroughly evaluate and treat this pathologic condition.

The roles of noninvasive hemodynamic monitoring and goal-directed therapy are also of considerable interest.[94,95] Stroke volume variation and pulse pressure variation have been investigated in numerous perioperative settings and demonstrate significant value in hemodynamic management.[96–98] However, their application to potential organ donation is presently limited because of lack of adequate supporting literature. Echocardiography is another modality of cardiac assessment that offers significant real-time information on hemodynamic status. Borbely et al[99] demonstrated that serial echocardiography provided clinicians with early recognition of cardiac dysfunction and subsequent implementation of therapeutic interventions to maintain hemodynamic performance. Recommendations for maintenance of cardiac function based upon echocardiography are to achieve an ejection fraction of > 45%.[13,69,100]

In the setting of hemodynamic compromise and dysfunction, other markers of inadequate resuscitation, such as a lactate value > 2 mmol/dL, may be suggestive of inadequate end-organ perfusion. To date, there is insufficient evidence to support using lactate as a specific therapeutic target in the potential organ donor, although it can be followed as an additional metabolic parameter.

Fluid Therapy

Fluid administration remains the initial therapy for hemodynamic resuscitation management.[92] Traditionally, an isotonic crystalloid is administered to replace intravascular volume. Despite recent debate regarding optimal choices for fluid administration in critically ill patients,[101,102] there are few data to guide the composition of fluid therapy in potential organ donors. The biochemical composition of each fluid and possible side effects, such as hyperchloremia with 0.9% saline and hypoosmolarity with Ringer's lactate, should be considered in the clinical context of the donor's physiology. Colloidal solutions are also options for targeted hemodynamic management, with 5% albumin being the colloid of choice for acute intravascular replacement.[13] Hydroxyethyl starch is not presently recommended for hemodynamic therapy because of adverse effects, such as acute kidney injury, coagulopathy, and DGF.[13,103,104] Ultimately, crystalloid or colloid fluid administration serves to achieve adequate intravascular volume status and hemodynamic parameters; transfusion of red blood cells may be necessary to correct deficiencies of anemia. There is presently no known optimal hemoglobin concentration in organ donors and therefore the exact threshold for red blood cell transfusion in most DMGs follows similar recommendations as those for critically ill patients, to maintain a hemoglobin above 7 g/dL.[13,91,92]

Despite replacement of intravascular volume fluid with crystalloid, colloid, and/or blood product transfusion, hemodynamic management frequently requires administration of vasoactive medication to achieve desired hemodynamic goals.[94,95] Cardiovascular decompensation mandates prompt recognition and treatment with an agent targeted to the etiology of shock. Dopamine has historically been the first-line vasopressor of choice for cardiogenic shock because of primary α_1-receptor and β_1-receptor activity at moderate doses.[13] In addition, dopaminergic activity may also confer immunologic properties that modify the inflammatory response and insulates organs from ischemia-reperfusion injury.[105] Literature demonstrates that administration of preprocurement, low-dose dopamine in DNDD is associated with a decreased incidence of dialysis dependence following renal transplant.[106] While primary α-receptor-specific infusions are commonly used in intensive care units, these vasopressors (eg, norepinephrine and

phenylephrine) may result in adverse physiological conditions, such as coronary and mesenteric vasoconstriction. Therefore, conservative use of norepinephrine and phenylephrine with targeted hemodynamic and physiological goals is recommended in organ donors. Vasopressin also plays a role in achieving blood pressure targets and augments cardiovascular function in pathophysiological states of vasodilatory shock.[107,108]

Endocrine Dysfunction

Progression of BD with cerebral injury and resultant ischemia promotes a series of endocrine abnormalities that originate in the hypothalamic-pituitary axis.[109] Decreased production of hormones, such as arginine vasopressin (AVP), thyroid stimulating hormone, and adrenocorticotropic hormone, has profound implications on donor physiology and subsequent success of organ procurement. Clinical signs of endocrine dysfunction manifest in a multitude of cardiovascular responses including hypotension due to vasodilation as a result of altered baroreceptor reflex–mediated AVP secretion and/or reduced intravascular circulating volume as a consequence of osmotic diuresis (secondary to DI or hyperosmotic hyperglycemic diuresis). Vasopressin infusion is the preferred treatment modality in organ donors with hypotension and vasodilatory shock despite adequate intravascular volume replacement, and is associated with decreased requirements for other vasopressors and inotropic support.[107,110] The optimal dosing regimen of vasopressin is not precisely defined as the routine dosing in critical care units of 0.04 U/min in patients with sepsis may be associated with fewer adverse vasoconstrictive side effects, but recent data suggest that higher infusion rates (ie, 0.06 to 0.08 U/min) are associated with improved restoration of hemodynamic parameters.[111] In addition to AVP replacement, desmopressin, a vasopressin analog with greater V_2 receptor activity in the renal collecting system, may be administered for cases of DI without associated hypotension.

Vigilant and serial monitoring of serum electrolytes is necessary in managing organ donors with DI, particularly in the potential liver donor. Hypernatremia at time of procurement has previously been demonstrated to be an independent risk factor for early liver graft failure[112,113] although more recent work has not been as conclusive.[114] Nonetheless, most DMGs include a target sodium of <155 mEq/L before liver retrieval.

Endocrine depletion may present with hemodynamic decompensation related to intrinsic cardiac dysfunction.[69] This mechanism is hypothesized to be related to a reduction in thyroid stimulating hormone and thyroid hormone that results in decreased myocardial energy stores with a compromise in contractility. Observations that

administration of thyroid hormone was associated with improved hemodynamic status and decreased need for inotropic support have led to empiric administration of thyroid replacement therapy in DNDD candidates. This has generated a considerable amount of debate as not all studies involving thyroid replacement have produced favorable results.[115] It is important to consider that despite reports of improved cardiovascular function in organ donors administered thyroid hormone, not all donors demonstrate hypothyroidism on testing. The majority of donors with abnormal thyroid function appear to manifest as a "sick euthyroid" state rather than true hypothyroidism.[116–118] Furthermore, reduced thyroid function is not always manifested by profound hemodynamic decompensation. Nonetheless, targeted thyroid hormone replacement, with either T3 or T4 administration, continues to frequently be used in organ donors with impaired hemodynamic function (ie, hypotension and/or reduced left ventricular ejection fraction).[69,91,92]

Finally, replacement of corticosteroid hormone following BD serves a multifaceted purpose. Corticosteroid deficiency in the setting of DNDD has been reported at variable rates.[88,109,116,119] The exact consequence of this phenomenon is not well elucidated as studies have not demonstrated a significant difference in inotropic and hemodynamic support.[120] However, addressing potential cardiovascular function is not the only target of steroid replacement therapy. As previously noted, there is a release of inflammatory mediators and excess of substrates associated with progression toward BD that have been attributed to produce poor graft function after procurement and transplant.[81,82] The administration of high-dose methylprednisolone to BD organ donors has demonstrated a reduction in these mediators, ischemia-reperfusion injury, and acute rejection in organ transplant recipients.[121]

The proinflammatory milieu and endocrine dysfunction following BD also stimulate an excess of glucose production, insulin resistance, and hyperglycemia. Similar to other populations of critically ill patients, there is no well-defined and exact target glucose level for potential organ donors. Notwithstanding, literature continues to suggest that hyperglycemia may likely be associated with worse graft outcomes and that uncontrolled and wide variations in serum blood glucose levels should be managed with insulin therapy, according to individual institutional guidelines for hyperglycemia in critically ill patients.[122] Overall, endocrine dysfunction after BD is most commonly managed with a combination of AVP replacement, thyroid hormone, corticosteroid administration, and insulin therapy.[13,92,94]

■ Conclusions

Management of the potential organ donor can be difficult and is certainly not without controversy. An increasing amount of evidence suggests that optimization of organ donation is best accomplished by close collaboration between OPOs, critical care professionals, and transplant teams working toward contributing to the care of the potential donor. The science of physiological management directed at organ preservation and procurement can create opportunities for future observational and randomized studies to provide more and clearer evidence. With increased use of protocolized care and integration of DMGs into the management of the potential donor from the ICU to the operating room, anesthesiologists have the ability to directly impact the shortage of organs worldwide and improve the lives of future transplant recipients.

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