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REVIEW ARTICLE/BRIEF REVIEW

Anesthetic considerations in organ procurement surgery: a narrative review

Considérations anesthésiques pour la chirurgie de prélèvement d'organes: une étude narrative

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Abstract

Purpose *While a few publications specify the anesthetic implications of either brain or cardiac death, they lack detail on how to provide anesthesia during organ donation surgery. We provide a thorough description of important anesthetic considerations during organ donation surgery in patients with either brain or cardiac death.*

Source *A thorough literature review was undertaken to locate all relevant articles that describe systemic effects of brain and cardiac death and their anesthetic implications. We searched PubMed, Pubget, and EMBASE™ for relevant articles using the following search terms: anesthesia, management, donation cardiac death, donation brain death. In addition, we reviewed the relevant protocols at our own institution.*

Principal findings *Highly specific intraoperative management by an anesthesiologist is required during organ procurement after brain death. To manage the heart-beating brain-dead donor, the anesthesiologist must incorporate knowledge of the effects of brain death on each organ system as well as the effects of the preoperative measures that the donor required in the intensive care unit. It is also important to know which organs are going to be procured in order to establish specific goals and implement strategies (e.g., lung-protective ventilation or intraoperative glycemic control) to optimize donor outcome. During organ procurement after cardiac death, an anesthesiologist's direct involvement is particularly important for lung donors.*

Conclusion *Anesthesiologist-guided physiological optimization of the brain-dead donor may be a factor in determining the outcome of the organ recipient. Additionally, anesthesiologists have an important role in helping to ensure that the highest quality and most appropriate care are rendered to non-heart-beating donors. This is achieved through establishing protocols in their hospitals for donation after cardiac death that maximize the number of available organs with the best chance for long-term graft viability.*

Résumé

Objectif *Alors que quelques articles abordent les implications anesthésiques de la mort cardiaque ou cérébrale, ceux-ci manquent de détails sur la façon d'assurer une anesthésie au cours d'une chirurgie de don d'organe. Nous proposons une description approfondie des questions anesthésiques importantes soulevées au cours de la chirurgie de don d'organe chez des patients en état de mort cardiaque ou cérébrale.*

Source *Une analyse rigoureuse de la littérature a été entreprise pour identifier tous les articles pertinents décrivant les effets systémiques de la mort cardiaque et cérébrale et leurs implications anesthésiques. Nous avons recherché les articles pertinents dans les bases PubMed, Pubget et EMBASE™ en utilisant les termes suivants: anesthesia, management, donation cardiac death, donation brain death. De plus, nous avons examiné les protocoles pertinents dans notre propre institution.*

Principales constatations *Une gestion peropératoire hautement spécifique par un anesthésiologiste est requise*

Author contributions *T. Anthony Anderson*, *Peter Bekker,* and *Parsia A. Vagefi* attest to the integrity of the original data and the analysis reported in this manuscript.

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au cours du prélèvement d'organe après mort cérébrale. Pour gérer le donneur en état de mort cérébrale à cœur battant, l'anesthésiologiste doit intégrer les connaissances des effets de la mort cérébrale sur chacun des systèmes d'organes et les effets des mesures préopératoires qui ont été nécessitées par le donneur en unité de soins intensifs. Il est également important de savoir quels organes vont être prélevés afin de fixer des objectifs spécifiques et de mettre en place des stratégies (par exemple, une ventilation protégeant le poumon ou un contrôle glycémique peropératoire) pour optimiser les chances de succès du don d'organe. Au cours d'un don d'organe après mort cardiaque, l'implication directe d'un anesthésiologiste est particulièrement importante en cas de don de poumons.

Conclusion *L'optimisation physiologique guidée par l'anesthésiologiste d'un donneur en état de mort cérébrale peut être un facteur pour la détermination des résultats chez le receveur d'organe. De plus, les anesthésiologistes ont un rôle important à jouer en contribuant à veiller à ce que les soins les mieux adaptés et de la plus haute qualité soient accordés à des donneurs à cœur non battant. On y parvient par la création de protocoles dans les hôpitaux pour le don d'organe après mort cardiaque qui augmentent au maximum le nombre d'organes disponibles ayant les meilleures chances de viabilité à long terme du greffon.*

The number of patients awaiting organ transplantation is much greater than the number of available solid organs.[1] In 2012, 15,967 kidney transplants were performed in the United States, while 92,885 candidates were on the active waiting list for a kidney transplant; 5,209 patients died awaiting a kidney transplant.[2] That same year, 15,308 people were on the liver transplant waiting list, 5,468 received a liver transplant, while 2,187 patients died while awaiting a liver transplant.[3] The use of every available donated organ is crucial, as is maximizing its viability.

An existing body of literature guides intensivists in the preoperative management of organ donors in the intensive care unit (ICU) setting prior to organ procurement.[4] Furthermore, studies are underway to investigate the effects of a protocol-based approach to donor management in the early hours following brain death.[5] Anesthesiologists frequently provide intraoperative management of organ donor patients, and the appropriate management of these patients is essential for maximizing the quality and success of the organs procured.[6] Nevertheless, scant literature exists specifically to guide anesthesiologists in the intraoperative management of the organ donor.

This review summarizes the available literature and expert opinions regarding the anesthetic management of organ donors during donation after brain death (DBD) and donation after cardiac death (DCD). We searched PubMed, Pubget, and EMBASE™ for relevant articles using the following search terms: *anesthesia, management, donation cardiac death, donation brain death*.

Donation after brain death donors are those patients who have suffered a terminal neurological insult and have been declared brain dead. The American Academy of Neurology has published criteria for the declaration of brain death,[7,8] and each institution should have its own relevant policies and procedures that are in accordance with local laws.[9] The Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death[8] issued a report that essentially redefined death, and subsequently, a formal legal definition of brain death was instituted in the 1970s. Prior to this significant redefinition of death, all cadaveric organ transplants were from non-heart-beating donors. Nevertheless, DBD led to improved outcomes secondary to decreased relative ischemic time. Subsequently, the number of DBD donors plateaued, and interest in the use of DCD donors has recently been revitalized.[10] The number of DCD donors has increased each year for the past decade (Figure).

A person who has suffered neurologic devastation and is suspected to fulfill the criteria for brain death should be identified by his or her treating physician as a potential DBD organ donor. Their suitability as a donor can then be assessed based on the presence of medical diseases and comorbidities. If the patient is considered to be a medically suitable organ donor and is declared brain dead in accordance with institutional and local guidelines, consent is obtained and organ procurement follows. Such a patient is considered a *utilized organ donor* if at least one procured organ is transplanted.[11]

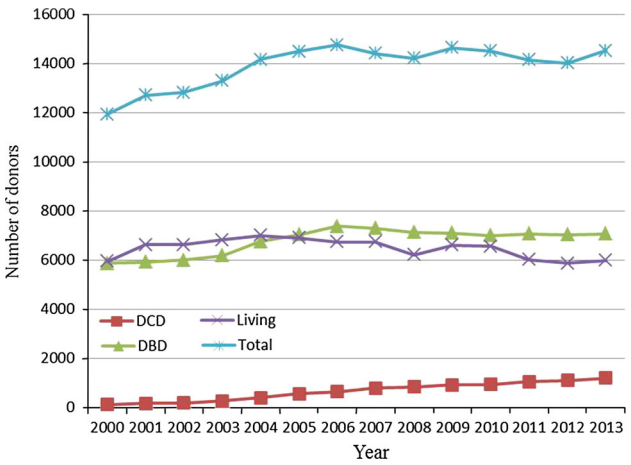

Figure Annual number of DCD, DBD, and living donors in the U.S. since 2000. DCD = donation after cardiac death; DBD = donation after brain death

For DCD donors, death is declared based on cardiopulmonary criteria and may be expected to be imminent due to underlying severe illness or accident. The DCD donor is a patient who does not meet the strict criteria for brain death but has suffered what is considered to be a devastating non-recoverable brain injury, and the family has decided to withdraw care. Donation is considered at the request of the patient's family. Following withdrawal of life support, the DCD donor is declared dead based on the cardiopulmonary criteria for death.[12,13] Typically, the potential DCD donor may have end-stage neuromuscular disease, severe neurologic injury, or terminally advanced pulmonary disease. Once cardiopulmonary function has ceased, resuscitative efforts are not undertaken, and a period of five minutes is allowed to elapse prior to organ procurement in order to ensure the absence of autoresuscitation. As with a DCD donor, the patient is considered a *utilized organ donor* if at least one procured organ is transplanted.

On the pathway from *potential* to *utilized* donor, numerous factors can supervene to prevent successful organ utilization. These supervening factors can be organ system failures, characteristics of the donor or organ, or an inability to obtain proper consent for organ donation, including the patient's prior expressed refusal to be an organ donor. Relative contraindications to organ utilization include advanced patient age, although there is no firm cut-off, and human leukocyte antigen (HLA)-mismatch.[14-17] There is significant variation amongst centres, surgeons, regions, and organ procurement organizations on what constitutes an acceptable donor for individual organs.

Donation after brain death

The discussion of DBD begins with the diagnosis of brain death. Physicians who discuss organ donation with the patient's family should be different from those who perform the organ procurement. Prior to proceeding to organ procurement, the anesthesiologist should ensure that diagnosis of brain death has been made in accordance with the American Academy of Neurology guidelines.[18] It is not the anesthesiologist's role to make this diagnosis.

The anesthesiologist plays a pivotal role in organ procurement from the brain dead patient, as hemodynamics, thermoregulation, intravascular volume status, and skeletal muscle paralysis require active management and are vital to the procurement of healthy organs. In the presence of brain death, spinal cord function is still intact and both somatic and visceral reflexes remain.[19,20] Effective anesthetic management of donation requires an understanding of the effects of brain death on each organ system.

Effects of brain death on organ systems and anesthetic considerations

The cause of an injury affects certain organ systems, but nearly every organ system is affected by brain death. The critical care literature supports the normalization of donor physiology to maximize the long-term viability of organs for donation.[21] This strategy should continue from the ICU into the operating room during donation surgery. Table 1 comprises a concise summary of the effects of brain death on each organ system along with recommendations for anesthetic management.

Cardiac

Hemodynamic instability and cardiac dysfunction take place after brain death. While a number of mechanisms have been proposed to explain these changes, the cause is still not completely understood.[22] It is clear that neural and humoral factors play a role as well as altered loading conditions and myocardial injury. Nevertheless, the opinion of some experts is that the long-term myocardial injury associated with brain death may be largely a function of decreased coronary perfusion. While cardiac function and intravascular tone and volume appear to be in a complicated interplay with coronary artery perfusion after brain death, there is evidence that cardiac function can be preserved if coronary perfusion pressure is maintained.[22] There is general agreement that, shortly after brain death, a prolonged period of increased sympathetic tone and cardiac output occurs as a result of a "catecholamine storm".[23] With this burst of catecholamines, the tachycardia and vasoconstriction can cause profound hypertension.[24] Associated myocardial injury can arise from the profound increase in systemic vascular resistance and result in left ventricular failure, decreased cardiac output, and even mitral valve regurgitation.[25-27] Cardiac arrhythmias may ensue along with electrocardiographic changes indicative of ischemia.[28] After several hours, a dramatic loss of sympathetic tone can occur and result in hemodynamic instability that may compromise the quality of donor organs.[29] As outlined below, this loss of sympathetic tone must be managed accordingly.[30]

Hypovolemia may exacerbate hemodynamic instability. There are multiple contributors to volume loss in the brain-dead patient. Although organ procurement surgery is generally not a lengthy procedure, significant fluid shifts with considerable interstitial accumulation of fluid can occur from the abdominal and/or thoracic incision made for organ procurement. Some evaporative losses and overt incisional blood losses also occur. Polyuria secondary to diabetes insipidus resulting from posterior pituitary infarction is common in brain death and can further contribute to

Table 1 Effects of brain death and recommended anesthetic management by organ system

System	Effects of Brain Death	Recommended Anesthetic Management[6,19,21,26,37,43-46,49,51,52,54,55,59,60]
Cardiac	• Myocardial injury • Loss of vascular tone • Hemodynamic instability • Hypovolemia	• Restore intravascular volume, replacing evaporative and DI urinary losses. • Use vasopressors as necessary to maintain adequate organ perfusion. • Maintain SBP > 100 mmHg, MAP > 70, HR 60-120 beats·min^{-1}.
Pulmonary	• Increased pulmonary capillary permeability • Pulmonary edema	• "Lung-protective" ventilatory strategy: TV 6-8 mL·kg^{-1} of predicted body weight, PEEP 8-10 cm H_2O. • Judicious intravenous fluid; CVP 4-8 (< 10) mmHg.
Endocrine	• Pituitary infarction may lead to diabetes insipidus and obliteration of thyroid axis • Hyperglycemia • Hypernatremia	• Vasopressin to support hemodynamics and control polyuria. • Insulin infusion to maintain serum glucose < 180 mg·dL^{-1} • Consider hormone replacement—thyroxine or T3 infusion, corticosteroids
Hematologic	• Coagulopathy, which may progress to disseminated intravascular coagulation	• Transfuse for hemoglobin < 7 or 8 g·dL^{-1} for optimal oxygen delivery to organs. • Correct coagulopathy with clotting factors or platelets if evidence of ongoing bleeding.
Musculoskeletal	• Reflex somatic movements mediated by spinal reflexes	• Skeletal muscle paralysis.

CVP = central venous pressure; DI = diabetes insipidus; HR = heart rate; MAP = mean arterial pressure; PEEP = positive end-expiratory pressure; SBP = systolic blood pressure; TV = tidal volumes

hypovolemia.[24] The intravascular fluid replacement strategy varies for different organs; thus, care must be exercised when making decisions regarding volume status and resuscitation of the donor. For example, moderate intravascular fluid administration may have no adverse effect on the liver or kidneys, but this fluid could potentially have deleterious effects on the transplanted lung or pancreas.[31] Accordingly, some surgeons consider intraoperative administration of fluid as the preferred method to improve blood pressure in a hypotensive donor patient, with vasopressors being relatively contraindicated due to vasoconstriction and decreased blood flow to vital organs.[32-34] Nevertheless, the dangers to long-term organ function arising from hypotension-related organ hypoperfusion and reduced oxygen delivery may outweigh the risks associated with using vasopressors. A balanced plan to maintain adequate blood pressure thus incorporates the replacement of intravenous fluid deficits while judiciously using vasopressors to counteract the decrease in systemic vascular resistance that occurs in patients after brain death. As detailed later, use of vasopressin as part of a hormone replacement strategy has been shown to increase the rate of successful organ procurement by restoring vascular tone and organ perfusion.[35]

Management of the cardiovascular changes resulting from the catecholamine surge after acute brain death improves systolic function and the chance of successful cardiac transplantation.[36] As previously mentioned, this autonomic storm takes place shortly after brain death and generally lasts only several hours. Consequently, it will not be an issue for management in the operating room during organ donation surgery; however, it is commonly managed with nitroprusside and/or esmolol.[36,37] In most cases, cardiovascular goals should include a systolic blood pressure > 100 mmHg, a mean arterial pressure > 70 mmHg, with a heart rate of 60-120 beats·min^{-1}. The first step in cardiovascular resuscitation should be the effective replacement of intravascular volume. Beyond the red cell transfusion strategy, which is described below, the choice of crystalloid or colloid may be guided by whether or not lung procurement is planned. No particular fluid has been shown to be advantageous, but 0.9% NaCl solutions should generally be avoided in large volumes in order to prevent hyperchloremic acidosis. Nevertheless, if colloid is used as an intravascular volume expander, it may be best to avoid some of the hydroxyethyl starch (HES) products as their use in brain-dead donors has been implicated in impaired immediate renal graft function.[38] A more recent study of a HES solution with a lower mean molecular weight and molecular substitution showed less of an impact on immediate and long-term renal graft function.[39] Nevertheless, given the potential for lasting renal impairment, we routinely avoid the use of HES products in brain-dead donors. If lung procurement is planned, colloid is the preferred agent.[40] Volume repletion should be guided by arterial waveform pulse pressure variation, central venous pressure, and urine output if diabetes insipidus is not an issue. Some centres target a mixed venous oxygen saturation

of > 60%[37]; however, there is a lack of evidence that this influences outcome in terms of the number of organs transplanted, graft, or recipient outcomes.[41] Presumably, this monitor is used as a surrogate means to ensure appropriate organ oxygenation and to ensure that oxygen delivery and consumption are appropriately balanced. Cardiovascular support with either dopamine or norepinephrine can be used. Evidence is currently lacking on the superiority of one agent over another in the management of the brain-dead organ donor, although it is prudent to avoid large doses of alpha-adrenergic agonists in order to optimize blood flow and oxygen delivery to the organs. Dopamine, phenylephrine, epinephrine, norepinephrine, and vasopressin are common agents and provide adequate hemodynamic support.[37,42,43] Vasopressin is considered by some to be the most ideal of these agents as it addresses the blood pressure as well as the diabetes insipidus. Furthermore, as previously mentioned, vasopressin has been shown to increase the rate of organ recovery both independently and as part of hormone replacement therapy in brain-dead organ donors.[35] Vasopressin infusion is dosed in the range of 0.01-0.04 IU·min^{-1} in order to minimize volume losses from diabetes insipidus and to assist blood pressure support.[44,45] Dopamine, at doses of < 5 μg·kg^{-1}·min^{-1}, improves blood flow to renal, mesenteric, and coronary vascular beds, thus enhancing organ perfusion,[46] but there is a lack of direct evidence that this effect leads to better graft survival or other beneficial outcomes.

Pulmonary

Brain death can lead to neurogenic pulmonary edema, as the initial increase in systemic vascular resistance may lead to increased blood volume within the venous system and subsequent pulmonary overload.[47,48] Pulmonary edema can also result from, or be exacerbated by, large-volume crystalloid resuscitation. Elevated pulmonary hydrostatic pressure can also give rise to pulmonary edema. In addition, the release of catecholamines during the initial hypertensive and hyperdynamic period after brain death causes elevated cytokine levels and, thus, pulmonary endothelial damage and capillary disruption. Resultant respiratory distress can progress to apnea and cardiac arrest.[19]

A lung-protective ventilatory strategy should be employed, with tidal volumes of 6-8 mL·kg^{-1} and a positive end-expiratory pressure (PEEP) of 8-10 cm H_2O,[6] especially if lung procurement is planned. Evidence is lacking to support the maintenance of respiratory alkalosis during organ procurement. If lung procurement for transplantation is planned, a minimally positive fluid balance should be maintained.[49] Standardized hormone replacement therapy (see below) along with careful attention to keeping the central venous pressure (CVP) < 10 mmHg has been shown to increase the number of hearts and lungs available for transplantation without decreasing the utilization of other organs.[43]

Endocrine

Impairment of the hypothalamic-pituitary axis occurs in the majority of patients with brain death and results in decreases in serum concentrations of anterior and/or posterior pituitary hormones.[50] Animal studies have shown a reduction in triiodothyronine (T3), cortisol, and insulin after brain death.[50] An early human trial provided evidence that therapy of brain-dead patients with thyroid hormone, cortisol, and insulin improved both the cardiovascular status and organ transplantation rates secondary to improved donor organ viability.[50] Although mixed evidence exists, much of it suggests that treatment of brain-dead donors with a combination of hormones, including thyroid hormone, glucocorticoids, vasopressin, and insulin increases organ donation rates and may improve graft and recipient patient survival.[26,51] Many treatment protocols for brain-dead donors now include therapy with each of these medications as standard practice.[37] This cocktail of hormones is commonly recommended for brain-dead patients with a low left ventricular ejection fraction and is considered for all donors (Table 2). Nevertheless, dose response studies need to be conducted for these hormones. Consequently, doses vary in different studies and institutions, and there is little evidence to support the use of one protocol over another. The recommendations in Table 2 are from the Canadian Forum on Medical Management to Optimize Donor Organ Potential.[37]

The evidence for corticosteroids after transplantation includes both randomized controlled trials and observational studies. Most of the randomized controlled trials examining corticosteroids included them in combination with other medications, with neutral effects. The observational studies generally show improved donor hemodynamics, oxygenation, organ procurement rates, graft survival, and recipient survival.[52] Brain-dead donor

Table 2 Recommended combined hormone therapy for organ donors with an ejection fraction < 40% or hemodynamic instability and consideration in all donors[37]

Hormone	Dose
Thyroid hormone (tetraiodothyronine)	20 μg *iv* bolus, 10 μg·hr^{-1} *iv* infusion
Vasopressin	1 U *iv* bolus, 2.4 U·hr^{-1} *iv* infusion
Methylprednisolone	15 mg·kg^{-1} *iv* q24hr

treatment is typically cortisol (3-5 mg·kg^{-1} *qd*) *vs* methylprednisolone (15-60 mg·kg^{-1} or 3-5 g once or *qd*).[37,52] A retrospective review of brain-dead donor high-dose (15 mg·kg^{-1} methylprednisolone) *vs* low-dose (300 mg hydrocortisone) corticosteroid treatment found that low-dose treatment led to no difference in donor pulmonary or cardiac function, a similar organ transplantation rate, a decreased insulin requirement, and improved glycemic control.[53]

Brain death leads to hormonal derangements that frequently precipitate hyperglycemia.[30] Hyperglycemia may be exacerbated by the release of epinephrine, exogenous steroid administration, or infusion of dextrose-containing solutions. Hyperglycemia is associated with a lower rate of organ suitability for transplantation and decreased renal graft survival.[54] Serum glucose control to levels < 200 mg·dL^{-1}, 11 mMol·L^{-1}, is associated with improved outcomes in pancreas transplant patients.[5] This level should be maintained during organ procurement, especially if a pancreas transplant is planned. An insulin infusion may be required, especially if dextrose-containing water is being infused to correct hypernatremia. Recommendations vary, but most experts agree that serum glucose should be kept < 150 mg·dL^{-1}, 8 mMol·L^{-1},[37,49,55] although it is unclear if there is any difference in organ transplantation rates or graft survival as long as the serum glucose is < 180 mg·dL^{-1}.[54]

As mentioned, brain death may also significantly disrupt the thyroid hormone axis, and thyroid hormone replacement may also be necessary with triiodothyronine or a thyroxine infusion in order to meet the hemodynamic goals with minimal vasopressor support.[49] Studies in brain-dead animals showed that cardiac function was improved after hormone supplementation with triiodothyronine, cortisol, and insulin. Subsequent reports in human donors showed improved cardiac function with thyroid hormone replacement.[56] Nevertheless, a recent meta-analysis of four randomized clinical trials that evaluated cardiac index in DBD showed that triiodothyronine did not improve hemodynamics[57] and suggests that triiodothyronine is not the cause of myocardial dysfunction in brain-dead patients. With mixed evidence and a meta-analysis showing no clear benefit from the administration of thyroid hormone replacement, some experts suggest that thyroid replacement therapy should not be part of the management of the brain-dead donor unless the patient has a history of hypothyroidism.[58] Even so, as mentioned, studies have shown that three-drug hormone replacement therapy with triiodothyronine/levothyroxine (T3/T4), methylprednisolone, and vasopressin increases the number of viable organs for transplant by $> 20\%$ and improves early graft function.[51,59,60] Accordingly, many transplant centres routinely give thyroid replacement therapy in this patient population. As part of continued hormone replacement therapy and to assist hemodynamic support, a T3/T4 infusion may be run in the operating room (triiodothyronine (T3) 0.4 μg bolus, 3 μg·hr^{-1} infusion; levothyroxine (T4) 20 μg bolus, 10-50 μg·hr^{-1} infusion).[43,60]

Posterior pituitary infarction in the setting of brain death can lead to diabetes insipidus, producing large amounts of dilute urine and resultant serum hyperosmolarity. Arginine vasopressin (AVP) should be used to reduce urine output and prevent a further increase in serum osmolarity. Furthermore, use of AVP in the brain-dead donor has been shown to increase the organ recovery rate and graft survival,[35] by decreasing plasma hyperosmolarity and improving systemic blood pressure as well as cardiac output.[44]

A hypotonic fluid or free water infusion may need to be used to correct hypernatremia. Donors with serum sodium levels > 155 mEq·L^{-1} showed a significantly increased rate of early graft loss, while those with corrected serum sodium levels did not show such an increased rate of early graft loss.[61] The hypernatremia in brain death should be considered a hypovolemic state. If serum sodium levels persist > 155 mEq·L^{-1} following adequate volume resuscitation, the authors suggest infusion of a hypotonic solution, such as 0.45% NaCl (77 mEq·L^{-1}), as a maintenance fluid. Generally, correction should occur at a rate of 0.5-1.0 mEq·L^{-1}·hr^{-1} to avoid cerebral edema and its sequelae. It is unknown, however, if correction of hypernatremia can occur at a faster rate in the brain-dead patient without negative consequences.

The water deficit can be estimated using the following equation:

$$\begin{aligned} \textit{Water deficit}\,(L) = {} & 0.6 \times [\textit{weight in kg}] \\ & \times [(\textit{current}\,Na^{+}/140) - 1] \end{aligned}$$

The change in serum Na^+ per 1 L of 0.45% NaCl solution infused can be calculated using the following equation:

$$\begin{aligned} & \textit{Change in}\,Na^{+}\textit{per L}\,0.45\%\,\textit{NaCl} \\ & = [\textit{Infusate}\,Na^{+} - \textit{Serum}\,Na^{+}] \,/\, [\textit{weight in kg} \times 0.6] \end{aligned}$$

To determine the rate of fluid infused to decrease serum Na + by 1 mEq·L^{-1}·hr^{-1}:

$$\begin{aligned} & 0.45\%\,\textit{NaCl hourly infusion rate} \\ & = 1,000mL \,/\, \textit{Change in}\,Na + \textit{per L}\,0.45\%\,\textit{NaCl} \end{aligned}$$

Musculoskeletal

Even in the setting of brain death, somatic movements can occur.[19] Animal studies show that these are mediated by spinal cord reflexes below the level of the brain stem. An animal study showed the minimal alveolar concentration was unaltered by high cervical cord section and suggested that anesthetics inhibit the motor

response via sites in the spinal cord.[62] The somatic movements are uninhibited spinally-mediated reflexes that occur in response to stimuli such as surgical incision or manipulation.

Skeletal muscle paralysis should be provided during organ procurement to optimize surgical conditions. Additionally, muscle relaxation will ameliorate the somatic response to surgical stimulus mediated by spinal cord reflexes, which may persist even in the presence of brain death.[46]

Hematologic

The reported incidence of coagulopathy after brain injury varies dramatically from $< 10\%$ to $> 80\%$, although this variability is likely due in part to inconsistent definitions of coagulopathy and brain injury.[63] Coagulopathy can occur in isolated head injury, and the development of coagulopathy after brain injury is associated with a worse outcome.[64] The release of tissue factor from injured cortical parenchyma may contribute to, or even be responsible for, the development of coagulopathy and, when severe, subsequent disseminated intravascular coagulation.[64] The release of cerebral gangliosides and plasminogen-rich substrates from damaged brain tissue is also thought to contribute to coagulopathy in patients with severe head injury.[65]On the other hand, in a recent prospective observational study of 345 patients with isolated severe traumatic brain injury, no association with the development of coagulopathy was found.[64]

In Canada, recommendations for organ donor patient management in the ICU include targeting a hemoglobin concentration of 9-10 $g{\cdot}dL^{-1}$ and no less than 7 $g{\cdot}dL^{-1}$[37] in order to optimize oxygen delivery to organs. Platelets and plasma should be given when clinically significant bleeding is evident, but not to target a specific coagulation test level or platelet count. Firm evidence is lacking for these recommendations in this patient population, but most experts and guidelines for management of brain-dead donors suggest similar transfusion goals. The recommendations for optimal hemoglobin concentration appear to be based on the idea that critically ill patients often have increased global oxygen consumption but may also have a limited ability to increase oxygen delivery if the hemoglobin concentration falls below some critical threshold.[66] Furthermore, some guidelines suggest targeting a mixed venous oxygen saturation of $\geq 60\%$ in order to ensure appropriate oxygen delivery.[37] In the event that reaching this goal is challenging, transfusion of packed red blood cells can improve the mixed venous oxygen saturation.

Additional considerations

Prior to the start of organ donation surgery, intravenous catheters adequate for rapid large-volume intravascular fluid replacement should be in place. In addition, the presence of a central venous catheter is recommended prior to the start of surgery. An arterial catheter should be placed so that blood pressure can be continuously followed and managed intraoperatively. Some guidelines suggest a pulmonary artery catheter for intensive care management of these patients in order to follow cardiac output, pulmonary capillary wedge pressure, and systemic vascular resistance,[37] but evidence is lacking to show that this changes outcome. Furthermore, it is important to communicate with the surgical team and know which organs will be procured for transplant as this can effect anesthetic management. As outlined above, if lung procurement is planned, a lung-protective ventilator strategy should be used, a minimally positive fluid balance should be maintained, and colloid is preferred over crystalloid for volume replacement. Prior to heparinization, the cardiac team may ask for removal of indwelling central lines or pulmonary artery catheters that traverse the superior vena cava, as they will subsequently clamp these vessels prior to removal of the heart. After the anesthesiologist administers heparin, the surgical teams cannulate the major arterial blood vessels; the cardiac team utilizes the ascending aorta, and the abdominal team utilizes the infrarenal abdominal aorta. Following cannulation and when all teams are in readiness, aortic cross-clamps are placed (one in the chest and one in the abdomen) and then intravascular flushing of cold solution is begun as well as topical cooling of the organs. For the heart, cold cardioplegia is utilized and it is often Celsior solution (CEL, Genzyme, Cambridge, MA, USA) (100 $mMol{\cdot}L^{-1}$ sodium, 15 $mMol{\cdot}L^{-1}$ potassium, 13 $mMol{\cdot}L^{-1}$ magnesium, 0.25 $mMol{\cdot}L^{-1}$ calcium, 80 $mMol{\cdot}L^{-1}$ lactobionate, 3 $mMol{\cdot}L^{-1}$ glutathione, 20 $mMol{\cdot}L^{-1}$ glutamate, 60 $mMol{\cdot}L^{-1}$ mannitol, 30 $mMol{\cdot}L^{-1}$ histidine). The abdominal team often uses University of Wisconsin (UW) solution (100 mM potassium lactobionate, 25 mM KH_2PO_4, 5 mM $MgSO_4$, 30 mM raffinose, 5 mM adenosine, 3 mM glutathione, 1 mM allopurinol, 50 $g{\cdot}L^{-1}$ hydroxyethyl starch).

There are numerous solutions with somewhat different compositions that can be used for either purpose, including the above mentioned UW and CEL solutions as well as the ET-Kyoto solution, Custodiol® histidine-tryptophan-ketoglutarate (HTK) solution, Perfadex® (PER), Euro-Collins, Papworth, and Plegisol. A recent literature review concluded that the use of UW solution for cardiac

transplants and PER for pulmonary transplants may improve graft and patient survival.[67] A recent review and meta-analysis of solutions for liver transplantation concluded that Celsior and Custodiol HTK solutions (15 mM sodium, 9 mM potassium, 4 mM magnesium, 15 μM calcium, 1 mM ketoglutarate, 198 mM histidine, 30 mM mannitol, 2 mM tryptophan) (Essential Pharmaceuticals, LLC, Ewing, NJ, USA) lead to similar immediate outcomes compared with UW solution.[68]

For lung procurement, the anesthesiologist will likely be asked to administer positive pressure breaths to inflate the lungs prior to removal and subsequent packaging for transport. At this point, the ventilator and monitors are turned off, and there is no longer a need for further anesthesia care while the organs are removed in the following order: heart, lung, liver, pancreas, kidneys.

Donation after cardiac death

Organ donation from patients who have not been declared brain-dead falls under the category of DCD. These donors are referred to as non-heart-beating donors (NHBDs). They are declared dead under the cardiopulmonary definition following the cessation of life-sustaining care in the setting of devastating and non-reversible neurologic injury, severe lung disease, or end-stage neuromuscular disease.[13] Each hospital that is a transplant centre or participates in organ procurement must have a specific protocol for DCD. The protocol must address issues of preoperative donor management, informed consent, withdrawal of life-sustaining measures, death pronouncement, organ recovery, and financial considerations.[1]

At our institution, cessation of care, including extubation, is carried out by the ICU or hospital staff with the presence of a representative from the organ procurement organization (OPO). The surgical transplant team is kept in a separate location during this process, awaiting progression to cardiac death, while the intensivist and OPO representative continue to monitor and record vital signs following extubation. If asystole is achieved, there is a five-minute period of further observation to ensure there is no auto-resuscitation, at which point, the donor is pronounced dead by the hospital staff. During this five minutes, or immediately afterwards, the patient is transported into the operating room and appropriately positioned. At this time, the surgical team can enter the operating room and proceed with organ procurement. Family members are often present from the time of extubation, or withdrawal of care, until the time procurement commences. Thus, appropriate planning must be undertaken for their exiting the operating room area prior to commencing procurement. If the lungs are to be procured, an anesthesiologist will reintubate the patient's trachea. Tracheal extubation is not performed at all institutions; rather, the ventilator circuit is simply disconnected from the endotracheal tube (ETT). In addition, in some institutions, the patients are on the operating room table, prepped and draped, prior to withdrawing care in order to minimize warm ischemia time. At our institution, care is withdrawn by critical care staff in a holding area immediately adjacent to the operating room, and the patient's family members are allowed to spend this time with the patient. Warm ischemic time limits are utilized to maximize organ suitability, as hypotension and cessation of circulation will lead to poor oxygen delivery to donor organs and compromise donor organ quality. Although transplant centres may vary in their definition and duration of ischemic time, typically the time begins with extubation/ ETT disconnection and ends with organ perfusion with a cold preservation solution. The maximum time allowed from withdrawal of care, including extubation, to asystole is different for different organs. If asystole does not occur within this time period, those organs are not harvested. That time is 30 min for the lung, liver, and pancreas, and 60 min for the kidney. The heart and bowel are not candidates for transplantation from a DCD donor, although the use of cardioplegia may offer some promise for use of the heart from a DCD donor. The order of organ procurement during DCD is lungs, liver, pancreas, kidneys.

The role of anesthesiologists in DCD organ procurement

Unlike critical care physicians, anesthesiologists do not have end-of-life training as part of their core curriculum.[69,70] Complete transfer of care to an anesthesiologist for the terminal stages of care risks violating a core principle of palliative medicine, i.e., patients deserve continuity of care and consistent providers throughout the dying process.[71] Accordingly, the critical care team may be directly involved in the final stages of life during the DCD process, although an anesthesiologist may provide some of the care in the operating room. Following the cessation of mechanical ventilation and vasopressor therapy, the ICU physician caring for the patient may direct administration of opioids and benzodiazepines titrated to patient comfort. Often an opioid and benzodiazepine are titrated with a goal heart rate of < 100 beats·min^{-1} and/or a respiratory rate of < 20 breaths·min^{-1}.[72] Following declaration of death, interventions that risk restoration of cerebral blood flow should be strictly avoided. These may include cardiopulmonary resuscitation, cardiopulmonary bypass, extracorporeal membrane oxygenation, and/or mechanical ventilation with oxygen for the purposes of lung retrieval.[73]

Specific organ considerations in DCD

Lung transplantation

If lung procurement is planned, an anesthesiologist is needed to reintubate the patient's trachea following the declaration of death. A single recruitment maneuver should be given and the lungs held open with 10 cm H_2O continuous positive airway pressure. Because ventilation with oxygenation may risk restoration of cerebral oxygen delivery, mechanical ventilation should not be initiated until cerebral circulation has been isolated via a cross-clamp across the aortic arch vessels.[44,74] Once mechanical ventilation is re-initiated, tidal volumes should be 6-8 $mg \cdot kg^{-1}$ with 8-10 cm H_2O PEEP in order to decrease the risk of acute lung injury.[6]

Liver transplantation

Although favourable outcomes have been achieved with the use of DCD liver grafts,[75] there has been a higher rate of biliary complications associated with these organs, and thus, they are considered to represent a higher risk option for the recipient. Factors such as patient weight, total ischemia time, and donor age can affect recipient outcome. Specifically, donor weight $>$ 100 kg, total ischemia time $>$ nine hours, and donor age $>$ 50 yr have been associated with a higher incidence of ischemic cholangiopathy.[70]

Kidney transplantation

Multiple studies have shown similar outcomes in recipients who receive a kidney from DCD or DBD donors.[70] As in DBD donors, a negative fluid balance should be avoided during DCD organ procurement.[9]

Heart transplantation

As with other organs, NHBDs represent a growing source of solid organ donation; however, the heart may be the most sensitive to warm ischemia time, with 30 min considered an acceptable limit.[45] Use of cardioplegia may offer some promise of a successful heart transplant in the setting of DCD, but further research is needed.[74]

Conclusions

Anesthesiologists play a vital role in the management of organ donors, and the intraoperative care may affect the outcome of the organ recipient. Donation after brain death procurement operations requires highly specific intraoperative management by an anesthesiologist. To manage the heart-beating brain-dead donor, the anesthesiologist must incorporate knowledge of the effects of brain death on each organ system as well as the effects of the preoperative measures that the donor required in the ICU. It is also important to know which organs are going to be procured so that specific goals can be established and strategies can be implemented (e.g., lung-protective ventilation or intraoperative glycemic control) to optimize donor outcome. The success of the anesthesiologist in physiological optimization of the brain-dead donor may eventually determine the outcome of the organ recipient. In the case of DCD, an anesthesiologist's direct involvement is necessary for lung donors. Additionally, they may help to ensure that the highest quality and most appropriate care is rendered to non-heart-beating donors by working to establish protocols in their hospitals for DCD that maximize the number of available organs with the best chance of long-term graft viability.

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