EVEN IN THE FACE OF THE URGENT NEED FOR TRANSPANTABLE ORGANS, there continues to be a disparity between the number of potential organ donors and that of actual donors. Reducing this disparity is one means of addressing the current shortage of organs. However, for this strategy to be effective, it is mandatory to retrieve organs that offer the greatest likelihood of successful outcomes for the recipients. This strategy necessitates the optimal care of the potential donor, that is, even after brain death has occurred. In this review we present a structured approach to the key issues for the clinicians involved in the care of the brain-dead organ donor.

STATUS OF THE POTENTIAL DONOR AND CONSENT

A potential organ donor is defined by the presence of either brain death or a catastrophic injury to the brain with the physician’s and the family’s intent to withdraw life support. The diagnosis of brain death requires the absence of brain-stem reflexes, motor responses, and respiratory drive in a normothermic, nondrugged, comatose patient with a known irreversible brain lesion and no contributing metabolic derangements. Patients with catastrophic brain injury accompanied by the intent to withdraw life support are considered to be potential organ donors. This group of patients is an increasingly important population of donors that has recently been discussed elsewhere. The Federal Conditions of Participation of the Centers for Medicare and Medicaid Services require hospitals to notify their local organ-procurement organization in a timely manner of an impending death. “Timely” should be defined as before brain death occurs or before the withdrawal of life support, so that the suitability of the potential donor can be determined and so that donation can be discussed with the family.

Overwhelming infection generally precludes donation. However, bacteremia or fungemia are not absolute contraindications to donation. Organs transplanted from bacteremic donors rarely transmit bacterial infection, and the data suggest that the outcomes for the recipients of organs from donors who have had infection are not significantly worse than those when donors do not have infection. Organs from potential donors infected with hepatitis B or C virus may be transplanted into recipients infected with the same virus and may be considered for those who are not infected and who are in need of a life-saving transplantation. Absolute contraindications to donation are infection with the human immunodeficiency virus, human T-cell leukemia–lymphoma virus, systemic viral infections (e.g., measles, rabies, adenovirus, enterovirus, and parvovirus), prion-related disease, and herpetic meningoencephalitis. Cytomegalovirus carried within organs can induce infection with cytomegalovirus and disease in recipients, especially in those who do not have cytomegalovirus at the time of transplantation. Routine prophylaxis against cytomegalovirus has markedly reduced the mortality and morbidity associated with infection with this virus, although cytomegalovirus re-
remains a major cause of virally mediated illness in recipients of solid-organ transplants. A localized infection should not preclude the use of uninfected organs. Active malignant disease effectively precludes donation, except in the case of nonmelanoma skin cancers and certain primary brain tumors. A history of these or other types of cancer with a potential donor, which increases in proportion to the length of time between the declaration of brain death and the procurement of the organs. The progression from brain death to somatic death results in the loss of 10 to 20 percent of the potential donors. Therefore, timely treatment of the donor is critical. The use of standardized treatments and algorithms that are focused on managing the hemodynamic status of the donor have proved to be beneficial in maintaining the stability of potential donors. These strategies may make possible the recovery of organs that were initially assessed as medically unsuitable, minimize the loss of donors during maintenance, and increase the number of organs that can be procured and transplanted with favorable outcomes. Finally, all organs potentially benefit from optimal hemodynamic management. The benefit of such management is best exemplified by the increase in the percentage of kidneys that are procured and the improved graft function when both the heart and kidneys are procured together, as compared with the procurement of the kidney alone.

**CARDIOVASCULAR EFFECTS**

Postmortem studies in animals and humans have shown that brain death adversely affects the cardiovascular system. Brain death represents the culmination of progressive rostral-to-caudal ischemia. At the medullary level, ischemia provokes a sympathetic surge to maintain cerebral perfusion pressure (the difference between mean arterial pressure and intracranial pressure). In human autopsy series and in a baboon model of brain death, brain ischemia is associated with the development of myocyte necrosis that is concentrated in the left ventricular subendocardium and with ischemic changes in the electrocardiogram.

In controlled models of brain death in dogs, spinal cord ischemia coincides with herniation and results in deactivation of the sympathetic nervous system, with the attendant vasodilation, low levels of serum catecholamine, and loss of cardiac stimulation. All these events produce cardiac dysfunction and vasodilation, which are usually coincident processes that contribute to hemodynamic instability in the potential donor.

The goals of management of the hemodynamic status of the donor are to achieve normovolemia, maintain blood pressure, and optimize cardiac output so as to achieve gradients of perfusion pressure and blood flow that promote organ function with the use of the least amount of vasoactive-drug support. Figure 1 presents a stepwise approach to man-

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**MEDICAL MANAGEMENT**

The period between the occurrence of brain death and the procurement of donated organs is often punctuated by the instability of the condition of the potential donor, which increases in proportion to time. This approach affords the family time to comprehend the death before the discussion of organ donation requires consent by the family and should be performed only after the patient has been declared brain dead.

The humanitarian aspect of organ donation is critical, as was emphasized in the Organ Donation Breakthrough Collaborative’s final report on best practices. Before consent for a donation is requested, it is important to have the family fully understand that brain death means that their loved one is dead. It is also important to convey to them that the donor’s body will not be disfigured during the donation procedure and that donation does not prohibit a funeral or preclude viewing of the body. The rate of consent is substantially higher when the request for the donation is made in a private setting and is separated from the pronouncement of brain death. This approach affords the family time to comprehend the death before the discussion of organ donation is initiated. It is also advantageous to have the request for consent made by experienced personnel in conjunction with the coordinator of the organ-procurement organization. The treatment of the patient as a donor should begin immediately after brain death occurs and should continue if consent for donation is obtained.

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agement of the hemodynamic status and assessment of thresholds of stability of the potential donor. Along with continuous assessment of the stability of the condition of the donor and conventional management in the intensive care unit, all patients considered as potential cardiac donors should undergo echocardiographic evaluation. Such testing can identify structural abnormalities that would preclude cardiac transplantation and define the ejection fraction.

Cardiac donation should not be excluded on the basis of the initial echocardiogram alone, however. Hearts from relatively young patients can recover left ventricular function both while still in the donor and after transplantation. In donors in whom thresholds of cardiovascular stability are not achieved (Fig. 1) or in whom the ejection fraction is less than 45 percent, pulmonary-artery catheterization should be performed to define the left ventricular filling pressures and the cardiac output, guide the administration of vasoactive medications, and adjust the fluid balance between competing organs. This approach has improved the management of the hemodynamic status of potential donors and increased the rates of recovery of donated organs.

Figure 2 presents a model of the circulation that is useful in defining the differential diagnosis and the treatment of hemodynamic instability in potential donors. Finally, a longer period of medical management is associated with a poorer outcome for cardiac allografts; this association reinforces the necessity for timely intervention in the care of potential donors.

Hypotension is associated with a decrease in organ function. Initial hypotension may be present in up to 80 percent of donors, and sustained hypotension may occur in 20 percent of donors, despite vasoactive-drug support. Hypotension is more common in hypovolemic donors treated with vasopressors and in patients with diabetes insipidus who do not receive antidiuretic hormone. Cardiac arrest in the donor, leading to the loss of the organs to transplantation, is more common in the setting of hypotension than in other settings. Thus, the recognition of multifactorial hypovolemia and its correction are crucial. Packed red cells should be transfused to achieve a hematocrit of 30 percent in order to maintain oxygen delivery. Lactated Ringer’s solution or half-normal saline solution (0.45 percent), with the addition of sodium bicarbonate at 50 mmol per liter if the donor has acidosis, should be used to reduce the incidence of hypernatremia (i.e., sodium levels of 150 mmol per liter or higher) in donors. Hypotonic solutions should be used after the initial volume expansion to correct persistent hypernatremia. The failure to correct hypernatremia in the donor has been linked with graft loss after liver transplantation.

The infusion of large amounts of dextrose solution to replenish deficits of free water can precipitate hyperglycemia, causing osmotic diuresis and electrolyte abnormalities. Blood glucose levels should be monitored closely, and insulin infusions should be used to maintain blood glucose levels between 80 and 150 mg per deciliter (4.4 to 8.3 mmol per liter). Hydroxyethyl starch should be avoided. It can induce injury to renal tubular epithelial cells and may impair early renal graft function (i.e., graft function during the immediate postoperative period). All infused fluids should be warmed to 37°C (98.6°F) to limit the risk of hypothermia.

Competing requirements for organ perfusion may produce antagonistic strategies for fluid replacement. A minimally positive fluid balance is associated with higher rates of lung procurement, whereas aggressive volume repletion facilitates the maintenance of kidney function. The early assessment of the suitability of the potential donor organs facilitates the development of focused strategies for medical management when one or more organs are clearly not suitable for transplantation. A more liberal strategy for fluid therapy is appropriate when contraindications to lung donation are evident. Otherwise, the fluid therapy should be guided by measurements made with the use of a pulmonary-artery catheter in order to achieve ade-
Evaluation of Stability and Echocardiographic Assessment:
Mean arterial pressure, ≥60 mm Hg and
Vasoactive-drug requirement,
≤10 µg/kg/min (DA, DOB) and
Urinary output, ≥1.0 ml/kg/hr and
Left ventricular ejection fraction, ≥45%

Pulmonary-Artery Catheterization for Assessment

Goals:
Volume: Pulmonary-capillary wedge pressure, 8–12 mm Hg
Central venous pressure, 6–8 mm Hg
Pump: Cardiac index, ≥2.4 liters/min
Left ventricular stroke work index, >15 g•meters/cm²/beat
Urine output, ≥1.0 ml/kg/hr
Resistance: Mean arterial pressure, ≥60 mm Hg
Systemic vascular resistance, 800–1200 dyn•sec•cm⁻⁵

Initial specific treatment:
Fluids or diuretics
Inotropic agents
Vasopressors

Monitor up to the time of procurement

Goals met and stability obtained with vasopressor- and inotropic-drug requirements,
≤10 µg/kg/min (DA, DOB), ≤0.05 µg/kg/min (EPI), or ≤0.05 µg/kg/min (NE) and
left ventricular ejection fraction, ≥45%

Hormone-Replacement Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bolus</th>
<th>Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triiodothyronine</td>
<td>4.0 µg</td>
<td>3.0 µg/hr</td>
</tr>
<tr>
<td>or Pharynxine</td>
<td>20 µg</td>
<td>10 µg/hr</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>15 mg/kg</td>
<td>Repeat in 24 hr</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>1 U</td>
<td>0.5–4.0 U/hr</td>
</tr>
<tr>
<td>Insulin</td>
<td>10 U (50% dextrose)</td>
<td>Maintain glucose between 80 mg/dl and 150 mg/dl (minimum insulin rate, 1 U/hr)</td>
</tr>
</tbody>
</table>

Monitor up to the time of procurement

Identify organs appropriate for procurement

Reassess goals and stability
quate urine output while avoiding pulmonary edema. Measurements of the central venous pressure may not correlate with those of the pulmonary-capillary wedge pressure and therefore could increase the gradient of alveolar to arterial oxygen in the donor. In potential lung donors, colloid solutions are recommended to sustain oxygenation and minimize the accumulation of pulmonary edema. Vasoactive-drug support is necessary when the hemodynamic instability persists despite adequate

Figure 2. Hydraulic Model of Circulation in the Potential Organ Donor.

Hypotension frequently occurs as a result of many factors and requires a structured approach to the differential diagnosis. Hypovolemia can be either absolute or effective, and an accurate assessment frequently requires the use of invasive monitoring techniques. Cardiac dysfunction and vasodilation are often coincident, but they can arise from disparate processes that should be sought and corrected.
volume resuscitation. High requirements for vasoactive-drug support in the donor do not preclude successful donation. Several recent series have reported either a limited association or no association between the vasopressor requirements of the donor and the recipient and the outcome of transplantation.\textsuperscript{34-41,43} However, in 70 to 90 percent of donors, hemodynamic support can be managed successfully with volume resuscitation and low doses of vasopressors (i.e., 5 to 10 µg of dopamine per kilogram per minute or less).\textsuperscript{20} The specific goals of management of the hemodynamic status of potential organ donors are shown in Figure 1. Dopamine has been the primary vasopressor administered to potential donors with hemodynamic instability; requirements for dopamine at a dose exceeding 10 µg per kilogram per minute generally necessitate the use of additional vasoactive-drug support.

Although there is no consensus on the specific combination of catecholamines that is most useful, combination therapy has been associated with a reduction in the rates of acute rejection after renal transplantation and with improved rates of graft survival.\textsuperscript{42} The finding that the catecholamines and dopamine all appear to have distinct immunomodulatory effects, such as inhibition of the up-regulation of adhesion molecules,\textsuperscript{43} may help to mitigate the inflammation associated with the state of brain death.\textsuperscript{44-46} Epinephrine not only improves systemic hemodynamic function but also maintains renal perfusion.\textsuperscript{47} However, high doses of single agents that have predominant alpha-adrenergic or vasoconstrictor effects should be avoided. Arginine vasopressin is an alternative vasopressor that can be administered to support potential donors who have hypotension\textsuperscript{48}; it enhances the vascular sensitivity to catecholamines while maintaining hemodynamic stability.\textsuperscript{49} Similarly, hydrocortisone may enhance vascular reactivity in critically ill patients with a relative adrenal insufficiency that is commonly associated with trauma and sepsis.\textsuperscript{50}

When therapy with the use of a pulmonary-artery catheter fails to achieve hemodynamic stability and echocardiographic thresholds, hormone-replacement therapy should be strongly considered. A large body of data from studies in animals and humans supports the finding that dysfunction of the hypothalamic–pituitary–adrenal axis during brain death results in the depletion of thyroid hormone and cortisol, thereby contributing to organ deterioration.\textsuperscript{51} Low levels of thyroid hormone may impair mitochondrial function, the use of metabolic substrate, and the production of ATP. In two studies, the transition from aerobic metabolism to anaerobic metabolism correlated with organ deterioration and hypotension,\textsuperscript{52,53} and in two others exogenous hormone replacement led to a dramatic improvement in cardiovascular lability, a reduction in electrocardiographic abnormalities, a reduction in acid–base disturbances, and improvement in the suitability of organs for transplantation.\textsuperscript{54,55}

However, hormone-replacement therapy remains controversial. Several series in humans have failed to establish firmly either the presence of endocrine dysfunction associated with brain death\textsuperscript{56-58} or a correlation between cardiovascular instability, inotropic requirements, and levels of serum lactate and hormones.\textsuperscript{56,57} Other studies have failed to show improved outcomes after exogenous hormone therapy.\textsuperscript{59,60} Recently, hormone-replacement therapy was shown to diminish requirements for vasoactive therapy in 100 percent of unstable donors and to abolish such a need in 53 percent of such donors.\textsuperscript{61} Similar outcomes have been reported when hormone-replacement therapy was incorporated into a protocol for hemodynamic stabilization before organ procurement,\textsuperscript{62} and a large retrospective analysis of more than 10,000 donors during the period from January 1, 2000, to September 30, 2001, found a substantial increase in the number of organs transplanted from donors receiving hormone-replacement therapy.\textsuperscript{62} These observations have provided the foundation for ongoing prospective clinical trials that are examining the efficacy and optimal timing of hormone-replacement therapy. Until the results are available, however, it remains prudent to reserve hormone-replacement therapy for unstable donors requiring dopamine at a dose of more than 10 µg per kilogram per minute or with an ejection fraction of less than 45 percent. Serial echocardiograms after hormone replacement are recommended in order to assess its therapeutic efficacy and to define the acceptability of the heart of a potential donor for transplantation.

Cardiac arrhythmias are common and are attributable to conduction-system necrosis that is secondary to the sympathetic surge (autonomic storm) that results from medullary ischemia, metabolic disturbances, or the presence of electrolyte abnormalities. These arrhythmias are highly resistant to antiarrhythmic treatment and frequently occur during brain herniation, with the initiation of vasoactive-drug support, or as the terminal event within
48 to 72 hours after brain death has occurred. Whenever possible, the initial treatment is targeted at the correction of the causes of the arrhythmias. Standard antiarrhythmic therapy for ventricular arrhythmia (lidocaine or amiodarone) or supraventricular arrhythmia (amiodarone) is appropriate. Bradyarrhythmias that are the consequence of vagus-nerve disruption in the brain stem will not respond to atropine, and isoproterenol or epinephrine will be required. In the event of cardiac arrest, standard advanced cardiac life support should be instituted, because the recovery of cardiac function in the potential donor can result in successful transplantation.

**Respiratory Effects**

Although there have been no randomized, controlled trials of this issue, it is likely that optimal management of the respiratory function in the potential donor will enhance the donor’s cardiopulmonary status and thereby improve the quality of the organs to be donated. Respiratory management is frequently complicated by injury to the lung, the presence of neurogenic pulmonary edema induced by brain death, and the potential for multiple respiratory complications, all of which are reflected in the low rate of lung procurement (20 percent).

The implementation of standardized approaches to the management of the respiratory function in potential donors has resulted in the recovery of lungs that were initially deemed unsuitable for donation and the successful recovery and transplantation of marginally suitable lungs without jeopardy to the procurement of other organs. Table 1 lists the goals of the management of respiratory function. The low arterial carbon dioxide tension and accompanying high minute ventilation frequently used to treat elevations in intracranial pressure should be normalized. Normalization will limit the potential for ventilator-induced injury to the lungs and for systemic effects of respiratory alkalosis (e.g., systemic vasoconstriction and the leftward shift of the oxyhemoglobin dissociation curve).

Recent recognition of lung injury and inflammation as a result of the use of mechanical ventilation suggests that the strategies for alveolar recruitment to treat atelectasis should be applied judiciously and that end-inspiratory plateau pressure should be limited to less than 30 cm of water. Increased levels of inspired oxygen, rather than increased levels of positive end-expiratory pressure, should be considered when the lungs of the donor are clearly unsuitable for transplantation. In cases in which there is abnormal gas exchange in a donor with unilateral disease, bronchoscopy in conjunction with chest radiography can facilitate the evaluation and use of the contralateral lung.

Atelectasis and excessive fluid resuscitation are two correctable causes of hypoxemia that often preclude the use of lungs for transplantation. Early bronchoscopy, frequent suctioning, and targeting of ventilatory techniques at lung expansion have resulted in dramatic increases in the rate of lung procurement and in the quality of the organs. As noted above, the judicious use of fluid resuscitation to ensure end-organ perfusion while minimizing the accumulation of extravascular lung water frequently requires the use of a pulmonary-artery catheter. Small changes in hydrostatic pressure may result in substantial increases in lung water, owing to changes in the permeability of the lung. Therefore, cardiac filling pressures should be adjusted to a pulmonary-capillary wedge pressure of 8 to 12 mm Hg (or a central venous pressure of 6 to 8 mm Hg). The use of diuretic therapy is often necessary to achieve these levels.

Albuterol has been shown ex vivo and in animal studies to augment the clearance of pulmonary edema and may be considered along with the administration of diuretic drugs. Corticosteroid (e.g., methylprednisolone at a dose of 15 mg per kilogram of body weight) may also stabilize lung function in this setting. The greatest yield with this aggressive approach will be the optimization of lung function in donors whose lungs traditionally might not have been considered for donation. Such therapeutic interventions have resulted in the achievement of a ratio of the partial pressure of arterial oxygen to the inspired oxygen concentration of more than 300 in 49 percent of marginal lung donors with an initially unacceptable ratio, ultimately culminating in successful procurement. Thus, any decision regarding the suitability of a potential donor’s lungs should be made after all therapies to optimize the pulmonary status of the donor have been exhausted.

**Supportive Care**

The therapies used to control intracranial pressure (i.e., volume restriction and diuresis) in the presence of newly diagnosed diabetes insipidus frequently precipitate hypernatremia in the potential donor. Hypernatremia in the donor can adversely affect the function of the transplant in the recipi-
ent. Diabetes insipidus results from the absence of vasopressin after the destruction of the posterior pituitary gland. It contributes to hyperosmolality, hemodynamic instability, and electrolyte abnormalities (e.g., hypernatremia, hypokalemia, hypocalcemia, hypophosphatemia, and hypomagnesemia) as a consequence of an excessive loss of free water. Diabetes insipidus must be differentiated from the polyuria induced by mannitol, hyperglycemia, or diuretic agents. Matching urine output milliliter for milliliter with a 5 percent solution of dextrose in water while monitoring for hyperglycemia should suffice if the urine output is less than 200 cc per hour. Higher levels of urine output require treatment with either arginine vasopressin or 1-desamino-8-D-arginine vasopressin. Arginine vasopressin acts on the V₁ and V₂-vasopressin receptors to produce vasoconstrictive and antidiuretic effects and is administered as a continuous infusion.

1-Desamino-8-D-arginine vasopressin is specific for the V₂-vasopressin receptor and has predominantly antidiuretic effects. It can be given subcutaneously, intramuscularly, intravenously, or intranasally and has an extended duration of action (6 to 20 hours). Arginine vasopressin at a low dose decreases serum osmolality and sodium levels, maintains blood pressure, and reduces the need for vasoactive medications in the potential donor, with no deleterious short-term or long-term effect on the function of the donated kidney in the recipient. Serum electrolytes should be monitored in the potential donor every two to four hours to guide fluid replacement and electrolyte supplementation. Glucose levels in the potential donor are frequently elevated. Physical stress, increases in the levels of counterregulatory hormones, changes in carbohydrate metabolism, the infusion of dextrose-containing solutions, and peripheral resistance to insulin contribute to the development of hyperglycemia. The results of glucose-tolerance testing in donors are biphasic: there is an initial phase of suppression of pancreatic endocrine function resulting in low insulin levels, and a subsequent phase of spontaneous normalization of insulin levels and an elevation in C-peptide levels. The histopathological features of the pancreas are normal. Early elevation of glucose levels should not be used as the sole determinant in deciding whether the donor’s pancreas is likely to be suitable for procurement and transplantation. Hyperglycemic damage to pancreatic beta cells is a risk factor for graft dysfunction in the recipient. This risk can be attenuated with the use of insulin therapy in the donor, a therapy that necessitates strict glucose control by means of an insulin infusion, if needed, to achieve euglycemia.

Disorders of blood coagulation are a common consequence of the release of thromboplastin, cerebral gangliosides, and plasminogen-rich substrate from traumatized or necrotic brain tissue. These factors, superimposed on ongoing hemorrhage, transfusion, hyperthermia, acidosis, and dilution of coagulant factors, can result in a profound state of coagulopathy. Blood-product replacement should be aimed at providing adequate oxygen delivery (hematocrit, >30 percent) with correction of the coagulopathy (international normalized ratio, <2.0; platelet count, >80,000 per cubic centimeter) and at minimizing the potential for sensitization by using cytomegalovirus-seronegative blood and leukocyte filters.

The loss of hypothalamic thermoregulation, combined with an inability to shiver or vasoconstrict, results in a poikilothermic donor. This condition can be exacerbated by environmental factors and by the infusion of unwarmed fluids and blood products. Adverse effects of hypothermia include cardiac dysfunction, arrhythmias, coagulopathy, a
leftward shift of the oxyhemoglobin dissociation curve, and cold-induced diuresis. The core temperature should be maintained at higher than 35°C (95°F) by means of the warming of replacement fluids, the humidification and heating of inhaled gases, and the liberal use of convective warming blankets. Hypothermia is easier to prevent than to reverse, and temperatures lower than 35°C preclude or delay the declaration of brain death.

The care of the donor is essentially the simultaneous care of multiple recipients. Vigilant medical management ensures that the greatest number of organs can be recovered in the best possible condition to provide optimal outcomes for the recipients. Current therapies appear to enhance successful organ procurement, and these therapies may be advanced by new insights into the role of hormone-replacement therapy, the pharmacogenomic identification of the donor’s responsiveness to various therapies, and the genomic assessment of characteristics of the donor and the recipient that would make possible individually directed interventions that facilitate successful transplantation.

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