REVIEW ARTICLE

CURRENT CONCEPTS

Care of the Potential Organ Donor

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EVEN IN THE FACE OF THE URGENT NEED FOR TRANSPLANTABLE ORGANS, there continues to be a disparity between the number of potential organ donors and that of actual donors.[1] 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.[2] 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.[3,4] 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.[5] 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.[6] 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.[7] 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.[8] 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.[9] 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-

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mains 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 long cancer-free interval represents a small risk of transmission of cancer.[10] However, patients with melanoma, choriocarcinoma, lymphoma, or carcinoma of the lung, breast, kidney, or colon and potential donors with high-grade brain tumors (e.g., glioblastoma or medulloblastoma), especially those who have undergone a craniotomy or a shunt procedure, pose a high risk for the transmission of malignant disease and use of their organs should be avoided.[11,12] With the permission of the family, blood sampling to determine the suitability of the potential donor may be performed before brain death occurs. Any invasive procedure performed for the purpose of organ donation requires consent by the family and should be performed only after the patient has been declared brain dead.[13]

The humanitarian aspect of organ donation is critical, as was emphasized in the Organ Donation Breakthrough Collaborative's final report on best practices.[13] 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.[14,15] The treatment of the patient as a donor should begin immediately after brain death occurs and should continue if consent for donation is obtained.

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 the length of time between the declaration of brain death and the procurement of the organs.[16] The progression from brain death to somatic death results in the loss of 10 to 20 percent of the potential donors.[17,18] 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.[19-22] 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.[22]

CARDIOVASCULAR EFFECTS

Postmortem studies in animals and humans have shown that brain death adversely affects the cardiovascular system.[23,24] 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.[25,26] 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.[27] 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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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.[28,29] 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.[21,30,31]

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[32]; this association reinforces the necessity for timely intervention in the care of potential donors.

Hypotension is associated with a decrease in organ function.[33] 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.[16] Hypotension is more common in hypovolemic donors treated with vasopressors and in patients with diabetes insipidus who do not receive antidiuretic hormone.[34] 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.[35] 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.[36]

Figure 1 (facing page). Management of the Hemodynamic Status of the Potential Organ Donor.

In all potential donors, hemodynamic management begins with an evaluation of the thresholds of stability (i.e., mean arterial pressure, vasoactive-drug requirement, urine output, and left ventricular ejection fraction), including the use of echocardiography in potential cardiac donors. Donors who meet the thresholds should be monitored up to the time of procurement. The failure to achieve the thresholds requires the placement of a pulmonary-artery catheter in order to assess the volume status and to adjust vasoactive-drug support. Continuing failure to achieve the hemodynamic thresholds requires the use of hormone-replacement therapy. DA denotes dopamine, DOB dobutamine, EPI epinephrine, and NE norepinephrine.

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).[37] 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,[38] 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-

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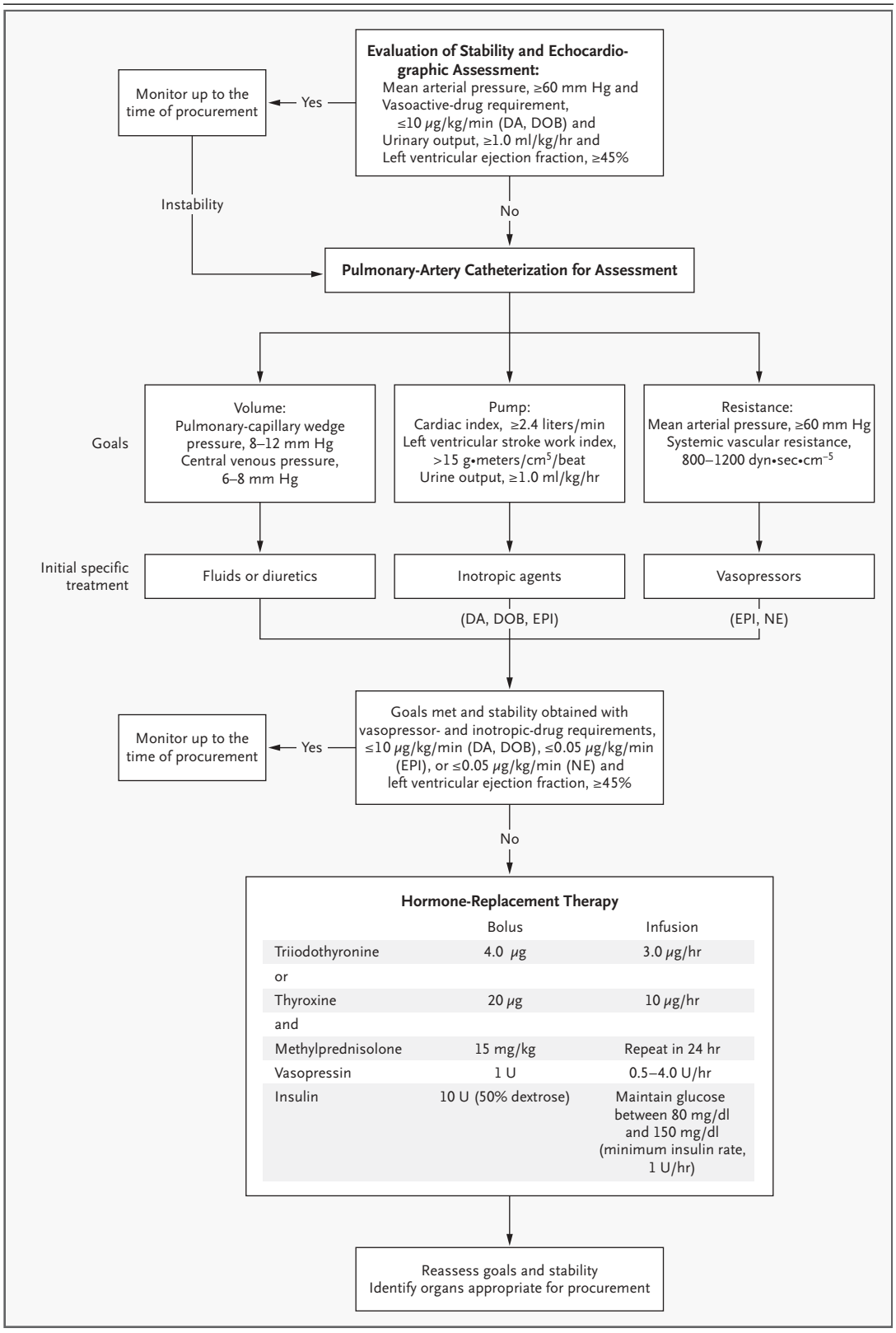

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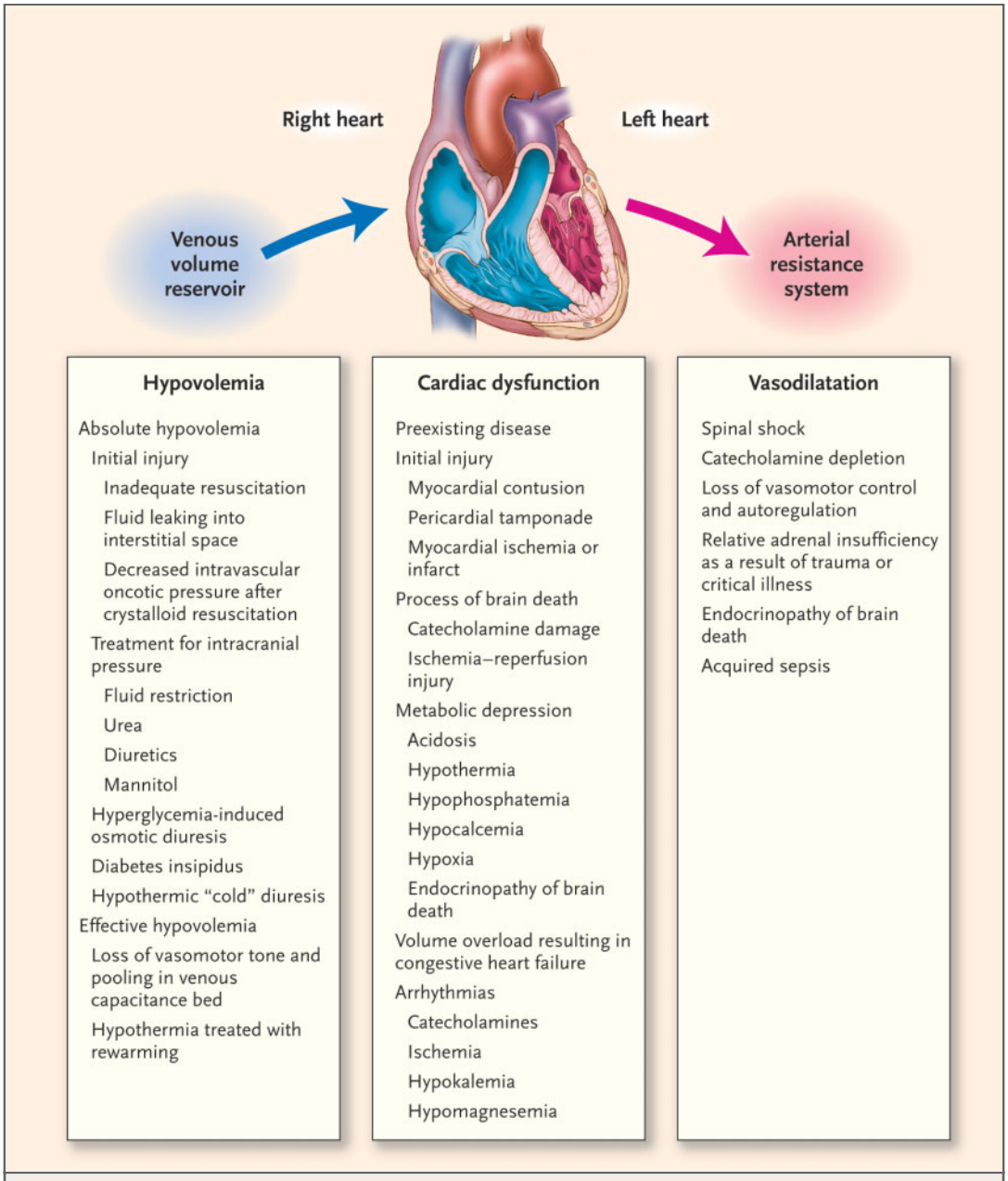

Figure 2. Hydraulic Model of Circulation in the Potential Organ Donor.
Hypotension frequently occurs as a result of many factors and requires a structured approach to the differential diagnosis. Hypovolemia can be either absolute or effective, and an accurate assessment frequently requires the use of invasive monitoring techniques. Cardiac dysfunction and vasodilation are often coincident, but they can arise from disparate processes that should be sought and corrected.

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.[39] In potential lung donors, colloid solutions are recommended to sustain oxygenation and minimize the accumulation of pulmonary edema.[40]

Vasoactive-drug support is necessary when the hemodynamic instability persists despite adequate

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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.[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).[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.[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,[43] may help to mitigate the inflammation associated with the state of brain death.[44-46] Epinephrine not only improves systemic hemodynamic function but also maintains renal perfusion.[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[48]; it enhances the vascular sensitivity to catecholamines while maintaining hemodynamic stability.[49] Similarly, hydrocortisone may enhance vascular reactivity in critically ill patients with a relative adrenal insufficiency that is commonly associated with trauma and sepsis.[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.[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,[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.[54,55]

However, hormone-replacement therapy remains controversial. Several series in humans have failed to establish firmly either the presence of an endocrine dysfunction associated with brain death[56-58] or a correlation between cardiovascular instability, inotropic requirements, and levels of serum lactate and hormones.[56,57] Other studies have failed to show improved outcomes after exogenous hormone therapy.[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.[61] Similar outcomes have been reported when hormone-replacement therapy was incorporated into a protocol for hemodynamic stabilization before organ procurement,[21] 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.[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

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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.[34]

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,[63] and the potential for multiple respiratory complications, all of which are reflected in the low rate of lung procurement (20 percent).[38]

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.[64,65] 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.[38] 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.[64,66,67] 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.[63] 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.[68] Corticosteroid (e.g., methylprednisolone at a dose of 15 mg per kilogram of body weight) may also stabilize lung function in this setting.[69] 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.[64,70] 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-

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Table 1. Management of Respiratory Function in the Potential Organ Donor.

Goals of mechanical ventilation
Fraction of inspired oxygen, 0.40
Partial pressure of arterial oxygen, >100 mm Hg; or oxygen saturation, >95 percent
Partial pressure of arterial carbon dioxide, 35–40 mm Hg
Arterial pH, 7.35–7.45
Tidal volume, 8–10 ml/kg of predicted body weight
Positive end-expiratory pressure, 5 cm of water
Static airway pressure, <30 cm of water
Goals of bronchoscopy
Evaluate anatomy
Assess for foreign body and assist in removal
Define and locate aspirated material, secretions, or apparent infection
Clearance of secretions
Goals of pulmonary hygiene
Prevent atelectasis with the use of suction, percussion, postural drainage, and lung-expansion techniques
Goals of fluid management
Central venous pressure, 6–8 mm Hg
Pulmonary-capillary wedge pressure, 8–12 mm Hg
Use of anti-infective therapy
Use of antibiotic agents on the basis of results of Gram's staining of aspirated secretions

ent. Diabetes insipidus results from the absence of vasopressin after the destruction of the posterior pituitary gland. It contributes to hyperosmolarity, 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 V_1- and V_2-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 V_2-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).[48,71] Arginine vasopressin at a low dose decreases serum osmolarity 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.[48] 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.[72] 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.[73]

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, hypothermia, acidosis, and dilution of coagulant factors, can result in a profound state of coagulopathy.[74] 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

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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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REFERENCES

1. Sheehy E, Conrad SL, Brigham LE, et al. Estimating the number of potential organ donors in the United States. N Engl J Med 2003;349:667-74.

2. Gasser M, Waaga AM, Laskowski IA, Tilney NL. Organ transplantation from brain-dead donors: its impact on short and long term outcome revisited. Transplant Rev 2001;15:1-10.

3. Wijdicks EF. The diagnosis of brain death. N Engl J Med 2001;344:1215-21.

4. *Idem.* Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. Neurology 2002;58:20-5.

5. Recommendations for nonheartbeating organ donation: a position paper by the Ethics Committee, American College of Critical Care Medicine, Society of Critical Care Medicine. Crit Care Med 2001;29:1826-31.

6. Angelis M, Cooper JT, Freeman RB. Impact of donor infections on outcome of orthotopic liver transplantation. Liver Transpl 2003;9:451-62.

7. Freeman RB, Giatras I, Falagas ME, et al. Outcome of transplantation of organs procured from bacteremic donors. Transplantation 1999;68:1107-11.

8. Lopez-Navidad A, Caballero F. Extended criteria for organ acceptance: strategies for achieving organ safety and increasing organ pool. Clin Transplant 2003;17:308-24.

9. Sarmento A, Freitas F, Tavares AP, Machado D. Organ donor viral screening and its implications in transplantation: an overview. Transplant Proc 2000;32:2571-6.

10. Kauffman HM, McBride MA, Delmonico FL. First report of the United Network for Organ Sharing Transplant Tumor Registry: donors with a history of cancer. Transplantation 2000;70:1747-51.

11. Kauffman HM, McBride MA, Cherikh WS, Spain PC, Marks WH, Roza AM. Transplant tumor registry: donor related malignancies. Transplantation 2002;74:358-62.

12. Buell JF, Trofe J, Sethuraman G, et al. Donors with central nervous system malignancies: are they truly safe? Transplantation 2003;76:340-3.

13. The Organ Donation Breakthrough Collaborative. Best practices final report (September 2003). (Accessed November 24, 2004, at http://www.organdonor.gov/bestpractice.htm.)

14. Gortmaker SL, Beasley CL, Sheehy E, et al. Improving the request process to increase family consent for organ donation. J Transpl Coord 1998;8:210-7.

15. Williams MA, Lipsett PA, Rushton CH, et al. The physician's role in discussing organ donation with families. Crit Care Med 2003;31:1568-73.

16. Nygaard CE, Townsend RN, Diamond DL. Organ donor management and organ outcome: a 6-year review from a Level I trauma center. J Trauma 1990;30:728-32.

17. Lopez-Navidad A, Domingo P, Viedma MA. Professional characteristics of the transplant coordinator. Transplant Proc 1997;29:1607-13.

18. Grossman MD, Reilly PM, McMahon DJ, et al. Loss of potential organ donors due to medical failure. Crit Care Med 1996;24:A76. abstract.

19. Jenkins DH, Reilly PM, Schwab CW. Improving the approach to organ donation: a review. World J Surg 1999;23:644-9.

20. Lopez-Navidad A, Caballero F. For a rational approach to the critical points of the cadaveric donation process. Transplant Proc 2001;33:795-805.

21. Wheeldon DR, Potter CD, Oduro A, Wallwork J, Large SR. Transforming the "unacceptable" donor: outcomes from the adoption of a standardized donor management technique. J Heart Lung Transplant 1995;14:734-42.

22. Rosendale JD, Chabalewski FL, McBride MA, et al. Increased transplanted organs from the use of a standardized donor management protocol. Am J Transplant 2002;2:761-8.

23. Wilhelm MJ, Pratschke J, Laskowski IA, Paz DM, Tilney NL. Brain death and its impact on the donor heart — lessons from animal models. J Heart Lung Transplant 2000;19:414-8.

24. Baroldi G, Di Pasquale G, Silver MD, Pinelli G, Lusa AM, Fineschi V. Type and extent of myocardial injury related to brain damage and its significance in heart transplantation: a morphometric study. J Heart Lung Transplant 1997;16:994-1000.

25. Novitzky D, Horak A, Cooper DK, Rose AG. Electrocardiographic and histopathologic changes developing during experimental brain death in the baboon. Transplant Proc 1989;21:2567-9.

26. Kolin A, Norris JW. Myocardial damage from acute cerebral lesions. Stroke 1984;15:990-3.

27. Shivalkar B, Van Loon J, Wieland W, et al. Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. Circulation 1993;87:230-9.

28. Kono T, Nishina T, Morita H, Hirota Y, Kawamura K, Fujiwara A. Usefulness of low-dose dobutamine stress echocardiography for evaluating reversibility of brain death-induced myocardial dysfunction. Am J Cardiol 1999;84:578-82.

29. Milano A, Livi U, Casula R, et al. Influence of marginal donors on early results after heart transplantation. Transplant Proc 1993;25:3158-9.

30. Jenkins DH, Reilly PM, McMahon DJ, Hawthorne RV. Minimizing charges associated with the determination of brain death. Crit Care (Lond) 1997;1:65-70.

31. Potter CD, Wheeldon DR, Wallwork J. Functional assessment and management of heart donors: a rationale for characterization and a guide to therapy. J Heart Lung Transplant 1995;14:59-65.

32. Cantin B, Kwok BW, Chan MC, et al. The impact of brain death on survival after heart transplantation: time is of the essence. Transplantation 2003;76:1275-9.

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33. Whelchel JD, Diethelm AG, Phillips MD, et al. The effect of high dose dopamine in cadaveric donor management on delayed graft function and graft survival following renal transplantation. Transplant Proc 1986; 18:523-7.
34. Finfer S, Bohn D, Colpitts D, Cox P, Fleming F, Barker G. Intensive care management of paediatric organ donors and its effect on post-transplant organ function. Intensive Care Med 1996;22:1424-32.
35. Power BM, Van Heerden PV. The physiological changes associated with brain death — current concepts and implications for treatment of the brain dead organ donor. Anaesth Intensive Care 1995;23:26-36.
36. Totsuka E, Fung JJ, Ishii T, et al. Influence of donor condition on postoperative graft survival and function in human liver transplantation. Transplant Proc 2000;32: 322-6.
37. Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P. Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. Lancet 1996;348:1620-2.
38. Reilly PM, Grossman MD, Rosengard BR, et al. Lung procurement from solid organ donors: role of fluid resuscitation in procurement failures. Chest 1996;110:222S. abstract.
39. Pennefather SH, Bullock RE, Dark JH. The effect of fluid therapy on alveolar arterial oxygen gradient in brain-dead organ donors. Transplantation 1993;56:1418-22.
40. Rosengard BR, Feng S, Alfrey EJ, et al. Report of the Crystal City meeting to maximize the use of organs recovered from the cadaver donor. Am J Transplant 2002;2:701-11.
41. Koning OH, Ploeg RJ, van Bockel JH, et al. Risk factors for delayed graft function in cadaveric kidney transplantation: a prospective study of renal function and graft survival after preservation with University of Wisconsin solution in multi-organ donors. Transplantation 1997;63:1620-8.
42. Schnuelle P, Lorenz D, Mueller A, Trede M, van der Woude FJ. Donor catecholamine use reduces acute allograft rejection and improves graft survival after cadaveric renal transplantation. Kidney Int 1999;56:738-46.
43. Schnuelle P, Berger S, de Boer J, Persijn G, van der Woude FJ. Effects of catecholamine application to brain-dead donors on graft survival in solid organ transplantation. Transplantation 2001;72:455-63.
44. Tilney NL, Paz D, Ames J, Gasser M, Laskowski I, Hancock WW. Ischemia-reperfusion injury. Transplant Proc 2001;33: 843-4.
45. Amado JA, Lopez-Espadas F, Vazquez-Barquero A, et al. Blood levels of cytokines in brain-dead patients: relationship with circulating hormones and acute-phase reactants. Metabolism 1995;44:812-6.
46. Stangl M, Zerkaulen T, Theodorakis J, et al. Influence of brain death on cytokine release in organ donors and renal transplants. Transplant Proc 2001;33:1284-5.
47. Ueno T, Zhi-Li C, Itoh T. Unique circulatory responses to exogenous catecholamines after brain death. Transplantation 2000;70: 436-40.
48. Pennefather SH, Bullock RE, Mantle D, Dark JH. Use of low dose arginine vasopressin to support brain-dead organ donors. Transplantation 1995;59:58-62.
49. Yoshioka T, Sugimoto H, Uenishi M, et al. Prolonged hemodynamic maintenance by the combined administration of vasopressin and epinephrine in brain death: a clinical study. Neurosurgery 1986;18:565-7.
50. Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: a new look at an old problem. Chest 2002;122:1784-96.
51. Lutz-Dettinger N, de Jaeger A, Kerremans I. Care of the potential pediatric organ donor. Pediatr Clin North Am 2001;48: 715-49.
52. Novitzky D. Donor management: state of the art. Transplant Proc 1997;29:3773-5.
53. Cooper DK, Novitzky D, Wicomb WN. The pathophysiological effects of brain death on potential donor organs, with particular reference to the heart. Ann R Coll Surg Engl 1989;71:261-6.
54. Novitzky D, Cooper DK, Reichart B. Hemodynamic and metabolic responses to hormonal therapy in brain-dead potential organ donors. Transplantation 1987;43: 852-4.
55. Novitzky D, Cooper DK, Morrell D, Isaacs S. Change from aerobic to anaerobic metabolism after brain death, and reversal following triiodothyronine therapy. Transplantation 1988;45:32-6.
56. Howlett TA, Keogh AM, Perry L, Touzel R, Rees LH. Anterior and posterior pituitary function in brain-stem-dead donors: a possible role for hormonal replacement therapy. Transplantation 1989;47:828-34.
57. Powner DJ, Hendrich A, Lagler RG, Ng RH, Madden RL. Hormonal changes in brain dead patients. Crit Care Med 1990;18: 702-8.
58. Gramm HJ, Meinhold H, Bickel U, et al. Acute endocrine failure after brain death? Transplantation 1992;54:851-7.
59. Randell TT, Hockerstedt KA. Triiodothyronine treatment in brain-dead multiorgan donors — a controlled study. Transplantation 1992;54:736-8.
60. Goarin JP, Cohen S, Riou B, et al. The effects of triiodothyronine on hemodynamic status and cardiac function in potential heart donors. Anesth Analg 1996;83:41-7.
61. Salim A, Vassiliu P, Velmahos GC, et al. The role of thyroid hormone administration in potential organ donors. Arch Surg 2001; 136:1377-80.
62. Rosendale JD, Kauffman HM, McBride MA, et al. Aggressive pharmacologic donor management results in more transplanted organs. Transplantation 2003;75:482-7.
63. Novitzky D, Wicomb WN, Rose AG, Cooper DK, Reichart B. Pathophysiology of pulmonary edema following experimental brain death in the chacma baboon. Ann Thorac Surg 1987;43:288-94.
64. Gabbay E, Williams TJ, Griffiths AP, et al. Maximizing the utilization of donor organs offered for lung transplantation. Am J Respir Crit Care Med 1999;160:265-71.
65. Follette D, Rudich S, Bonacci C, Allen R, Hoso A, Albertson T. Importance of an aggressive multidisciplinary management approach to optimize lung donor procurement. Transplant Proc 1999;31:169-70.
66. Parry A, Higgins R, Wheeldon D, Bethune D, Wallwork J. The contribution of donor management and modified cold blood lung perfusate to post-transplant lung function. J Heart Lung Transplant 1999;18:121-6.
67. Cummings J, Houck J, Lichtenfeld D. Positive effect of aggressive resuscitative efforts on cadaver lung procurement. J Transplant Coordination 1995;5:103-6.
68. Sakuma T, Folkesson HG, Suzuki S, Okaniwa G, Fujimura S, Matthay MA. Beta-adrenergic agonist stimulated alveolar fluid clearance in ex vivo human and rat lungs. Am J Respir Crit Care Med 1997;155:506-12.
69. Follette DM, Rudich SM, Babcock WD. Improved oxygenation and increased lung donor recovery with high-dose steroid administration after brain death. J Heart Lung Transplant 1998;17:423-9.
70. Sundaresan S, Semenkovich J, Ochoa L, et al. Successful outcome of lung transplantation is not compromised by the use of marginal donor lungs. J Thorac Cardiovasc Surg 1995;109:1075-9.
71. Richardson DW, Robinson AG. Desmopressin. Ann Intern Med 1985;103:228-39.
72. Masson F, Thicoipe M, Gin H, et al. The endocrine pancreas in brain-dead donors: a prospective study in 25 patients. Transplantation 1993;56:363-7.
73. Gores PF, Gillingham KJ, Dunn DL, Moudry-Munns KC, Najarian JS, Sutherland DE. Donor hyperglycemia as a minor risk factor and immunologic variables as major risk factors for pancreas allograft loss in a multivariate analysis of a single institution's experience. Ann Surg 1992;215:217-30.
74. Hefty TR, Cotterell LW, Fraser SC, Goodnight SH, Hatch TR. Disseminated intravascular coagulation in cadaveric organ donors: incidence and effect on renal transplantation. Transplantation 1993;55:442-3.
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