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Management of the potential organ donor

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Abstract

Management of the potential organ donor in critical care units is the most immediate and practical solution to the current crisis in organ donation. Brain death physiology significantly impacts upon the management process. Cardiovascular support is the cornerstone of donor management because it ensures donor somatic survival for procurement and maintains all of the donor organs in the best possible conditions. General applications of cardiovascular management for critically ill patients are applicable to donor management and include invasive monitoring and adjustment of vasoactive medications. Adjudicating the delicate balance between the adequacy of fluid resuscitate for organ perfusions versus minimizing the extravascular lung water from overzealous fluid resuscitation is challenging and requires vigilance with invasive monitoring. The use of hormonal resuscitation remains controversial with studies showing mixed results. Donor management is analogous to managing six to eight critically ill patients simultaneously; this period can impact the quality of the organ, the quality of life of the recipient and should be undertaken with the same level of intensity that is applied to any other critically ill patient.

1. Introduction

The most immediate and practical solution to the current organ donor crisis is the maximum use and the optimal management of the existing donor pool in critical care units. Throughout the country, there is enormous variability in the conversion rates of potential to actual donors and the medical management of the potential organ donor. Similar to approaches used in industry, standardization of processes and mitigation of variability within medicine produces more consistent outcomes. A standardized approach to successful organ donor management begins with surveillance to identify patients with severe neurologic injury likely to progress to brain death, a standardized methodology for brain death declaration, and a uniform request for consent and optimal medical management of the potential organ donor. Medical management requires a continued level of intensity; however, there is a focus shift away from cerebral protective strategies to optimizing donor organs for transplantation. In effect, this is the provision of simultaneous critical care to the organs of the recipients on the waiting list. Optimal medical management during this period is critical; it facilitates donor somatic survival so that procurement may be undertaken and maintains the organs to be procured in the best possible condition. With the increasingly recognized inflammatory response associated with brain death and the proposed immunologic continuum between donors and recipients, minimizing hemodynamic instability and ischemia reperfusion injury can improve the functionality of the graft and the quality of life in the recipient.

2. Brain death physiology

Before the declaration of brain death, the thrust of medical therapy should be toward the patient with the severe neurologic injury, seeking to minimize increased intracranial pressure and promote the survivorship of that individual. The rostral-caudal progression of ischemia that results in herniation and brain death frequently produces a stereotypic hemodynamic pattern. Ischemia at the medullary area produces an autonomic surge as a final effort to maintain cerebral perfusion pressures. This is followed by herniation and spinal cord ischemia resulting in a denervated and vasodilated state characterized by hemodynamic instability. The interval between the preceding herniation event or physiologic brain death and the actual

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declaration of brain death is frequently unknown and may be substantial. It is reasonable to aggressively treat the hypotension after the autonomic surge while awaiting the formal declaration of brain death. Similarly, aggressive support should be continued until the family has been notified of brain death and provided the opportunity to donate. In cases where consent is obtained, continued aggressive management is warranted. Insofar as cardiopulmonary management is the cornerstone of donor management, this review will focus upon strategies targeting cardiopulmonary function beginning with the post–autonomic surge hypotensive period.

3. Cardiovascular effects of brain death

The hemodynamic instability that characterizes the potential organ donor is reflective of a series of events that conspire to produce cardiac dysfunction and vasodilatation. It has become increasingly recognized that severe neurologic injury may precipitate significant cardiac dysfunction in the survivors of severe brain injury. Insofar as the magnitude of the injury is greater in nonsurvivors than survivors, it is likely that antecedent cardiac dysfunction associated with brain injury will contribute to the cardiac dysfunction in the brain-dead organ donor. It has long been recognized that neurogenic cardiac injury manifests after severe brain injury. Cerebral T-wave inversion on the electrocardiogram (ECG) and elevated troponin levels have been described, suggesting myocardial necrosis. Similarly, abnormalities in left ventricular systolic function have been described after subarachnoid hemorrhage (SAH). Recent studies suggest that the severity of the initial event will predict the degree of myocardial necrosis. There appears to be a biphasic response related to the initial event: a neural phase that occurs within hours and a humeral phase, related to the release of inflammatory cytokines, that may evolve over days. This is best reported with SAH, where diastolic dysfunction is reported to occur in approximately 70% of patients and systolic dysfunction in 10% to 28% of patients. There is an associated unique distribution of apical sparing, with the cardiac contractile abnormalities being reversible in most cases [1]. In the SAH population, it appears that the magnitude of the cardiac damage, as evidence by troponin release, is correlative with the degree of the Hunt-Hess severity score. Approximately 80% of patients with a Hunt-Hess score of 5 will show evidence of troponin release, with the highest mean troponin release occurring in the first 2 days of the event. Mechanistically, the catecholamine release hypothesis, with its impact upon sympathetic innervation, has been proposed to account for these abnormalities because perfusion imaging demonstrates normal coronary blood flow. It has been reported that this global cardiac denervation is related to the lowest ejection fraction and the most impaired regional wall motion score. In patients with SAH not manifesting cardiac denervation, the ejection fraction was preserved [2,3]. Although not studied in other populations with severe brain injury, it is likely that a similar manifestation of cardiac dysfunction would be associated with severe head trauma and non-SAH brain injury. In those patients who eventuate in brain death, these cardiac manifestations will become apparent during the evaluation and management of the potential organ donor. It is important to recognize that the reported literature suggests that this neurocardiogenic injury may be reversible.

Similar to the antecedent neurogenic cardiac injury from severe brain injury, there is evolving evidence to suggest that traumatic brain injury precipitates endocrine failure. Pathophysiologically, this is thought to be related to diminished input from the cortical structures that will secondarily affect the hypothalamic pituitary axis release of hormones (catecholamines, somatomedin); neuroendocrine effects altering the hypothalamic pituitary axis; and multiple systemic processes, including inflammation, infection, hypoxemia, and hypotension. In addition, there may be direct injury to the hypothalamus and pituitary secondary to compression with edema, fracture, hemorrhage, or abnormalities in the vascular supply secondary to the traumatic injury [4,5]. Although not well reported, there is evolving literature that suggests significant endocrine failure after traumatic brain injury. Several studies have found evidence of anterior pituitary dysfunction in approximately 30% of survivors of traumatic brain injury and abnormal function in at least 1 anterior pituitary axis present in 53% of survivors. Other reviews have reported the incidence of hormonal reduction to reflect adrenal dysfunction in 15%, thyroid dysfunction in 5% to 15%, growth hormone dysfunction in 18%, vasopressin deficiencies in 3% to 7%, and gonadal abnormalities in 25% to 80% of survivors. Reported associations include basilar skull fracture, hypothalamic edema, prolonged unresponsiveness, hypernatremia, and associated hypotension [4-6]. Similar to the preceding discussion of cardiac dysfunction related to severe brain injury before brain death, it would appear that there are significant endocrine abnormalities associated with severe neurologic injury. This assumes greater importance given the evolving literature, suggesting benefit with hormonal resuscitation for organ donors with cardiac dysfunction.

In conjunction with the previously described pre–brain death events, the rostral-caudal progression of cerebral spinal ischemia or coning produces significant cardiovascular abnormalities. Ischemia at the medulla oblongata produces autonomic storm, which is a profound sympathetic stimulation. This is the patient's final effort to maintain cerebral perfusion pressures. Dramatic elevations in levels of catecholamines occur during this period, producing ECG, hemodynamic, histopathologic, and biochemical changes in cardiac function. With continuing ischemia at the spinal cord level and subsequent herniation, there is sympathetic deactivation characterized by

bradycardia with low cardiac output and low blood pressure. Brain death and herniation with the accompanying hemodynamic abnormalities are thought to produce a significant ischemia reperfusion injury with an intense inflammatory response that is associated with diffuse endothelial injury. The magnitude of the brain death event on cardiac function is evident in a recent study that compared brain-dead organ donor cardiac function in patients whose autonomic storm was treated with donors in whom treatment was not undertaken. Previously, only animal models showed attenuation of the cardiac dysfunction with the treatment of the autonomic surge. Using a diagnosis of autonomic storm that included an increase in systolic arterial pressure to more than 200 mm Hg associated with tachycardia of more than 140 beats per minute, an autonomic surge was observed in approximately 63% of patients. The duration of the autonomic surge was approximately 1.2 hours (with a range of 30 minutes–6 hours). Associated hypotension uniformly followed the autonomic storm, but hypotension was never present when the autonomic storm was absent. The autonomic surge occurred less frequently with head injury. The treatment group received esmolol, Urapidil, or nicardipine. Left ventricular ejection fraction was significantly higher in the donor patients treated for autonomic storm, who were found to be independently associated with a left ventricular ejection fraction of more than 50%. Treatment of the autonomic storm or the lack of autonomic storm was associated with an increased probability of successful cardiac transplantation. The authors concluded that the treatment of the autonomic surge may attenuate brain death–induced myocardial dysfunction and increase the number of available cardiac grafts [7]. This study is presented to underscore the magnitude of the cardiac injury associated with catecholamine surge and the extent to which it can compromise cardiac function after brain death, mitigating against cardiac procurement. Recommendations regarding the treatment of patients with incipient herniation remain problematic as the catecholamine surge is that brain injured patient's compensatory mechanism to maintain cerebral perfusion pressure gradients. Aborting that compensatory mechanism in a patient who has not been pronounced brain dead raises significant concern. Corroborating evidence of significant cardiac dysfunction related to the brain death event is evident in the limited literature that has evaluated cardiac allograft vasculopathy. The catecholamine surge associated with brain death is reported to precipitate coronary vasoconstriction, subendocardial ischemia, focal myocardial necrosis, and endothelial injury. In donors succumbing to an explosive mode of death, there is a higher incidence of intimal thickening of the coronary arteries, sudden death, myocardial infarction, and need for revascularization. In cases of domino transplantation, there is a reduced incidence of coronary artery disease in recipients of domino hearts compared with recipients of cadaver hearts [8-11].

Hypothalamic and pituitary destruction consequent to brain death are thought to precipitate the endocrinopathy of brain death. This is characterized by significant diminutions in the production of anterior and posterior pituitary hormones. Resulting deficiencies in thyroid and adrenal hormones are thought to jeopardize energy stores and impair myocardial contractility in the brain-dead organ donor. The absence of thyroid hormone is thought to impair mitochondrial function and energy substrate use and mediate the transition from aerobic to anaerobic metabolism. Diminished cardiac contractility is thought to be partially reflective of low thyroid hormone levels. Significant animal evidence and limited human data suggest that hormonal cocktails consisting of thyroid hormone, corticosteroids, and vasopressin may effectively improve cardiac contractility. These hormonal therapies will be discussed in subsequent sections. In addition to this, Szabo [12] has suggested that there are significant abnormalities in preload and afterload conditions and that impaired cardiac perfusion pressure gradients are the main determinants of impaired myocardial contractility. His experimental models have suggested that reduced myocardial contractility after brain death may be seen as a physiologic response to decreased preload and afterload conditions and impaired coronary perfusion pressures.

4. Cardiovascular and hemodynamic management

Independent of which of the preceding mechanisms are predominantly operative, it is clear that there are multiple reasons for hemodynamic instability and cardiac dysfunction in the potential organ donor. Hemodynamic and cardiovascular management form the cornerstone of potential organ donor management. Optimal cardiovascular management ensures that the potential organ donor will somatically survive for procurement and maintains the other organs in the best condition for procurement. The management approach requires a continued level of intensity recognizing that the management of the potential organ donor is the medical management of 7 other recipients. Similar to the care of any other critically ill patient, this requires a collaborative multidisciplinary approach that uses the specific skill sets of intensivists, pulmonary consultants, cardiac consultants, nurses, and respiratory therapists in conjunction with the organ procurement organization (OPO) coordinator. Standardizing the organ donor management process with recommendations for general management, laboratory and diagnostic studies, respiratory therapy treatments, intravenous fluids, and medications from referral to declaration, including management and recovery, resulted in a 10.3% increase per 100 donors and a 3.3% increase in total organs per 100 donors transplanted [13]. Recently, the University of Southern California (Los Angeles, CA) donor management team hypothesized that brain death–related complications

would have no significant impact on the number of organs donated, provided an aggressive organ donor management protocol was in place. The following were identified as complications: vasopressor requirement (97.1%), coagulopathy (55.1%), thrombocytopenia (53.3%), diabetes insipidus (46.4%), cardiac ischemia (30.4%), lactic acidosis (24.6%), renal failure (20.3%), and acute respiratory distress syndrome (13%). With an aggressive management approach, there was no significant effect of complications on the mean number of organs procured, with the exception of an increase for the organs procured in the presence of diabetes insipidus [14]. Benefits of an aggressive donor management protocol were reported by the same group that compared a policy of aggressive donor management with conventional treatment. Aggressive donor management consisted of early identification of potential organ donors, a dedicated team that provided medical management and aggressive fluid resuscitation along with hormonal replacement using solumedrol and thyroxine. The aggressive donor management policy resulted in multiple benefits: a decrease in the number of family declines for transplantation, a dramatic diminution in the number of donors lost from cardiovascular collapse (42%–5%), improvement in conversion rates from 26.6% to 41.2%, and an increase in number of organs recovered [15]. This strongly suggests that a standardized multidisciplinary approach, similar to that for any other critically ill patient, will have multiple beneficial effects upon the organ donor management process. This takes on added importance given the nonuse of hearts and lungs after consent has been obtained. A Canadian multicenter study revealed a rate of use of 39% for heart and 28% for lung donors. Organ function was the most frequently cited reason for nonuse, followed by donor characteristics and logistic issues. In 31% of the hearts and 18% of the lungs, suggestions for alternative management that may have potentially resulted in organ use were made but were not successfully implemented [16].

Fig. 1 represents an algorithm approach to the hemodynamic management of the potential organ donor. Stability assessments consisting of a mean arterial blood pressure, vasoactive drug requirements, urinary output, and echocardiographic assessment should be undertaken in all potential organ donors. Donors achieving the thresholds in Fig. 1 should be considered to be stable and monitored to the time of procurement. Although echocardiography should be performed in all potential donors, the timing of the echocardiography is crucial. Echocardiography performed immediately after diagnosis of brain death is likely to be abnormal, especially if acid-base, electrolyte, and hemodynamic stability are not achieved. The impact of left ventricular dysfunction on cardiac donor transplant rates is substantial. In a recent study assessing the reasons for nontransplantation, 44% of potential heart donors were not used. Echocardiographic abnormalities were the reason for exclusion in 28% of potential heart donors, and multivariable analysis revealed that a diminished ejection fraction was the most significant predictor for nonuse, with an odds ratio of 1.48 per 5% decrease in ejection. The authors concluded that efforts to improve cardiac yield should focus upon the prevention or reversal of left ventricular dysfunction [17]. Given the previously defined echocardiographic abnormalities associated with neurocardiac injury and those related to the physiology of brain death, echocardiographic abnormalities are very common in the potential organ donor. In a recent study that evaluated clinical, echocardiographic, and pathologic features of myocardial dysfunction in brain death, systolic dysfunction was reported in 42% of potential organ donors. This dysfunction was not predicted by clinical, ECG, or head computed tomographic characteristics. More importantly, there was a very poor correlation between the area of echocardiographic abnormality and the histopathology of hearts that were not procured [18]. It is highly likely that a substantial degree of myocardial dysfunction after brain death is reversible, and no heart should be excluded after 1 initial echocardiogram. In a retrospective review of all donors with ejection fractions of less than 50% or regional wall motion abnormalities on the initial echocardiogram, significant improvement was seen in 12 of 13 patients, with a mean ejection increase from 41% to 56%. Medical management during this period consisted of guidelines that mandated invasive hemodynamic monitoring, inotropic support with dopamine, a central venous pressure (CVP) goal of 5 to 8 mm Hg, and corticosteroid supplementation. In this retrospective review, it should be noted that none of the donors received thyroid hormone. The responders were transplanted, with a 92% survival at 16 months. The authors recommended that before the first echocardiogram, volume status, acidosis, hypoxia, hypercardia, electrolyte, abnormalities, and anemia should be corrected [19].

In patients failing to achieve the stability threshold defined in Fig. 1, invasive monitoring to assess the adequacy of intravascular volume, cardiac function, and peripheral resistance, is necessary. Traditionally, this has been interpreted to mean placing a pulmonary artery catheter from which the preceding hemodynamic variables can be derived. The success in the studies that have reported use of the pulmonary artery catheter for donor management is most likely related to the added level of vigilance and commitment to management rather than the actual pulmonary artery catheter itself because there are very limited data in the world's literature to uniformly support the use of a pulmonary artery catheter. Contemporary assessments of intravascular volume pressure and flow using continuous echocardiography, cardiac output devices, or other means, are likely to yield the same improved results. Hemodynamic instability is common in most potential organ donors. Fig. 2 represents an overview of the causes of hemodynamic instability in the potential organ donor. In many instances, the potential organ donor represents the triad of hemodynamic instability characterized by hypovolemia, cardiac dysfunction, and

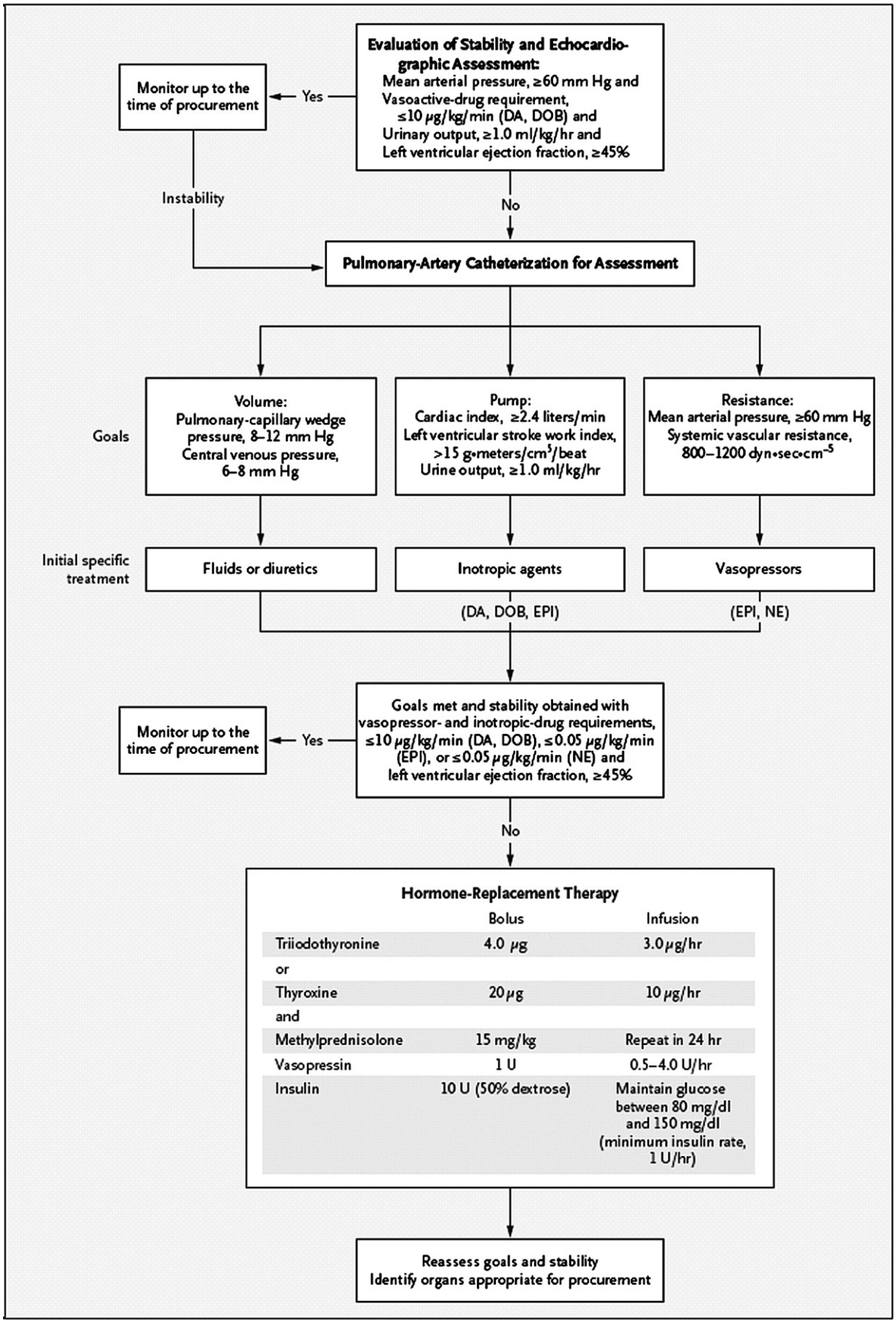

Fig. 1. Approach to hemodynamic management. Reprinted with permission from the Massachusetts Medical Society [20]. Copyright © 2004 Massachusetts Medical Society. All rights reserved. DA indicates dopamine; DOB, dobutamine; EPI, epinephrine; NE, norepinephrine.

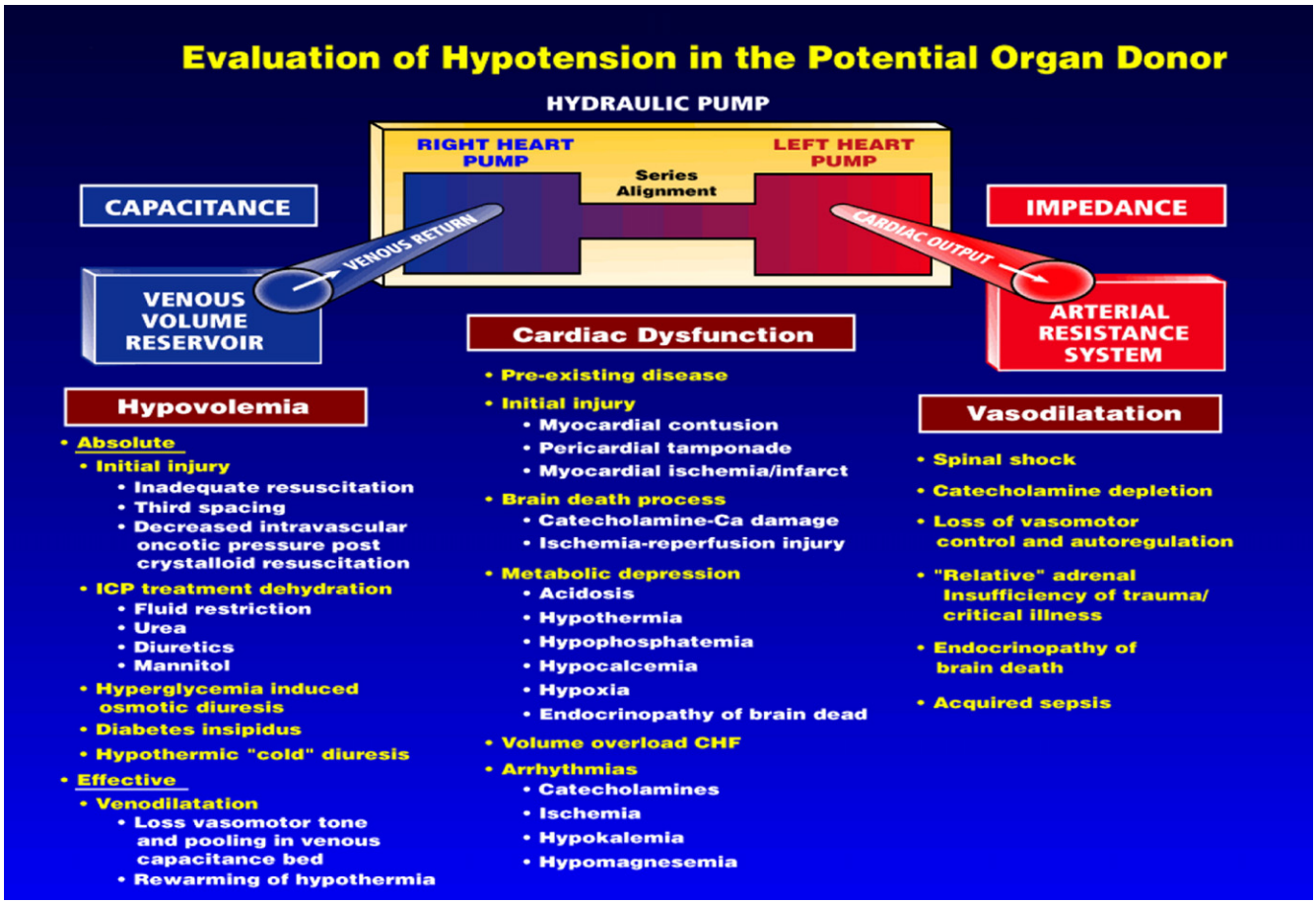

Fig. 2. Causes of hemodynamic instability.

vasodilatation. The hypovolemia is usually related to fluid restriction, diuretics, and mannitol treatment for increased intracranial pressure. Posterior pituitary dysfunction manifesting as diabetes insipidus and hyperglycemic-induced osmotic diuresis further contribute to decreased intravascular volume. The hypothermic patient may also undergo a cold diuresis, and the preceding may be superimposed upon inadequate volume resuscitation during the initial injury. Loss of the central nervous system sympathetic outflow results in vasodilatation, and the loss of vasomotor tone precipitates pooling of volume in the venous capacitance reservoir. Similarly, rewarming of the patient may precipitate vasodilatation and contribute to low effective intravascular volume.

Frequently, there are antagonistic and competing interests between the above-the-diaphragm organs and the below-the-diaphragm organs. Kidney function is enhanced by the maintenance of adequate urine output and a diminution in the creatinine level related to expanded intravascular volume. Alternatively, lung function is enhanced by diminished intravascular volume. This facilitates gas exchange and improves the cosmetic appearance on the chest x-ray, especially when large tidal volumes are used. This combination may facilitate achieving the goals of the ideal lung for procurement. Adjudicating these competing organ interests oftentimes requires invasive monitoring to achieve optimal fluid balance and ensure adequate perfusion to the kidneys while mitigating against the accrual of extravascular lung water that would jeopardize pulmonary procurement. One strategy to achieve this balance requires the initial assessment of lung suitability. In cases where the lungs are clearly not suitable (massive aspiration or a gun shot to the chest), a more liberal fluid strategy would be appropriate, provided the ability to maintain systemic oxygenation is preserved. Other instances require invasive monitoring to accurately define intravascular volume. Similar to any other intensive care unit patient, judicious fluid resuscitation is appropriate because progressive pulmonary dysfunction associated with a significant positive fluid in balance is thought to represent one of the greatest reasons for lung nonsuitability [21]. All fluids should be warmed to avoid hypothermia. Ringer's lactate is preferred over normal saline to minimize the risks of hypernatremia, which has been showed to jeopardize liver graft function postoperatively [22]. In this study, a serum sodium level of less than 155 mmol/L was

associated with a 12.7% incidence of graft dysfunction at 90 days. A serum sodium level in the donor of more than 155 mmol/L was associated with a 33% graft dysfunction at 90 days. Donors who initially had a serum sodium level of more than 155 mmol/L but were subsequently treated and had a final sodium level of less than 155 mmol/L had an incidence of graft dysfunction similar to those with a sodium level that was maintained at less than 155 mmol/L. Limited evidence suggests that hetastarch promotes renal tubular toxicity and probably should be avoided [23]. Packed red blood cells should be used to achieve a hematocrit level of approximately 30% in an effort to optimize organ oxygen delivery. The management of diabetes insipidus will be discussed subsequently. Hypotonic solutions should be used after the initial volume expansion to correct persistent hypernatremia. It is crucial to ensure that hyperglycemia does not result from large amounts of dextrose-containing solutions that may additionally precipitate osmotic diuresis and associated electrolyte abnormalities in addition to those observed with diabetes insipidus.

Cardiac dysfunction and vasodilatation are almost uniformly coincident processes in the potential organ donor. Cardiac dysfunction may arise from preexisting disease, initial injury associated with myocardial contusion, pericardial tamponade, ischemia, or the previously described neurogenic cardiac injury with residua of the brain death event. Similarly, acidosis, hypothermia, hypocalcemia, hypoxia, hypophosphatemia, and the endocrinopathy associated with brain death may all be contributory. Vasodilatation results from the loss of vasomotor control and autoregulation associated with brain death. Other contributing processes may be spinal shock, catecholamine depletion, the relative adrenal insufficiency of trauma or critical illness, the endocrinopathy of brain death, and acquired sepsis. Most organ donors require vasoactive support either with a single agent or in combination. Unfortunately, there are no randomized controlled trials to allow for a strong recommendation regarding the choice of vasopressors. Similarly, previous recommendations regarding the adverse effects of catecholamines were derived from many retrospective series where there was a lack of attention to the adequacy of intravascular volume. Consequently, the reported medical literature contains series that highlight the adverse outcomes of vasopressors. Adverse effects of catecholamines are thought to arise from the biochemical and histopathologic functional effects characterized by high-energy substrate depletion, intramyocardial norepinphrine depletion, and down-regulation of the myocardial β-adenoreceptors. Poor functional outcomes have been observed with high-dose dopamine and higher inotropic support with norepinphrine [24-29]. The rationale for the beneficial effects of catecholamines relates to the well-described decrease in circulating catecholamines post–autonomic surge, resulting in a loss of vascular tone and the reduction of inotropy. Avoidance of catecholamines fosters a reliance on fluids to maintain blood pressure, which will only provide limited periods of hemodynamic stability, may further jeopardize right ventricular function, and potentially increases extravascular lung water, jeopardizing lung procurement. Endogenous catecholamines are postulated to counteract the decrease in catecholamine levels after the autonomic surge and facilitate perfusion pressure gradients and add inotropic support to the myocardium. Other studies have not found adverse biochemical, histopathologic, or functional outcomes with catecholamine use [30-34]. Recently, improved 4-year survival for renal grafts was reported with donor catecholamine use. This was attributed to an immunomodulatory effect of dopamine at conventional doses. However, there was significant organ variance, and a negative effect was seen on cardiac 4-year survival [35].

Traditionally, dopamine has been the inotrope of choice in doses titrated to ensure cardiac output and vasoconstriction to ensure perfusion pressure gradients to the myocardium and the renal circulation. Given posterior pituitary destruction with the resultant vasopressin deficiency, vasopressin has been recommended for hemodynamic support and for the treatment of diabetes insipidus [36]. As illustrated in Fig. 1, therapy should be as specific as possible to achieve the thresholds for procurement. Adequacy of intravascular volume should be ensured, and inotropic support should be used for donors with a predominantly low cardiac output and vasoconstrictors used in donors with a predominant decrease in vascular resistance. When a donor fails to achieve the defined thresholds, hormonal replacement therapy should be considered in an effort to achieve stabilization. This is a controversial issue, and recommendations span the spectrum of using hormonal resuscitation in all donors immediately after brain death to selectively reserving hormonal resuscitation for unstable donors who have failed to respond to conventional hemodynamic stabilization. Given this controversy, it is prudent to thoroughly examine the pathophysiology of the endocrinopathy of brain death in the existing studies.

5. Endocrine therapy

The hypothalamus lies at the base of the brain between the third ventricle and the optic chiasm and derives its blood supply from the superior hypophyseal artery. The median eminence of the hypothalamus forms an intricate vascular connection with the anterior portion of the pituitary gland within the pituitary stalk. The pituitary gland, located outside the dura in the sella turcica, is formed from 2 distinct embryologic tissues. The adenohypophysis, or anterior pituitary, is derived from Rathke's pouch within the embryologic oral cavity. The neurohypophysis, or posterior pituitary, is derived from neural ectoderm in the embryologic forebrain. During early brain development, these tissues combine to form the complete pituitary gland. However,

these 2 portions remain distinctly different in their blood supply, innervation, and specific hormone production.

The anterior pituitary does not have a direct arterial supply and instead derives it blood supply from the hypothalamus. As blood drains from the capillary plexus supplying the median eminence of the hypothalamus, it empties into a portal venous system that follows the pituitary stalk and enters a second capillary plexus bathing the anterior pituitary. Eventually, this second vascular capillary network drains to the petrosal sinuses and enters the systemic circulation through the internal jugular vein. This series of capillary networks permits a direct, low-pressure vascular connection between the hypothalamus and the anterior portion of the pituitary gland, allowing for exquisitely sensitive stimulation and control through this portal vascular capillary network. The median eminence of the hypothalamus contains multiple neuronal terminals, which release regulatory hormones directly into the vascular bed. These hypothalamic hormones are small peptides that lack binding proteins and are easily degraded in the systemic circulation. However, given the direct vascular connection and close anatomical proximity, high concentrations of hypothalamic hormones are easily achieved without significant degradation. In addition, the anterior pituitary is exquisitely sensitive to pulsatile stimulation from the hypothalamic hormones, facilitated by seclusion of this vascular network from interference of the systemic circulation. The hypothalamus stimulates anterior pituitary production and release of various hormones, including adrenocorticotropic hormone, growth hormone, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, melanocyte-stimulating hormone, and various endorphins. The hypothalamus also provides inhibitory control over the anterior pituitary's production and release of somatostatin and prolactin.

Conversely, the blood supply for the posterior pituitary gland is derived from the inferior hypophyseal artery. Whereas the portal pituitary vascular network connects the hypothalamus–anterior pituitary glands, the hypothalamic–posterior pituitary connections are primarily neuronal in nature. These neurons originate in the supraoptic and paraventricular nuclei of the hypothalamus and terminate in the posterior pituitary. The 2 primary hormones produced through this system are vasopressin and oxytocin, which are then released into the peripheral circulation via inferior hypophyseal veins.

The combination of regulatory mediators and hormones produced via the hypothalamic-pituitary axis encompass virtually every aspect the human endocrine system. The unique blood supply of the anterior pituitary from the hypothalamus allows close regulation without significant interference from systemic mediators and factors. When a catastrophic injury affects the brain, causing elevated intracranial pressures and subsequent herniation, this vascular network is disrupted, both in terms of the arterial supply through the superior and inferior hypophyseal arteries and through venous drainage. With complete loss of the hypothalamic-pituitary axis, sustained survival without exogenous hormonal supplementation would be unlikely. However, the effect of acute brain injury on systemic hormonal production and regulation, and the impact upon hemodynamic instability in the potential organ donor, remains controversial.

The impact of severe brain injury and catastrophic neurologic illness upon the neuroendocrine axis has recently been described. There is evolving evidence for at least temporary dysfunction of the endocrine system during severe critical illnesses, with a significant portion of those patients developing long-term endocrine abnormalities [37]. Powner et al [4] have recently reported the presence of neuroendocrine abnormalities related to hypothalamic-pituitary axis dysfunction in up to 40% of subjects after acute brain injuries. Ceballos [38] has previously shown evidence of pituitary hemorrhage or necrosis present at the time of autopsy in more than 80% of subjects after traumatic brain injury. Neuroendocrine dysfunction may develop subacutely after traumatic brain injury and may complicate the rehabilitation process if unrecognized. In addition, the extent of neuroendocrine dysfunction is difficult to predict across the broad range of severity in brain injuries. However, at the extreme end of this spectrum, when the traumatic event leads to diffuse brain injury, hemorrhage, and subsequent herniation, dysfunction of the hypothalamic-pituitary axis should be expected. Animal models have demonstrated significant dysfunction in the neuroendocrine axis after experimental brain death induction [39-41]. In these experimental models, brain death has typically been induced through the sudden expansion of a balloon inserted into the skull, producing massive elevation in intracranial pressures [39]. After an initial rise in catecholamine levels, marked by extreme hypertension and tachycardia consistent with autonomic storm, these animal models have demonstrated decline in both anterior and posterior pituitary hormones [40]. Early animal studies have also suggested improvement in hemodynamic status of the brain-dead animal and improvement in ultimate graft function with hormonal supplementation [42,43].

Studies designed to assess for the presence of this neuroendocrine dysfunction in human organ donors and evaluate the role of exogenous hormonal supplementation have been less convincing, producing both supportive and conflictive results. Some studies have demonstrated improvement in the hemodynamic status of brain-dead donors with exogenous hormonal supplementation, with less need for vasoactive support and improved aerobic metabolism [44,45]. Others have not shown a consistent decline in pituitary hormones after brain death or improvement with hormonal supplementation. In these studies, aggressive volume replacement was sufficient for hemodynamic support, with similar outcomes between groups [46,47]. The disparity between these various studies

Table 1

Critical Pathway for the Organ Donor

Patient name: _____

ID number: _____

Collaborative Practice	Phase I Referral	Phase II Declaration of Brain Death and Consent	Phase III Donor Evaluation	Phase IV Donor Management	Phase V Recovery Phase
The following professionals may be involved to enhance the donation process. *Check all that apply.* ❍ Physician ❍ Critical care RN ❍ Organ Procurement Organization (OPO) ❍ OPO coordinator (OPC) ❍ MedicalExaminer (ME)/ Coroner ❍ Respiratory ❍ Laboratory ❍ Pharmacy ❍ Radiology ❍ Anesthesiology ❍ OR/Surgery staff ❍ Clergy ❍ Social worker	❍ Notify physician regarding OPO referral ❍ Contact OPO ref: Potential donor with severe brain insult ❍ OPC on site and begins evaluation Time _____ Date _____ ❍ Ht_____ Wt _____ as documented ❍ ABO as documented _____ ❍ Notify house supervisor/ charge nurse of presence of OPC on unit	❍ Brain death documented Time _____ Date _____ ❍ Pt accepted as potential donor ❍ MD notifies family of death ❍ Plan family approach with OPC ❍ Offer support services to family (clergy, etc) ❍ OPC/Hospital staff talks to family about donation ❍ Family accepts donation ❍ OPC obtains signed consent & medical/social history Time _____ Date _____ ❍ ME/Coroner notified ❍ ME/Coroner releases body for donation ❍ *Family/ME/Coroner denies donation—stop pathway—initiate post-mortem protocol—support family.*	❍ Obtain pre/post transfusion blood for serology testing (HIV, hepatitis, VDRL, CMV) ❍ Obtain lymph nodes and/or blood for tissue typing ❍ Notify OR & anesthesiology of pending donation ❍ Notify house supervisor of pending donation ❍ Chest & abdominal circumference ❍ Lung measurements per CXR by OPC ❍ *Cardiology consult as requested by OPC (see reverse side)* ❍ *Donor organs unsuitable for transplant—stop pathway—initiate post-mortem protocol—support family.*	❍ OPC writes new orders ❍ Organ placement ❍ OPC sets tentative OR time ❍ Insert arterial line/ 2 large-bore IVs ❍ Possibly insert CVP/Pulmonary Artery Catheter ❍ **See reverse side**	❍ Checklist for OR ❍ Supplies given to OR ❍ Prepare patient for transport to OR ❍ IVs ❍ Pumps ❍ O_2 ❍ Ambu ❍ Peep valve ❍ Transport to OR Date _____ Time _____ ❍ OR nurse ❍ reviews consent form ❍ reviews brain death documentation ❍ checks patient's ID band
Labs/Diagnostics		❍ Review previous lab results ❍ Review previous hemodynamics	❍ Blood chemistry ❍ CBC + diff ❍ UA ❍ C & S ❍ PT, PTT ❍ ABO ❍ A Subtype ❍ Liver function tests ❍ Blood culture X 2 / 15 minutes to 1 hour apart ❍ Sputum Gram stain & C & S ❍ Type & Cross Match _____# units PRBCs ❍ CXR ❍ ABGs ❍ EKG ❍ Echo ❍ Consider cardiac cath ❍ Consider bronchoscopy	❍ Determine need for additional lab testing ❍ CXR after line placement (if done) ❍ Serum electrolytes ❍ H & H after PRBC Rx ❍ PT, PTT ❍ BUN, serum creatinine after correcting fluid deficit ❍ Notify OPC for ___ PT >14___ PTT > 28 ___ Urine output ___ < 1 mL/Kg/hr ___ > 3 mL/Kg/hr ___ Hct < 30 / Hgb <10 ___ Na >150 mEq/L	❍ Labs drawn in OR as per surgeon or OPC request ❍ Communicate with pathology: Bx liver and/ or kidneys as indicated
Respiratory	❍ Pt on ventilator ❍ Suction q 2 hr ❍ Reposition q 2 hr →	❍ Prep for apnea testing: set FiO_2 @ 100% and anticipate need to decrease rate if PCO_2 < 45 mm Hg	❍ Maximize ventilator settings to achieve SaO_2 98 - 99% ❍ PEEP = 5cm O_2 challenge for lung placement FiO_2 @ 100%, PEEP @ 5 X 10 min ❍ ABGs as ordered ❍ VS q 1° →	❍ Notify OPC for ____ BP < 90 systolic ____ HR < 70 or > 120 ____ CVP < 4 or > 11 ____ PaO_2 < 90 or ____ SaO_2 < 95%	❍ Portable O_2 @ 100% FiO_2 for transport to OR ❍ Ambu bag and PEEP valve ❍ Move to OR →
Treatments/ Ongoing Care		❍ Use warming/cooling blanket to maintain temperature at 36.5° C - 37.5 °C ❍ NG to low intermittent suction	❍ Check NG placement & output ❍ Obtain actual Ht _____ & Wt _____ if not previously obtained	→	❍ Set OR temp as directed by OPC ❍ Post-mortem care at conclusion of case
Medications			❍ Medication as requested by OPC →	❍ Fluid resuscitation—consider crystolloids, colloids, blood products ❍ DC meds except pressors & antibiotics ❍ Broad-spectrum antibiotic if not previously ordered → ❍ Vasopressor support to maintain BP > 90 mm Hg systolic ❍ Electrolyte imbalance: consider K, Ca, PO_4, Mg replacement ❍ Hyperglycemia: consider insulin drip → ❍ Oliguria: consider diuretics ❍ Diabetes insipidus: consider antidiuretics ❍ Paralytic as indicated for spinal reflexes	❍ DC antidiuretics ❍ Diuretics as needed ❍ 350 U heparin/kg or as directed by surgeon →
Optimal Outcomes	The potential donor is identified & a referral is made to the OPO.	The family is offered the option of donation & their decision is supported.	The donor is evaluated & found to be a suitable candidate for donation.	Optimal organ function is maintained.	All potentially suitable, consented organs are recovered for transplant.

Shaded areas indicate Organ Procurement Coordinator (OPC) Activities.

This Critical Pathway was developed under contract with the U.S. Department of Health and Human Services, Health Resources and Services Administration, Division of Transplantation.

likely reflects the heterogeneous patient population that is represented collectively as potential organ donors. In addition, inconsistencies in the timing of brain death declaration throughout different institutions and centers may lead to further variation.

The role for exogenous hormonal supplementation in brain-dead organ donors continues to be largely speculative. Several studies have demonstrated normal anterior pituitary function after brain death [48,49]. More importantly, these studies have not demonstrated a correlation between hemodynamic instability and endogenous hormonal levels [46-48].

Much of the debate regarding hormonal supplementation has focused on abnormalities of thyroid hormone stimulation and production. Multiple studies have demonstrated diminished levels of thyroxine, free thyroxine, thyroid-stimulating hormone, and triiodothyronine after brain death. When measured, many of these studies have also demonstrated a reciprocal rise in reverse triiodothyronine more consistent with euthyroid sick syndrome rather than loss of central regulatory function. In studies where exogenous supplementation of thyroid hormone demonstrated improved cardiac function and hemodynamic stability, this may reflect more the positive inotropic properties of thyroid hormone in the setting of euthyroid sick syndrome rather than replacement therapy.

Similarly, the role of endogenous steroid supplementation in organ donor management remains poorly supported with randomized trials. Dimopoulou et al [50] have demonstrated impaired adrenal cortisol secretion after dynamic stimulation in brain-dead potential donors, suggesting a role for exogenous supplementation. However, controlled trials have not consistently demonstrated an abrupt decline in cortisol levels after clinical brain death.

Finally, there is convincing evidence in animal models regarding the presence of posterior pituitary dysfunction, with marked depletion of vasopressin, leading to diabetes insipidus [51]. This is frequently encountered clinically with excessive, poorly concentrated urine output in the setting of volume depletion after brain death. Supplementation with arginine vasopressin in this setting quickly restores urine osmolarity and minimizes the excessive losses due to lack of endogenous production.

In the management of brain-dead potential organ donors, an initial emphasis should be placed on aggressive supportive care, including adequate volume replacement and pressor support as needed to maintain a reasonable mean arterial pressure. Invasive monitoring, including accurate assessment of CVP through central catheter insertion, is critical in this process. In addition, correction of electrolyte abnormalities, many of which develop as a result of diuretic therapy such as mannitol in the treatment of elevated intracranial pressures, should be initiated. Normalization of temperature and correction of acid-base abnormalities should also be included in the initial management strategy. In the setting of low CVPs with excessive urine output, arginine vasopressin should be initiated for posterior pituitary hormonal supplementation for diabetes insipidus.

When adequate volume has been replaced and hemodynamic instability persists, pressor support to maintain adequate mean arterial pressure should be initiated, and consideration of additional invasive monitoring with a pulmonary artery catheter is recommended to adequately assess left cardiac filling pressures, cardiac function, and systemic vascular resistance. Once filling pressures are maximized, if continued instability persists, supplementation of exogenous anterior hormones is a reasonable consideration. Protocols implementing management using these principles have demonstrated improved yield of organs procured [44]. This strategy is summarized in Table 1, from the United Network of Organ Sharing recommendations for organ donor management.

Aggressive donor management and incorporation of hormonal resuscitation to benefit potential organ donor management is best exemplified in the series reported from Papworth, England. In a large series of potential multiorgan donors reported more than 12 years ago, the authors defined 35% of the potential organ donors to have unacceptable hemodynamic characteristics; 40% had a mean arterial pressure of less than 55 mm Hg despite inotropic support, 19% had a CVP of more than 15 mm Hg, and 25% had a pulmonary capillary wedge pressure of more than 15 mm Hg. The authors subjected this unacceptable group to optimal donor management consisting of invasive monitoring, bolus steroids, insulin and glucose solutions, vasopressin, and thyroid hormone. This optimization approach resulted in 44 of 52 unacceptable donors yielding transplantable organs; 93% of those initially deemed unacceptable were capable of functional resuscitation. This study suggests that there is an enormous opportunity to optimally medically manage potential organ donors and transform unacceptable donors into acceptable donors [52].

6. Pulmonary management

Management of the potential lung donor becomes increasingly important when it is recognized that lungs are procured from only 16% of multiorgan donors. There are multiple factors that jeopardize pulmonary function and influence the low procurement rate. These include pulmonary damage during the causative event, which includes aspiration, pulmonary contusion, shock with ischemia reperfusion injury, as well as pulmonary insults during the period of mechanical ventilation, including atelectasis, acquisition of nosocomial pneumonia, barotrauma or volutrauma, and the effects of oxygen toxicity. Recently, it has been recognized that there are multiple elements in the brain death process that significantly compromise

pulmonary function and impair pulmonary physiology. This as been attributed to the effects of the sympathetic surge and the induction of inflammatory process [53]. Brain death, and the accompanying catecholamine surge, is responsible for the production of neurogenic pulmonary edema. Etiologically, neurogenic pulmonary edema is thought to arise from either a blast injury with associated hydrostatic injury and/or sympathetic alterations of capillary permeability. During the sympathetic surge, which is dominated by α-adrenergic stimulation and resultant systemic vasoconstriction, there is an abrupt increase in systemic vascular resistance. This precipitates left ventricular dysfunction and a rise in left atrial pressure, which is translated into a hydrostatic gradient precipitating pulmonary edema. Similar vasoconstritive forces occur in the venous capacitance reservoir, which facilitates augmentation of venous return to the right heart. The combination of impaired left ventricular function with an increase in left atrial pressure along with an increase in venous return secondary to venoconstriction results in a significant increase in the total lung blood volume. Animal models have reported that up to approximately 72% of the effective circulating volume may be stored in the pulmonary vasculature during the brain death event [54]. The significant increase in capillary hydrostatic pressure precipitates stress to the capillary alveolar membrane and hydrostatic flux into the alveolar space. In addition to the hydrostatic flux previously discussed, there is a speculation that sympathetic stimulation may directly affect pulmonary capillary permeability, further precipitating a rise in fluid and protein elements across the capillary endothelium. It is likely that both mechanisms are operative and contribute to the extravascular lung water and opacification frequently seen on the chest x-ray of potential lung donors.

In conjunction with the sympathetic surge, there is a parallel inflammatory response associated with brain death. Elevated levels of tumor necrosis factor-α and interleukin (IL)−1 are reported to activate endothelial cells to express adhesion molecules and promote the production of IL-8, which is a potent neutrophilic attraction activator and chemoattractant cytokine. Subsequent neutrophil infiltration and migration into the interstitium and alveolar spaces precipitates injury to the lung in the potential organ donor. In a study of potential organ donors with nontraumatic brain death, there was a significant increase in the neutrophil concentration (31.85% vs 3%) and bronchioloalveolar lavage levels of IL-8 (1282 vs 85 pg/mL). The extent of neutrophilic infiltration correlated with the IL-8 level [55]. A subsequent study by the same group correlated the extent of IL-8 expression and neutrophilic infiltration with recipient graft function and survivorship. The IL-8 signal in the donor correlated with the percentage of neurtrophils in the bronchioloalveolar lavage donor fluid, the degree of graft impairment and oxygenation, the development of severe early graft dysfunction, and early recipient mortality [56].

Alvonitis et al [53] have proposed that there are connections between the adrenergic and inflammatory mechanisms of lung injury in the potential organ donor. It is likely that both mechanisms are operative and synergistically produce functional abnormalities in the donor lung physiology. It appears that the initial brain injury may precipitate the release of inflammatory mediators, which are followed by the associated catecholamine storm that is responsible for the sympathetic alteration of capillary permeability and hemodynamic changes precipitating injury to the endothelium, further producing an inflammatory response. Similar to the cardiovascular system, it would appear that there are multiple antecedent events that conspire to jeopardize pulmonary function and complicate the management of the potential lung donor.

Assessment of the potential lung donor is similarly difficult. The criteria for ideal lungs (which include a Pa_{O_2}/fraction of inspired oxygen [F_{IO_2}] ratio of more than 300 mm Hg; positive end-expiratory pressure of 5 cm Hg; a clear chest x-ray; age less than 55 years; tobacco use of less than 20 pack-years, and absence of trauma, aspiration, secretions, or malignancy) have been characterized as arbitrary and capricious. It is highly likely that many acceptable lungs are not procured because of rigid adherence to ideal lung criteria. Autopsy series of organ donors from whom no lungs were procured revealed that in the 47% of lungs that were deemed suitable, 40% had significant pulmonary disease, and in the 53% that were deemed nonsuitable, 14% had only minor pulmonary abnormalities [34]. Similarly, in single-lung donor series, the pathologic assessment of the nontransplanted lung revealed significant abnormalities [57]. In a recently reported series of potential donors from whom lungs were not procured, 83% were found to have absent or mild pulmonary edema, 74% had intact alveolar fluid clearance, and 62% had normal or mildly abnormal histology. The study concluded that 41% of rejected lungs were potentially suitable for transplantation [58]. Fisher et al [59] concluded that current selection criteria are poor discriminators of pulmonary injury and infection and lead to the exclusion of potentially usable donor lungs. He reported that there were negligible differences in lungs that were accepted compared with those that were excluded by clinical criteria related to bronchioloalveolar lavage concentrations of neutrophils and inflammatory mediators . The potential impact of aggressive pulmonary organ donor management upon the procurement of lungs was first reported by Gabbay et al [60]. In this study, aggressive donor management consisting of manipulations in mechanical ventilation and positive end-expiratory pressure, chest physiotherapy, attention to fluid balance, bronchial toilette, antibiotics, and bronchoscopy showed that a significant number of lungs that were initially deemed unsuitable could be successfully managed to allow for procurement. Approximately 29% of potential organ

donors had a Pa_{O_2}/F_{IO_2} ratio of less than 300 mm Hg; 31% of these were clearly unsuitable. Those remaining were subjected to aggressive pulmonary organ donor management. Approximately 50% were able to subsequently achieve a Pa_{O_2}/F_{IO_2} ratio of more than 300 mm Hg and were successfully procured and transplanted, with outcomes identical to the ideal lung [60]. Other studies have reported similar outcomes with ideal and marginal lungs over the past 15 years [60-63].

Recently, it has been reported that the implementation of a standardized protocol for the management of the potential lung donors resulted in a dramatic improvement in the procurement rate of lungs. Using the San Antonio Lung Transplant (SALT) protocol, the mean rate of lung procurement was significantly higher during the protocol period, 25% vs 11.5%, with an estimated risk ratio of 2.2 in favor of the protocol period. During this time, more patients received transplants (121 vs 53), and of the 98 actual lung donors during the SALT protocol period, 54% had initially been considered poor donors. These donors provided 53% of the 121 lung transplants performed during this period. The SALT protocol focused upon education and active donor evaluation and management. Donor education initiatives consisted of transplant pulmonologists meeting with the organ procurement staff for training sessions on donor selection and management. There was an emphasis upon approaching every organ donor as a potential lung donor and requesting and obtaining consent for lung donation on every organ donor. In addition, education was provided about donor management strategies. The active donor evaluation and management consisted of management by a transplant pulmonologist and the OPO staff. Specific elements of the strategy included performing ventilator recruitment maneuvers, restricting fluid administration, administrating diuretics, and implementing techniques for the prevention of aspiration. Alveolar recruitment was undertaken when the initial blood gas analysis demonstrated a Pa_{O_2}/F_{IO_2} ratio of less than 300 mm Hg, the presence of pulmonary infiltrates/pulmonary edema, and/or atelectasis. Recruitment strategies consisted of pressure control ventilation with an inspiratory pressure of 25 mm H_2O and a positive end-inspiratory pressure of 15 mm H_2O for 2 hours. The ventilatory mode was subsequently returned to a conventional volume control ventilation with a tidal volume of 10 mL/kg and positive end-inspiratory pressure of 5 mm Hg. Successful recruitment was defined by an improvement in Pa_{O_2}/F_{IO_2} ratio to at least 300 mm Hg and significant improvement in the chest radiograph. Fluid balance was assessed clinically with a focus upon the minimal use of crystalloids and administration of diuretics to maintain a neutral or negative fluid balance. Aspiration risk was diminished by elevating the head of the bed to 30° and inflating the balloon to the endotracheal tube to 25 mm H_2O. Bronchoscopy was performed in all patients with bilateral bronchioloalveolar lavage to evaluate areas of pulmonary infiltrates, contusion, or aspiration on the chest radiograph. These management processes were continued until lung procurement.

7. Summary of recommendations

The axioms of donor care are based upon the principles of aggressive critical care management that would be applied to any unstable patient. Frequently, the antecedent illness, combined with the cerebral protective management aimed at minimizing intracranial pressures during the initial stabilization, leads to significant abnormalities in fluid, glucose, and electrolyte balances. The approach to any potential organ donor begins with assessment of the current volume status of the patient, combined with careful assessment of electrolytes, glucose, acid-base abnormalities, core body temperature, and underlying comorbidities. As such, the initial management begins with correction of these issues with appropriate volume replacement, electrolyte supplementation, and strict glucose control. A prerequisite to accomplishing these goals involves the appropriate placement of monitoring devices including, at a minimum, both an arterial and a central venous catheter.

A reasonable initial approach involves intravascular volume replacement with a goal CVP of 6 to 8 mm Hg to achieve adequate filling pressures. Typically, hypernatremia is present, and careful attention to free water replacement as volume resuscitation is accomplished is required. Hyperglycemia is frequently encountered, and initiation of an insulin drip is generally required to achieve normoglycemia. If significant acidosis is present because presence of lactic acid, correction with intravenous bicarbonate should be considered, with a goal pH of more than 7.3. In addition, if significant anemia or coagulopathy is present, transfusion with appropriate blood products, using standard transfusion thresholds, should be considered to improve oxygen delivery. Finally, given the potential for thermal dysregulation associated with traumatic brain injury, careful attention to the temperature of infused volumes should be maintained, and fluid warmers should be used to prevent significant hypothermia during this resuscitation.

After these initial parameters are accomplished, and if the patient has stabilized (with adequate urine output [1 mL · kg^{-1} · h^{-1}], minimal pressor requirements, and a mean arterial pressure of more than 60 mm Hg), it reasonable to continue with the current management parameters while awaiting the final assessments regarding the specifics of which organs will be appropriate for procurement and suitable recipients are finalized. However, when these stability thresholds have not been achieved, further evaluation with more invasive monitoring should be considered. In this scenario, the placement of a pulmonary artery catheter or other monitoring modality provides vital information regarding further assessment of filling pressures, cardiac function,

and systemic vascular tone. Based on the additional information provided through this monitoring, further volume replacement with a goal CVP of 6 to 8 mm Hg and a pulmonary capillary wedge pressure of 8 to 12 mm Hg should be targeted. In addition, based on the underlying cardiac parameters, inotropic support should be initiated and titrated to achieve a cardiac index of more than 2.4 L/min. Finally, further titration of the pressor requirements can be adjusted to maintain a systemic vascular resistance in the 800 to 1200 range while maintaining an adequate mean arterial pressure of more than 60 mm Hg.

As discussed, diabetes insipidus is common in the setting of severe traumatic brain injury resulting in disruption of posterior pituitary function. Excessive urine output should prompt consideration of this process during the resuscitation process. This must be differentiated from the effects of medications such as mannitol or other diuretic therapeutic agents that may be administered as part of the cerebral protective management. Once the patient has been adequately resuscitated as described, matching urine output with intravenous fluid replacement is a reasonable approach. In the setting of high urine output, typically more than 200 mL/h, administration of arginine vasopressin, intravenously, intramuscularly, intranasally, or subcutaneously, should be initiated.

In the setting of continued instability after these goals have been accomplished, it is reasonable to consider the addition of exogenous hormonal supplementation given the potential of underlying hypothalamic-pituitary dysfunction and subsequent endocrinopathy. As discussed previously, although the data available on the absolute presence of endocrinopathy associated with brain death are somewhat conflicting, administration of a combination regimen consisting of glucocorticoids, thyroid hormone, vasopressin, and insulin as part of management protocols of potential brain-dead donors is common.

This process of stabilization must be performed in concert with repeated communication with the local OPO. While this resuscitation is occurring, a detailed evaluation as to the appropriateness of each individual organ system for donation will ensue. Each situation will present a unique combination of underlying comorbid or preexisting conditions that may impact the appropriateness or suitability of different organ systems for donation. Given the relative competing interests of different organ systems on issues such as volume status during resuscitation, it is crucial that decisions regarding which organs are being targeted for procurement are continually reassessed throughout this process. In general, a potential lung donor will be managed with a more restrictive fluid replacement strategy to prevent accumulation of excess volume within the lung parenchyma. If, however, there are contraindications to lung donation, either due to preexisting lung disease or as a result of an acute event compromising suitability, a more liberal fluid management strategy may be adopted. Continual monitoring and frequent reevaluations as to the current hemodynamic and volume status of the patient while the final preparations of the specific organs and recipients are completed will maximize organ retrieval and minimize loss of appropriate donors to somatic death during this crucial period.

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