

## How I Manage the Adult Potential Organ Donor: Donation After Neurological Death (Part 1)

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**Abstract** The need for organ donation has become a growing concern over that last decade as the gap between organ donors and those awaiting transplant widens. According to UNOS, as of 8/2009, there were 102,962 patients on the transplant waiting list and only 6,004 donors in 2009 (UNOS.org. Accessed 4/8/2009). In 2008, an estimated 17 patients died each day awaiting transplant (OPTN.org). Though currently most organ donations come after brain death (DND or donation after neurological death), tissue donation (cornea, skin, bone, and musculo-skeletal tissue), and donation after cardiac death (DCD) and are also possible. The term “extended criteria donor” refers to potential donors over 60 years of age or age 50–59 years plus 2 of the 3 following criteria: stroke as the cause of death, creatinine > 1.5 meq/dl, or a history of hypertension. Historically, extended criteria donors have had a lower organ yield per donor. In order to preserve the choice of organ donation for the family, intensive management of the potential organ donor is necessary. Since each potential donor could save seven lives or more, nihilism in the care of such patients can have far reaching ramifications. This article describes intensive care management practices that can optimize organ donation.

**Keywords** Brain death · Organ donation · End of life · Hormonal therapy · Organ sparing therapy · Donation after neurological death

### Case Report

A 63 year physically fit woman with a history of peripheral vascular disease, left femoral artery stenting, and ovarian cysts was admitted to the hospital for elective right superficial femoral artery stenting. She was maintained on her home dose of aspirin 325 mg daily, clopidogrel 75 mg daily, and cilostazol 100 mg twice a daily. Her preoperative coagulation studies and platelet count were normal. During the procedure she received 9,500 units of heparin and her blood pressures were maintained between 117–146/45–74 mmHg. Her activated clotting time during the procedure was measured at 135 s. Shortly after the procedure the patient complained of a headache and right sided weakness. She became progressively obtunded and a head CT revealed a 132 ml left frontal/temporal/parietal intracerebral hemorrhage with a fluid–fluid level indicative of coagulopathy and 1.14 cm of midline shift. She was administered DDAVP, protamine, and transfused platelets, with normalization of her labs. She was also hyperventilated and given osmotic therapy, but her exam rapidly deteriorated to brain death. The regional organ donor network was notified and the brain death protocol initiated. She was transferred to the ICU where her blood pressure at admission was 70/40 mm Hg. An arterial line and central venous catheter were placed. She initially received norepinephrine and volume resuscitation, but required increasing pressor doses. Hormonal therapy was then initiated with levothyroxine at 10 mcg/h, insulin infusion, and solumedrol 15 mg/kg IV bolus. Her blood pressure improved markedly to 140–180/70–80 mmHg and norepinephrine was tapered off. A transthoracic echocardiogram revealed an ejection fraction of 55%. Shortly thereafter the patient’s urine output increased to 275–500 ml/h and she was started on a vasopressin drip at 0.5 units/h. Her urine

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output decreased to 125–175 ml/h and her sodium levels stabilized on vasopressin. The patient underwent two neurological exams and an apnea test that were confirmatory for brain death. The family was approached for organ donation and consented. The patient underwent bronchoscopy as part of her evaluation and went on to donate both kidneys and her liver.

## Comments

### Identifying Potential Organ Donors

The first step in managing a potential organ donor should always be notification of the local organ donor network. Transplant and family service coordinators should be dispatched to screen the patient for donation, liaison with the family, and assist in organ sparing therapy management. Organ donor networks should be notified for all patients with impending brain death, patients with planned withdrawal of care (for potential donation after cardiac death) and after all deaths within 1 h, for potential tissue donation regardless of etiology of death or age of the patient. Some local organ donor networks have trigger cards which suggest notification if brain death testing is being discussed, with the absence of one or more cranial nerve reflexes (pupils fixed and dilated, no blink, no cough, or gag) or a Glasgow Coma Score  $\leq 4$ . Physicians are not expected to screen patients for potential organ donation, but general contraindications to donation are listed in Table 1. Even patients who may be medical rule-outs should be reported to the local organ donor network since a screening log is maintained by most organ procurement centers.

Prior to the initiation of a protocol to declare brain death, the main goals of management are focused on the care of the neurologically injured patient. After the first brain death exam is performed, the time to declaration is typically a minimum of 6 h, since most hospitals mandate a second brain death exam. During this time, physicians are expected to keep family members informed of the clinical status of the patient and to maintain the patient in a hemodynamically stable state. In the past, once a patient has completed the protocol for the declaration of brain death, the organ procurement officer (OPO) has taken over medical care. Now in many institutions, intensivists are jointly involved in the management of these patients up until the point of procurement. Cooperative management between the intensivist and OPO may provide more consistent care.

### Consent

At most centers, the approach for consent for organ or tissue donation is performed by the organ donor network team, typically after the second brain death exam. Maintaining a clear distinction between the patient care team and the organ donation team can minimize any perceived conflict of interest. However, some centers are beginning to couple the process of notification of brain death and the initial approach for donation. This means that the treating physician and family services coordinator from the organ donor network are present for both discussions. Some centers have noted an increased conversion rate of potential to actual donors with coupling, though more data are needed.

Intensive management of the brain-dead patient may be necessary while the family is being approached for consent

**Table 1** General contraindications to organ donation

	Contraindication	Notes
	Multi-system organ failure due to sepsis	
	History of cancer	Except: skin cancer other than melanoma, certain primary brain tumors, remote prostate cancer
Please confer with your local organ donor organization as some contraindications are relative	Viral infections	HIV, HTLV I, II, rabies, reactive HbsAg, measles, West Nile virus, SARS, adenovirus, enterovirus, parvovirus, active HSV, VZV, EBV, viral encephalitis/meningitis
<i>HTLV</i> Human T lymphotropic virus, <i>HbsAg</i> Hepatitis B surface antigen, <i>SARS</i> severe acute respiratory syndrome, <i>HSV</i> herpes simplex virus, <i>VZV</i> varicella zoster virus, <i>EBV</i> Epstein-Barr virus, <i>CMV</i> cytomegalovirus, <i>CJD</i> Creutzfeldt–Jakob disease, <i>vCJD</i> variant Creutzfeldt–Jakob disease	Hepatitis B or C	organs can be transplanted into recipients with the same virus
	CMV +	organs can be transplanted- better success if recipient is prophylaxed
	Bacterial infections	Tuberculosis, gangrenous bowel, bowel perforation, intra-abdominal sepsis
	Fungal infections	Active cryptococcus, aspergillus, Histoplasma, coccidioides, candidemia, invasive yeast infections
	Parasitic infections	Leishmania, trypanosoma, strongyloides, malaria
	Prion disease	CJD, vCJD, fatal familial insomnia, Gerstmann–Straussler Scheinker

in order to maintain viable organs for transplant. Since brain-dead patients are frequently hemodynamically unstable, failure to treat these patients will de facto eliminate the possibility of a choice to donate, and can be viewed as a paternalistic approach to patient care. In the case of a living will or a family that does not wish to pursue donation, clear documentation of this sentiment after appropriate counseling by an organ donor network representative should occur and life sustaining therapy can be withdrawn in accordance with the patient's or family's wishes.

### Managing Hemodynamic Instability

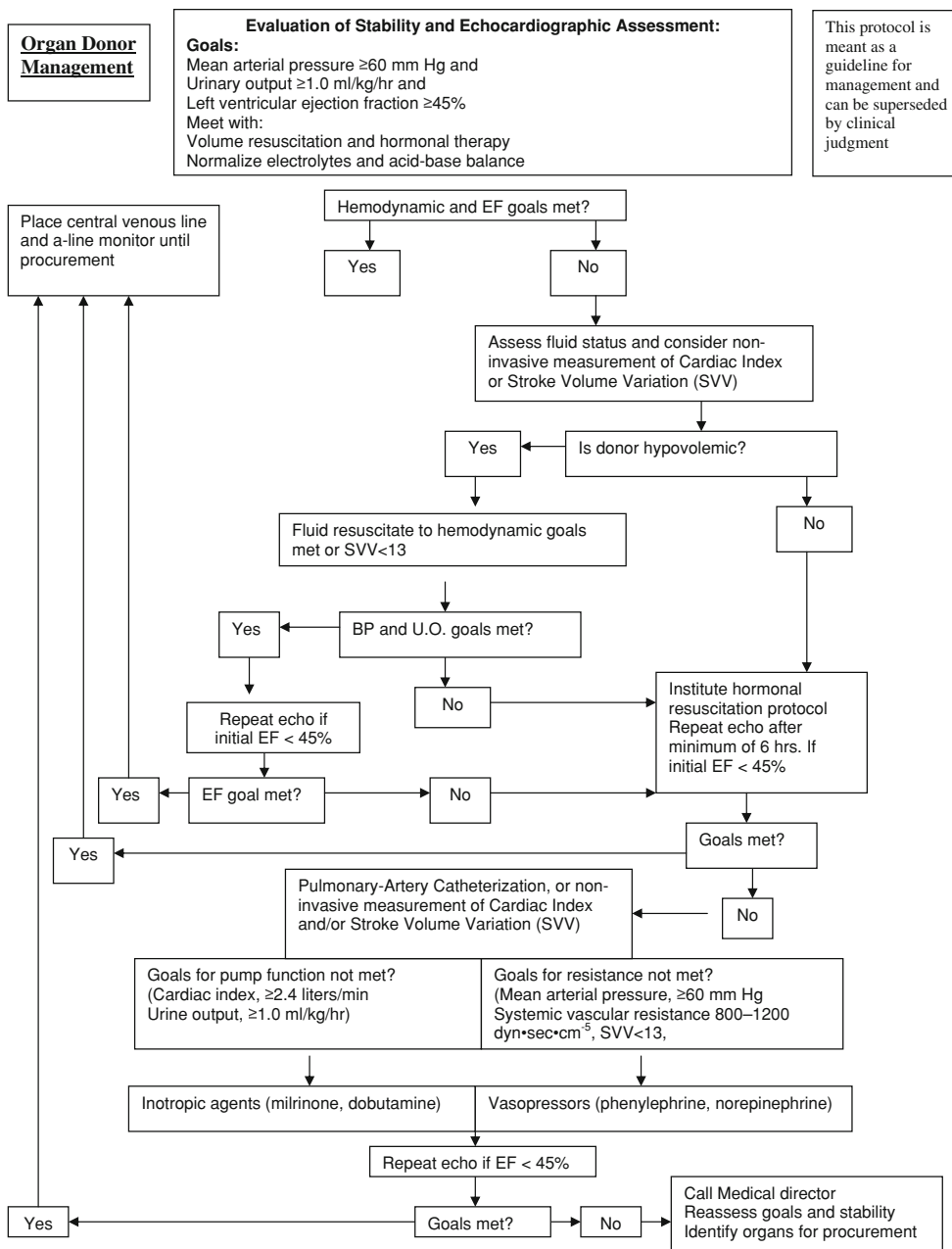
The progression from brain death to somatic death results in the loss of 10–20% of potential donors. Hemodynamic instability following brain death can be attributed to three main causes. First, a sympathetic surge immediately preceding medullary level brain death leads to a massive release of catecholamines from postganglionic sympathetic nerve endings leading to elevated systemic vascular resistance, hypertension, left ventricular dysfunction, cardiac stunning, neurogenic pulmonary edema, and arrhythmias [1, 2]. Second, herniation following brain death leads to spinal cord infarction and loss of sympathetic tone resulting in further hypotension [3]. Third, pituitary hormonal secretion ceases and the body enters a panhypopituitary state characterized by low cortisol, T3, T4, insulin, and ADH levels [2, 4, 5]. Ensuing diabetes insipidus leads to further hypotension as the patient becomes volume depleted.

Conventional management of hypotension in brain-dead patients is inadequate and leads to persistent hemodynamic instability in 34–45% of patients [6–8]. Though many reputable publications have advocated using a combination of fluid resuscitation and standard inotropes (dopamine, dobutamine, or epinephrine) or vasopressors (norepinephrine, phenylephrine or epinephrine) as first line therapy [9, 10], I favor a more physiologically rational approach of fluid resuscitation followed by replacement of hormonal deficiency (Fig. 1). In the case of volume depletion, crystalloid resuscitation is initiated unless the patient is actively bleeding or has a hemoglobin < 7 g/dl, in which case blood product replacement can be utilized. Acceptable hemodynamic goals include a mean arterial pressure  $\geq$  65 mmHg, heart rate 60–100 bpm, and a urine output of 0.5–3 ml/kg/h. Patients who are hypotensive or demonstrate evidence of diabetes insipidus should be initiated on hormonal replacement therapy without delay. If DI is present (see diagnostic criteria in Table 2), I usually initiate therapy with a vasopressin infusion beginning at 0.5 u/h to a maximum of 6 u/h targeted to a urine output of 0.5–3 ml/kg/h and a serum sodium of 135–145 meq/l. DDAVP

is an alternate choice (1–4  $\mu$ g IV, then 1–2  $\mu$ g IV every 6 h), but is less easily titrated and does not add substantial hemodynamic support. Serum sodium values should be checked every 6 h to assist with vasopressin titration. Side effects of vasopressin include hyponatremia, digital vasoconstriction, and thrombosis.

### Hormonal Replacement Therapy

Hormone replacement therapy should be instituted to address the panhypopituitary state that accompanies brain death and leads to refractory hypotension. This typically consists of administration of levothyroxine, solumedrol, insulin, and vasopressin (Table 2). Hormonal replacement therapy has been shown to decrease cardiovascular lability, ECG changes, and acid–base disturbances [11–13]. In a prospective study of 19 hemodynamically unstable brain-dead patients refractory to fluid resuscitation, traditional vasopressors, and inotropes, hormone replacement therapy with levothyroxine and solumedrol led to a significant decrease in pressor requirement such that 53% of patients were able to be weaned completely off traditional pressors [14]. Not only does hormonal therapy improve hemodynamics, but it also improves organ donation rates and graft function [6, 15]. In a retrospective study of 10, 292 brain-dead patients, those who received hormonal replacement therapy with T3, insulin, and vasopressin were found to have a 22.5% higher organ yield than those who did not receive hormonal replacement. Additionally, there was a significant increase in donation of kidney, heart, liver, lung, and pancreas [16]. In a multivariate model, both steroid and desmopressin use predicted organ yield [17]. Similarly, in a study of 4,543 heart transplant recipients, donor organs that were exposed to hormonal therapy suffered 3.8% graft loss and 5.6% graft dysfunction compared to 7.9% graft loss and 11.6% graft dysfunction in those that did not receive hormonal therapy ( $P = 0.01$ ). There was a 46% reduction in the odds of recipient death in 30 days among those who received organs exposed to hormonal therapy [18]. Use of hormonal replacement therapy has steadily increased from 8.8% of all brain dead organ donors in 2000 to 20% of donors in 2004 [4]. I usually initiate the solumedrol and insulin components of hormonal replacement therapy after the first brain death exam and initiate levothyroxine and/or vasopressin if the patient is hypotensive or has diabetes insipidus. There are some, however, who advocate use of levothyroxine and vasopressin even in hemodynamically stable brain dead patients. Common side effects of levothyroxine include tachyarrhythmias and hypertension. Clinical studies that are routinely performed for the potential donor are listed in Table 3.



**Fig. 1** Flow diagram for organ donor management. *EF* ejection fraction, *UO* urine output, *SVV* stroke volume variation

**Hemodynamic Monitoring**

As with any ICU patient, adequate monitoring and intra-vascular access are crucial to donor management. Most patients have an arterial line and central venous catheter in place prior to brain death. In patients that do not have these lines, we will routinely approach the family for consent for line placement if the family is considering organ donation. We do not routinely place pulmonary artery catheters for management, but instead use non-invasive means of monitoring cardiac function and volume status using stroke volume variation and/or pulse contour analysis (Flotrak,

Vigileo, Irvine, CA; PiCCO, PULSION Medical Systems AG, Munich, Germany; LiDCO Ltd, London, England). Since central venous pressure (CVP) has been shown to have a poor relationship with volume status, we do not routinely measure CVP and do not use CVP as a hemodynamic target [19].

**Pulmonary Management**

Certain organ specific management strategies should be mentioned. The greatest disparity between organ supply and demand exists for the lungs [20]. Lung transplantation

**Table 2** Organ sparing hormonal therapy

Drug	Dosage	Comments
Thyroxine T4	Administer 10 U regular insulin with 1 ampule of D50 (unless glucose > 300 mg/dl) then 20 mcg T4 IV bolus (mixed 200 mcg in 500 ml NS) followed by 10 mcg/h of T4 IV maximum dose 20 mcg/h	Inotropic effect, can be used as a pressor Causes hyperkalemia with bolus- must administer insulin and D50 prior to initiation T4 shown to be more beneficial than T3 [4, 12, 14, 18]
Vasopressin	0.5 units/h IV (25 u in 250 ml NS or D5W) maximum dose 6 u/h	Check for DI: UOP $\geq$ 5 cc/kg/h for $\geq$ 2 hours, urine specific gravity < 1.005, serum Na > 145 meq/l, OR serum osmolality > 300 mOsm/kg and urine osmolality < 200 mOsm/kg Titration should be based on BP, UOP, Na <sup>+</sup> levels and urine specific gravity
Insulin	1 unit/h IV (25 u in 250 ml NS)	Adjust to maintain glucose 100–140 mg/dl
Methylprednisolone	15 mg/kg IV bolus repeat daily	Improves potential for lung donation

D50 50% dextrose solution, IV intravenous

**Table 3** Routine studies for the potential organ donor

Team requesting/ performing studies	Clinical studies	Timing
Organ donor network	Serum: HIV 1,2 antibody; HTLV 1,2 antibody; Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis B core IgM, Hepatitis C antibody, Hepatitis B/C and HIV RNA testing, CMV IgM and IgG, EBV IgM and IgG, RPR, toxoplasmosis IgG, Chagas disease antibody (for patients with travel to Texas or South America)	Once
Primary care team	Serum: Complete blood count, arterial blood gas, liver function tests including GGT, coagulation studies, fibrinogen, troponin/CK, chemistry panel including calcium, phosphorus and magnesium, LDH, amylase, lipase	Every 6 h
Primary care team	CXR, ECG, blood culture, urine culture, urinalysis, sputum culture and gram stain, HgbA1c (once), type and screen (once)	Daily and as needed
Primary care team	2-D Transthoracic echocardiogram	At least once, may repeat depending on hemodynamic status
Organ donor network/primary care team/cardiology	Coronary catheterization	May be required for potential heart donors
Organ donor network/primary care team/pulmonology	Bronchoscopy	Required for potential lung donors

HTLV Human T lymphotropic virus, EBV Epstein-Barr virus, CMV cytomegalovirus, CXR chest X-ray, ECG electrocardiogram

is particularly limited due to stringent donation criteria, though there is little evidence to support a specific lung management protocol. Criteria for lung donation are listed in Table 4 [21]. These selection criteria, however, have been shown to have poor predictive power for early graft outcome [22, 23]. Procurement of donor lungs is hampered by a high incidence of gas exchange disturbance that fail to meet consensus criteria for transplant. It has been

hypothesized that donor ventilator strategy may impact on allograft integrity, recipient gas exchange, and the development of peri-transplant complications including primary graft dysfunction that in part may reflect ventilatory induced lung injury (VILI) [24, 25]. Strategies to improve these impediments to successful transplant are limited by the absence of controlled trials or clearly defined models that guide donor ventilatory strategy decision making.



**Table 4** Criteria for lung donation [21]

History	
Age	< 55 years
Smoking history	$\leq 20$ pack-years
History of primary pulmonary disease	No history of primary pulmonary disease
Chest trauma	Absence of chest trauma
Pulmonary infection	No active pulmonary infection
Sepsis	No sepsis
Laboratory values	
PaO <sub>2</sub> to FiO <sub>2</sub> ratio	of $\geq 300$
Evidence of aspiration or purulent secretions at bronchoscopy	No evidence of aspiration or purulent secretions at bronchoscopy
Sputum or bronchoalveolar lavage with a gram stain	free of bacteria, fungus or a significant number of white cells
Chest X-ray	Normal chest X-ray

### Ventilator Management

Typical ventilator strategies in potential organ donors have included high tidal volume and low PEEP settings. A prospective, multi-center observational study found that the average tidal volume in brain dead donors was 9.7 ml/kg of ideal body weight and the PEEP ranged from 0 to 8 cm H<sub>2</sub>O. Ninety-seven percent of patients had no adjustments to ventilator settings after brain death was declared [20]. A ventilator strategy of high tidal volumes (8–10 ml/kg) and serial recruitment maneuvers has been favored by various organ donor networks because of concerns regarding atelectasis and suboptimal oxygenation in brain dead donors. This strategy may, however, produce additional inflammation and barotrauma. Additionally, severe brain injury in the donor pool is thought to contribute to lung injury and gas exchange disturbance, in part resulting from systemic and brainstem derived inflammatory mediator release. Neurogenic pulmonary edema and an increase in lung inflammatory markers has been well described following brain death [26] and broncho-alveolar lavage markers of inflammation such as the ratio of IL-6/IL-10 have been shown to be predictive of primary graft failure [27].

**Table 5** Causes of ventilator induced lung injury (VILI)

Type of injury	Causative factors
Volume trauma	Excessive end-tidal volume
Barotrauma	Excessive transpulmonary pressure
Atelectrauma	closing volume at end-expiration
Biotrauma	Stimulation of cellular response to mechanical and other injury (such as hyperoxia) by resident and recruited cells

The manner by which these inter-related aspects of VILI (Table 5) are affected by ventilatory strategy and the impact on recipient outcome are largely untested and unknown. However, it may be prudent to consider safe ventilator practices that extrapolate from extensive data sets derived from a broader ICU population. High tidal volume ventilation exacerbates pulmonary and systemic inflammation and worsens acute lung injury/acute respiratory distress syndrome (ALI/ARDS) in living patients [20, 28, 29]. Furthermore, a regimen of high tidal volumes can actually lead to the development of ALI as demonstrated in a study of patients with traumatic brain injury, in which high tidal volumes and high respiratory rates were independent predictors of acute lung injury [30]. The cornerstone and widely adopted management recommendation for patients with ALI/ARDS is a low tidal volume targeting 6 ml/kg of ideal body weight with moderate and graded PEEP, along with a protocol designed to address plateau pressures exceeding 30 cm H<sub>2</sub>O with further limitation on cycle volume. Recent studies have shown that even patients who do not have ALI/ARDS may benefit from lung protective ventilation using low tidal volumes targeting 6 ml/kg of ideal body weight and plateau pressure targets of  $\leq 30$  cm H<sub>2</sub>O [31].

Another important message that may be garnered from controlled clinical studies in ALI is that improvement in oxygenation, per se, is a poor surrogate for outcome, despite the defining role for gas exchange disturbance in acute lung injury. Improved oxygenation has not been shown to correlate with improved clinical outcomes in living patients in many studies. For example, randomized trials testing inhaled NO, prone posture, recruitment maneuvers that employ high levels of PEEP, and direct measurement of transpulmonary pressures all achieved significant gas exchange improvement, but in each case failed to show mortality benefit [32–37]. Lung recruitment strategies utilized by some organ donor networks have included trials of increased PEEP to levels of 30–40 cm H<sub>2</sub>O for several minutes followed by a return to baseline PEEP levels. Such recruitment strategies have not been shown to change mortality in large randomized trials of patients with ALI/ARDS, but do improve oxygenation [35]. A major concern with such recruitment strategies is that when PEEP is reduced to baseline, alveoli will de-recruit and recurrent recruitment episodes can lead to shearing stress. Cyclic stretch has been shown to upregulate alveolar epithelial TGF  $\beta$ -1 and interleukin-8 [38], which in turn may worsen pre-existing lung inflammation. Ischemia–reperfusion injury that occurs during transplant may further compound lung damage. Targeting oxygen levels as the primary criteria for lung donation may be misguided. Infact, hyperoxia induced lung injury is

intimately related to an inflammatory cascade activating both cellular apoptosis and necrosis [39].

The impact of specific ventilatory mode, such as volume targeted versus pressure limited strategies, deserves additional comment. Whereas a volume cycled modality that adheres to low tidal volume strategy has the largest data set accrual, alternative modes that achieve target volume have been used in acute lung injury, but do not appear to have measurable impact on outcome. This also implies that pressure targeted modes of ventilation may be acceptable alternatives to volume cycled ventilation, as long as end-inspiratory volume targets are not exceeded. Recently, many organ donor centers have moved toward the use of pressure cycled modes such as airway pressure release ventilation (APRV), inverse ratio and bi-level ventilation to improve recruitment. These ventilator settings increase intrathoracic pressure, auto-PEEP and ambient oxygen tension, which may lead to reduced preload, cardiac arrhythmias and hyperoxic lung injury. All pressure targeted modes result in dependent variables of volume and peak flow, and utilization imposes a greater vigilance on the operator to be watchful for fluctuation and regional variability. Purported advantages of pressure targeted modes such as enhanced comfort, decreased dyssynchrony and variable and initial high flow rates that match patient effort are moot in the donor population without spontaneous inspiratory effort. A risk of enhanced barotrauma associated with pressure targeting is suggested by exaggerated inflammatory signs including neutrophil influx in lungs subjected to high flow [25, 28, 29, 38]. There have been no studies in either brain dead or living patients that have shown a superiority of APRV or bilevel over other ventilatory modes.

Lung management strategies that have some supportive data include early referral to an organ donor network and high dose steroids (methylprednisolone 15 mg/kg IV daily), both of which appear to improve oxygenation and lung procurement rates [40, 41]. Additionally, a protocol of aggressive donor management with early bronchoscopy, chest physical therapy, strict fluid management, antibiotic therapy, and titration of the ventilator based on blood gas measurements has been shown to improve lung donation rates [42]. I favor using lung protective ventilation targeting 6 ml/kg of ideal body weight and plateau pressures < 30 cm H<sub>2</sub>O using assist control volume control mode and aggressively treating atelectasis with moderately elevated PEEP (7.5–10 cm H<sub>2</sub>O), early bronchoscopy, chest physiotherapy, periodic rotation to the lateral position, diuresis to normovolemia, directional suctioning, mucosyst nebulizers, and aggressive pulmonary toilet to minimize mucous plugging.

## Cardiac Management

In regard to cardiac donation, an early transthoracic echocardiogram (TTE) should be performed to assess ejection fraction (EF). Patients who initially have an EF < 45% should be optimized with inotropic support. Since levothyroxine provides inotropy, this should be the first agent applied. Frequently, patients with stunned myocardium will recover their ejection fraction and may still be candidates for donation. Therefore, a repeat TTE should be performed after medical optimization. In patients who are potential heart donors, coronary angiography may be required prior to donation particularly in males > 55 years of age, females > 60 years, patients with a history of cocaine use, or in younger patients with several risk factors including: smoking, hypertension, diabetes, hyperlipidemia, elevated body mass index, family history of cardiac disease, history of cardiac disease, abnormal ECG, regional wall motion abnormalities on TTE or an EF ≤ 40% [10]. If an organ donor network requests cardiac catheterization this should be performed expediently, even if it means opening the cardiac catheterization lab. Prolonged medical care and a delay to harvest have been shown to lower the yield of cardiac allografts [43].

## Conclusions

In summary, proactive management of the potential organ donor, including early notification of the organ donor network, hormonal replacement therapy, lung protective ventilation with aggressive pulmonary toilet, and intensive cardiac monitoring may help narrow the gap between the supply and demand for organ transplantation. More outcomes research is needed to identify optimal donor management strategies.

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