Inhalational Anesthesia for Organ Procurement: Potential Indications for Administering Inhalational Anesthesia in the Brain-Dead Organ Donor

Laurie J. Elkins, CRNA, MS, CCRN
2009 Student Writing Contest Winner

In 2005, approximately 89,000 patients were on waiting lists for various organs. Even when potential donors are stabilized and consent is obtained for transplant, 17% to 25% of those donors become medically unsuitable.1 It is therefore desirable to improve the viability of transplanted organs. Research has afforded clinicians with growing knowledge to better support these potential donors and increase the viability of the organs procured. This benefits the recipients by providing less acute and chronic rejection, better functioning organs, and ultimately a longer lifespan with a better quality of life.

Evidence-based practice has led to meticulous care being provided to potential organ donors.2-5 While in intensive care units, these brain-dead individuals receive vigorous hormonal and fluid resuscitation to achieve hemodynamic stability and the maintenance or improvement of organ function. A current problem is that there is a minimal amount of research concerning perioperative care of the brain-dead organ donor during the procurement procedure.

The purpose of this article is to generate interest in researching and measuring the effect of administering inhalational anesthetic agents during the perioperative phase of organ procurement. Current research attributes a great deal of organ damage to the autonomic or sympathetic storm that occurs during brain death. The sympathetic insult leads to a cascade of other metabolic and inflammatory irregularities. This cascade greatly increases the likelihood of acute rejection or delayed graft function in the recipient and increases the potential for ischemia reperfusion injury in the grafted organ itself.1,3,6-12 Current guidelines for maintenance of potential organ donors are increasing the number of acceptable organs and improving the organ function in the recipients.1,6,7,13-15

There are no clear recommendations regarding perioperative management of the brain-dead organ donor outside of administering neuromuscular blocking agents to prevent spinal reflexes or movements in response to surgical stimulation, fluid resuscitation, and maintenance of certain hemodynamic values.16-18 The same intact spinal cord that exhibits spinal reflexes to noxious stimuli is also capable of inducing the release of catecholamines through the adrenergic loop.2,8,19-22 Many researchers compare this sympathetic catecholamine surge in organ donors to that which occurs in autonomic hyperreflexia in the living patient with a previous spinal

Organs needed for transplantation far outweigh their availability. There is minimal research regarding perioperative care of the brain-dead organ donor during the procurement procedure. Current research attributes a great deal of organ damage to autonomic or sympathetic storm that occurs during brain death.

Literature searches were performed with the terms brain death, organ donor, organ procurement, anesthesia and organ donor, anesthesia and brain death, anesthesia and organ procurement, inhalational anesthetics and organ procurement, and inhalational anesthetics and brain dead. Additional resources were obtained from reference lists of published articles.

The literature review showed there is a lack of published studies researching the use of inhalational anesthetics in organ procurement. No studies have been published evaluating the effect of preconditioning with inhalational agents (administering 1.3 minimal alveolar concentration of an inhalational agent for the 20 minutes before periods of ischemia) in the brain-dead organ donor population.

Further studies are required to determine if administration of inhalational anesthetics reduces catecholamine release occurring with surgical stimulation during the organ procurement procedure and whether this technique increases viability of transplanted organs. Anesthetic preconditioning before the ischemic period may reduce ischemia-reperfusion injury in transplanted organs, further increasing viability of transplanted organs.

Keywords: Brain-dead organ donor, inhalational anesthesia, organ procurement.
cord injury. This is a well-documented phenomenon that can occur with noxious stimuli of any type. The uncontrolled sympathetic outflow can cause deleterious effects to body systems if it is not treated.

When the potential donor is managed appropriately in the intensive care unit, sympathetic discharge during the autonomic storm can be attenuated or eliminated, resulting in less organ damage. Healthcare researchers should determine if the sympathetic discharge that occurs with surgical stimulation in the brain-dead organ donor results in the same degree of damage. If this discharge does lead to further organ damage, determination of treatments to attenuate or eliminate this response would contribute to a greater number of successful transplantations with less acute graft rejection, delayed organ function, and ischemia reperfusion injury in the organ recipients.

**Literature Search Strategy**

The terms brain death, organ donor, organ procurement, anesthesia and organ donor, anesthesia and brain death, anesthesia and organ procurement, inhalational anesthetics and organ procurement, and inhalational anesthetics and brain dead were entered in the search engines Ovid, Medscape, MEDLINE, and Cumulative Index to Nursing & Allied Health Literature (CINAHL). Searches were performed separately to comprehensively search for any studies concerning the use of inhalational anesthetics with organ procurement procedures. Additional resources were obtained from reference lists of published articles, and all relevant literature was reviewed. Published articles reviewed dated from 1985 to present.

**History**

Brain death, referred to as coma dépassé, was described as early as 1959 by Mollaret and Goulon, who spoke of a state “beyond coma” in which neurologic function and reflexes were lost and patients were apneic. The authors witnessed many of the derangements we see in brain-dead patients today, such as the inability to maintain adequate blood pressure, fluid volume, and temperature.

The first human heart was transplanted in South Africa in 1967. Shortly thereafter, a Harvard Medical School committee issued a paper titled “A definition of irreversible coma, report … to examine the definition of brain death.” This report established the term of brain death, defined it as a “permanently non-functioning brain,” gave diagnostic criteria for determining brain death, and redefined brain death as a legally equivalent to death. In 1970, Kansas legally recognized brain death as a form of legal death and set precedence for the rest of the United States. Over the next 11 years, half of the remaining states adopted nearly identical criteria. The guidelines for determining brain death in the 1981 President’s Commission eventually led to the issuing of the Uniform Determination of Death Act, a legislative act that provides a model or guideline that most of the states have adopted.

In the early 1980s, South African physicians hypothesized that with aggressive hormone therapy for hemodynamic instability in brain-dead organ donors, approximately 20% of hearts that were initially deemed unsuitable for transplant secondary to decreasing function of the myocardium could be salvaged for transplantation. Today, the United Network for Organ Sharing (UNOS) lists “hormone resuscitation” (HR) as the recommended treatment for comprehensive donor management. (Figure 1). The effectiveness of HR was solidified after UNOS performed a retrospective analysis of 10,292 brain-dead donors from January 1, 2000, to September 30, 2001. It was determined that significantly more organs (22.5% greater) were successfully retrieved from the 701 donors who received HR with the drugs methylprednisolone, arginine vasopressin, triiodothyronine (T3), and thyroxine (T4) when compared with organ donors who did not receive the treatment.

Hormone resuscitation with these 3 drugs also increased the number of transplantable organs in donors older than 40 years. After transplantation, patients who received hearts from donors managed with the 3-drug HR had significantly better 1-month survival and significantly less 1-month graft loss and early graft dysfunction. Multivariate analyses showed a 46% reduced odds of death within 30 days and a 48% reduced odds of early graft dysfunction when 3-drug HR was used. In addition to increasing viability of organ grafts, treatment with HR has been shown to decrease or eliminate requirements for exogenous catecholamine infusions.

**Donor Management During and After Autonomic Storm**

Autonomic or sympathetic storm (AS) is a phenomenon that develops when the brain stem becomes ischemic. Generally AS results in the massive systemic release of catecholamines. The catecholamine release triggers a cascade of derangements that leads to inflammatory responses and ischemia in all organs of the body. Some of the end products resulting from this insult are interleukins, cytokines, altered gene expression, coagulopathies, and infiltration of neutrophils and monocytes. These end products increase the odds of nonviable organs and acute rejection of transplanted organs in the recipient. During AS, circulating norepinephrine levels can rise 100%, epinephrine levels can rise 700%, and dopamine levels can rise 800%. In 2006, researchers documented improved myocardial function and increased probability of successful transplant in brain-dead organ donors after treating AS with the antihypertensive medications esmolol, urapidil, or nicardipine. Arbour recommended treatment of AS with esmolol and nitroprusside because...
they are effective, titrated easily, and have short durations of action. Usually AS will be followed by a short period of hemodynamic stability, then dramatic hypotension. Autonomic storm leads to extensive endothelial cell injury, resulting from ischemia-reperfusion injury and shearing stress. Studies in canines using intravenous L-arginine supplements (an essential amino acid), have demonstrated a reversal of the endothelial dysfunction, converting a formerly unusable donor heart to one that can be transplanted. L-arginine enhances the supply of endogenous nitric oxide, a local vasodilator. Through the actions of nitric oxide, the endothelial dysfunction is repaired and the myocardial function is improved.

When circulating levels of antidiuretic hormone or vasopressin are decreased, diabetes insipidus develops, which if not corrected leads to catastrophic imbalances in electrolytes, cellular dehydration, and hypovolemia. Treatment with desmopressin (DDAVP) or arginine vasopressin can correct this phenomenon. Because of a longer half-life, DDAVP is a better choice for hemodynamically stable patients. Vasopressin has also been demonstrated to reduce the need for exogenous catecholamines. Vasodilatory shock causing ischemia results in increased levels of hydrogen ion (H+) and lactate. This leads to adenosine triphosphate-sensitive potassium (K<sub>ATP</sub>) channels opening and potassium diffusing out, causing an inhibition of muscle contraction by hyperpolarizing smooth muscles.

Vasopressin may allow the weaning of catecholamines and helps restore vascular tone by facilitating the closure of the K<sub>ATP</sub> channels. By decreasing the need for inotropic

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**Figure 1. Cardiothoracic Donor Management**

Na indicates sodium; K+, potassium ion; pCO2, partial pressure of carbon dioxide; PA, pulmonary artery; SVR, systemic vascular resistance; q 24<sup>°</sup> PRN, every 24 hours as needed; PT, prothrombin time; PTT, partial thromboplastin time; CVP, central venous pressure; and PCWP, pulmonary capillary wedge pressure.

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1. Early echocardiogram for all donors—Insert pulmonary artery catheter (PAC) to monitor patient management (placement of the PAC is particularly relevant in patients with an EF <45% or on high dose inotropes.)
   - Use aggressive donor resuscitation as outlined below

2. Electrolytes
   - Maintain Na < 150 meq/dl
   - Maintain K+ > 4.0
   - Correct acidosis with Na Bicarbonate and mild to moderate hyperventilation (pCO2 30 -35 mm Hg)

3. Ventilation—Maintain tidal volume 10-15 ml/kg
   - Keep peak airway pressures < 30 mm Hg
   - Maintain a mild respiratory alkalosis (pCO2 30 -35 mm Hg)

4. Recommend use of hormonal resuscitation as part of a comprehensive donor management protocol—key elements
   - Tri-iodothyronine (T3): 4 mcg bolus: 3 mcg/hr continuous infusion
   - Arginine Vasopressin: 1 unit bolus: 0.5—4.0 unit/hour drip (titrate SVR 800 -1200 using a PA catheter)
   - Methylprednisolone: 15 mg/kg bolus (Repeat q 24<sup>°</sup> PRN)
   - Insulin: drip at a minimum rate of 1 unit/hour (titrate blood glucose to 120 -180 mg/dl)
   - Ventilator: (see above)

5. When patient is stabilized/optimized repeat echocardiogram. (An unstable donor has not met 2 or more of the following criteria.)
   - Mean Arterial Pressure ≥ 60
   - CVP ≤ 12 mm Hg
   - PCWP ≤ 12 mm Hg
   - SVR 800 -1200 dyn/sec/cm<sup>5</sup>
   - Cardiac Index ≥ 2.5 l/min/M<sup>2</sup>
   - Left ventricular stroke work index > 15
   - Dopamine dosage < 10 mcg/kg/min
drugs, myocardial oxygen consumption is decreased and myocardial energy stores are preserved. It has been shown that vasopressin decreases pulmonary edema and pulmonary capillary leak, reduces the levels of chemokines and cytokines (factors that contribute to the systemic immune and inflammatory responses and cell death), and reduces the expression of certain genes and neutrophils that are known to infiltrate organs in acute rejection.

Thyroid hormones exercise control over the cardiovascular system by maintaining a high cardiac output (CO) and a low systemic vascular resistance (SVR). With brain death, CO decreases and SVR increases, leading to diffuse hypoperfusion of the tissues and organs and anaerobic metabolism. By administration of thyroid supplementation (T₄ or T₃), CO and SVR are improved, rendering better tissue perfusion and oxygenation and reducing lactic acidosis. Triiodothyronine is primarily responsible for the physiologic effects of thyroid hormones; approximately 80% of T₃ is formed in the peripheral tissues via the deiodination of the T₄ outer ring. Owing to the expense of T₃, T₄ is used in many centers, but the brain-dead organ donor’s ability to convert T₄ to T₃ is unreliable, so T₄ may not be as effective in supporting the donor. A theory explaining this phenomenon is that the conversion of T₄ to T₃ in the brain-dead organ donor is inhibited by cytokines released during AS. Also, once brain death has occurred, there is an increased conversion of T₄ to an inactive reverse T₃, which is called sick euthyroid syndrome.

For prevention of further osmotic diuresis and cellular dehydration, glucose concentrations should be maintained between 120 and 180 mg/dL. After brain death there are decreased levels of circulating insulin; thus, insulin resistance develops, leading to hyperglycemia from catecholamine surges.

The intense release of inflammatory mediators that follows brain death leads to more circulating cytokines in the donor organs. This can cause an additional immune response in the donor organs when they are transplanted. Serum cortisol levels are decreased in the brain-dead organ donor when compared to the donor, and the immune response in the recipient is attenuated.

The brain-dead donor cannot maintain normal body temperature. Without treatment, the donor’s temperature will quickly decrease to ambient temperature. Normothermia must be maintained with fluid warmers, warming blankets, a higher room temperature, and heated or humidified ventilator circuits. Hypothermia affects clotting times and platelet aggregation and can lead to disseminated intravascular coagulopathy.

**Surgery for Organ Procurement**

Common recommendations for the perioperative management of the brain-dead organ donor include the use of neuromuscular blocking agents to prevent reflex movements during surgical stimulation. Spinal reflexes include cardiovascular responses that commonly occur during the organ procurement surgery. Importantly, some authors suggest that the administration of a volatile anesthetic agent prevents this from occurring. Cardiovascular stimulation is believed to involve a reflex arc to the adrenal medulla and may be exaggerated by the increased excitability of the spinal cord distal to the lesion. In this case, the lesion is at or below the brain stem, which potentially leads to excitability of the entire spinal cord.

In 1985, Wetzel et al published a retrospective chart review of 10 organ procurement surgeries. The authors summarized that within minutes of surgical stimulation, each of the donor’s systolic and diastolic blood pressures and heart rates increased substantially (31 mm Hg, 16 mm Hg, and 23/min, respectively). These same responses have been observed and are mentioned throughout the available literature.

In 2003, Fitzgerald et al hypothesized that the administration of fentanyl could suppress this intraoperative release of catecholamines associated with the hemodynamic changes during the organ procurement surgery. Although these authors were not successful in proving their hypothesis, they published valuable data regarding the intraoperative increases in circulating catecholamines. Measured serum epinephrine and norepinephrine levels were taken at baseline (before injection of fentanyl, 7 µg/kg, or placebo), 10 minutes after injection of the bolus, 5 minutes after skin incision, and 5 minutes after sternotomy. In addition to finding that fentanyl, 7 µg/kg, was not sufficient in blocking intraoperative release of catecholamines with surgical incision or sternotomy, they found that serum levels of epinephrine increased with surgical incision in all cases and that these changes were not consistent with changes in the donor’s heart rates and mean arterial pressures. Many of the documented changes in heart rate and blood pressure seen in this study exceeded those previously reported in conjunction with AS.

**Potential Indications for Use of Volatile Anesthetics**

Even in living animals, the spinal cord appears to be more responsible for cardiovascular responses to noxious stimuli than the brain. In 1995, Antognini and Berg published a study indicating that the brain has little to do with the suppression of adrenergic responses when isoflurane anesthesia was administered. The minimal alveolar concentration blocking adrenergic response (MAC-BAR) for isoflurane was determined in goats. In
one group isoflurane was administered in the conventional fashion (whole body group). In the remaining 2 groups, circulation to the cranium and the torso were isolated and perfused by separate cardiopulmonary bypass machines to determine if there were differences in MAC-BAR of the cranium (representing the brain) and MAC-BAR of the torso (representing the spinal cord). In each bypass machine, blood was oxygenated and isoflurane was delivered by a vaporizer and returned to the goat. In the spinal cord group, the brain concentration of isoflurane was 0.2% to 0.3%, and spinal cord concentration of isoflurane was titrated to achieve MAC-BAR. In the brain group, spinal cord concentration of isoflurane was 0.2% to 0.3%, and brain concentration of isoflurane was titrated to achieve MAC-BAR.

The authors found that they were sometimes unable to deliver sufficient concentrations of isoflurane to the brain to achieve MAC-BAR, even when using an enflurane vaporizer that enabled them to deliver higher concentrations than the isoflurane vaporizer would allow. In this study, whole body MAC-BAR averaged 3.7% ± 0.4%, MAC-BAR of the brain averaged 5.6% ± 2.4%, and MAC-BAR of the spinal cord averaged 2.2% ± 0.7%. These results demonstrated a significant decrease in MAC-BAR requirements, and interestingly, minimal decreases in mean arterial pressure in the spinal cord group compared with the whole body and brain groups (12 ± 9 mm Hg, 31 ± 22 mm Hg, and 21 ± 16 mm Hg, respectively).

In addition to preventing or reducing adrenergic responses to noxious stimulation, isoflurane and other inhalational agents have been shown to reduce ischemia-reperfusion injury and resulting organ dysfunction in the heart, kidneys, liver, and brain (Figure 2). Ischemia-reperfusion injury is defined as "a complex process involving the generation and release of inflammatory cytokines, the accumulation and infiltration of neutrophils, and cell death." Studies on living animals have shown a significant decrease in ischemia-reperfusion injury and resulting organ dysfunction when 1.5% isoflurane is administered for the 20 minutes before periods of ischemia. This technique is referred to as anesthetic preconditioning. The authors studied the differences between 2 groups that were subjected to renal ischemia. One group received isoflurane before ischemia and the other did not.

The serum urea nitrogen and creatinine levels were monitored at 0, 12, 24, and 48 hours after reperfusion. In the group that did not receive isoflurane, serum creatinine levels were 2.4 ± 1.2 mg/dL and 2.9 ± 0.9 mg/dL at 24 and 48 hours after reperfusion, respectively, and serum urea nitrogen levels were 99 ± 29 mg/dL and 187 ± 31 mg/dL. The group that received isoflurane showed significantly decreased levels. Serum creatinine levels were 1.2 ± 0.7 mg/dL and 1.1 ± 0.2 mg/dL, and serum urea nitrogen levels were 62 ± 19 mg/dL and 79 ± 20 mg/dL at 24 and 48 hours after reperfusion.

Anesthetic preconditioning has also been shown to protect the heart from damage during periods of ischemia. With preconditioning, areas of myocardial injury...
are decreased and myocardial contractility is better preserved. In addition to the effects on the myocardium itself, the endothelium and vasculature are protected. Preconditioning also attenuates the inflammatory responses occurring with ischemia/reperfusion.30

The increased release of tumor necrosis factor α (TNF-α), a proinflammatory cytokine, worsens the cascade of events occurring with ischemia-reperfusion injury and its attack on endothelium (Figure 3). Researchers have demonstrated the ability of isoflurane, xenon, and nitrous oxide, all at 0.43% MAC, to suppress the effects of TNF-α on certain gene and protein expressions that further damage the endothelium.32

Conclusions
These findings call into question the routine recommendations of the organ procurement agencies that the donors require no anesthesia.16 It only seems reasonable to consider that it is not the organ donor who requires the anesthesia; instead, the administration of inhalational anesthesia to the brain-dead organ donor can potentially benefit each of the recipients of that donor’s organs. Because the literature suggests so strongly that AS in the donor causes deterioration of body systems and ultimately of organs, it makes sense that by preventing sympathetic surge of catecholamines during surgical stimulation, the likelihood of successful transplantation will increase.

Ischemia-reperfusion injury is known to be a major contributing factor in acute organ rejection. Although the studies cited were performed on live subjects, reduction in ischemia-reperfusion injury as a result of anesthetic preconditioning is well documented in the heart and kidneys. Further research would determine if anesthetic preconditioning would prove to be beneficial for preserving the viability of transplanted organs.

Given the shortage of viable organs for transplantation, any treatment regimen that improves their viability would benefit the recipient population. Increasing the number of adequately functioning organs will reduce the need for repeated transplantations and will lead to better quality of life in recipients.

REFERENCES


**AUTHOR**

Laurie J. Elkins, CRNA, MS, CCRN, is a staff nurse anesthetist at Charleston Area Medical Center, Charleston, West Virginia. At the time this article was written, she was a student at Charleston Area Medical Center School of Nurse Anesthesia, Charleston, West Virginia. Email: m418@aol.com.