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Intraoperative Blood Pressure and Effect of Volatile Anesthetic in Brain Dead Organ Donors

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Intraoperative Blood Pressure and Effect of Volatile Anesthetic in Brain Dead Organ Donors

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Abstract

Background: There is a large disparity between the number of people waiting for organ transplants and the number of organs available. Optimal hemodynamic management can influence transplant outcomes, therefore evidence-based hemodynamic management should be practiced to maximize scarce donor organs.

Purpose: The purpose of this study was to examine intraoperative blood pressures and administration of volatile anesthetics during brain dead organ donor procurements. Use of volatile anesthetics was examined to determine how use and dose affected the ability to maintain mean arterial pressure (MAP) between 60 to 90 mmHg.

Design: This study was a retrospective chart review.

Results: Twenty-eight cases were analyzed using the mean MAP calculated for each donor. Mean scores ranged from 61.04 to 99.34 mmHg with a mean of $M= 84.51$ mmHg. Twenty-two donors (78.6%) received volatile anesthetic gas, and six donors (21.4%) received no volatile anesthetic gas. Mean end-tidal concentrations of volatile anesthetic gas in the 22 donors who received volatile anesthetic gas ranged from 0 to 1.25% with a mean end-tidal concentration of $M= 0.39\%$. Mean MAP in donors that did not receive volatile anesthetic gas was $M= 78.49$ mmHg ($SD= 9.78$ mmHg). Mean MAP in donors that received volatile anesthetic gas was $M= 86.16$ mmHg ($SD= 7.02$ mmHg). An independent samples t test performed between these two groups demonstrated that the difference between mean MAPs of the two groups was statistically significant ($t= 2.182, p= 0.038$), but no statistically significant correlation was found between mean MAP and mean end-tidal volatile anesthetic gas ($r_s= -0.184, p=0.414$).

Conclusions: This study demonstrated that intraoperative hypertension is more prevalent than intraoperative hypotension, and volatile anesthetic gas is often used at this medical center during organ procurements at relatively low concentrations.

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Introduction

Background and Significance

Over 120,000 people are currently on the waiting list for organ transplants in the U.S. according to data from the United Network for Organ Sharing (UNOS) as of April 17, 2016 (UNOS, n.d.). The vast majority of organ transplants come from deceased donors, and the incidence of organ transplantation in the U.S. has increased substantially since its official beginnings in 1988. However, during the past decade, deceased donor transplants have increased approximately six percent, down from the decade before when donations had increased 31 percent according to data from the Organ Procurement and Transplantation Network (OPTN) as of April 8, 2016. While the growth of transplantation has slowed, the number of patients waiting for transplants has continued to climb, increasing 25.8% from 2005 to 2015 (OPTN, n.d). This gap has created a shortage of suitable, available organs for transplantation. This shortage has led to over 6,000 patients dying every year during the past decade while waiting for an organ transplant (OPTN, 2016).

Several options have been proposed and trialed to increase the number of organs available for transplant including extended criteria donors, splitting organs, increasing living donors and donation after circulatory death, increasing donor registration, and organ perfusion devices utilized after procurement prior to implantation (Saidi & Hejazii Kenari, 2014). Optimizing the utilization of donor organs through better donor management preoperatively and intraoperatively allows more organs to be transplanted per donor, thereby increasing the number of patients being transplanted without an increase in the number of donors. Previous studies have reported that blood pressure (BP) control and treatment is crucial to organ perfusion and can greatly impact the quality and success of the transplant (Mukadam et al., 2005, Powner, 2005).

Sandid, Assi, and Hall (2006) found intraoperative hypotension during cadaveric organ donor procurement was an independent risk factor for slow kidney graft function in recipients (defined as a decline in serum creatinine by less than 50 percent by day three).

Anderson, Bekker, and Vagefi (2015) assert that “[t]he success of the anesthesiologist in physiological optimization of the brain-dead donor may eventually determine the outcome of the organ recipient” (p. 537). Additional research and dissemination of evidence on intraoperative BP control in brain dead organ donors could increase the success of transplantation by minimizing recipient graft function complications related to hypotension. “Both initial and late circulatory changes can lead to severe ischemic damage in donor organs before their removal, causing deterioration of the quality of the transplanted graft” (Pratschke et al., 1999, p. 344).

According to McKeown, Bonser, and Kellum (2012), hypotension occurs in approximately 81-97% of brain dead donors according to studies they reviewed. Conversely, elevations in BP can also occur intraoperatively as demonstrated by the study by Wetzel, Setzer, Stiff, and Rogers (1985). Ideal pharmacological treatment for BP derangements in brain dead donors differ from intraoperative care of living patients due to the pathophysiological changes of brain death and its sequelae.

Significant variations in practice exist among anesthesia providers in regards to management of BP intraoperatively for brain dead organ donors. Many organ procurement organizations (OPOs) provide donor anesthesia guidelines to anesthesia providers for the procurement. Protocols for OPOs vary regionally, and many of these guidelines for BP management lack evidence based in current research. For example, the 2015 consensus statement on organ donor management by the Society of Critical Care Medicine, American College of Chest Physicians, and the Association of Organ Procurement Organizations (Kotloff et al., 2015)

B.C. Transplant, all still recommend dopamine as a first line agent for hypotension after the donor has been fluid resuscitated. Kotloff et al. (2015) acknowledge dopamine as a first-line agent, but that it only continues to remain a first-line agent due to a lack of evidence to change the practice. Anesthesia providers' adherence to guidelines is difficult to assess, and intraoperative donor management is often subject to an anesthesia provider's anecdotal experience, as well as comfort with, and understanding of brain death.

Problem Statement

The cascade of brain death induces many physiological changes, which are well-established in the literature. As a result, brain dead organ donors cannot be managed the same as living patients. Regulation of BP affects end-organ perfusion which is of key importance in viability of an organ transplant. Although gaps remain in the literature that prevent development of a comprehensive set of evidence based guidelines for BP management of brain dead organ donors, anesthesia providers should be equipped with the current evidence and guidelines available to manage BP in the setting of this unique physiology.

Anesthesia providers infrequently encounter organ procurements surgeries, resulting in very little experience managing these unique physiological abnormalities. These procedures are often urgently added during off-peak hours, leading to additional stress and little time for preparation for an unfamiliar case. It is common for OPOs to provide the anesthesia team with a sheet of guidelines for intraoperative donor management for the procurement surgery. However, advisement and consensus of BP management during these surgeries is inconsistent and controversial when comparing the available evidence and the published guidelines.

Purpose

The purpose of this study was to examine intraoperative BPs and administration of volatile anesthetics during brain dead organ donor procurement surgeries at a large medical center in the U.S. that encounters a large number of organ procurements. Hypotension was defined as a mean arterial pressure (MAP) less than 60 mmHg intraoperatively, and hypertension was defined as a mean arterial pressure (MAP) greater than 90 mmHg intraoperatively. Use of volatile anesthetics was examined to determine how use and dose affected the ability to maintain MAP between 60 to 90 mmHg.

Hemodynamic stability is crucial to organ perfusion in order to prevent ischemia. Van der Hoeven et al. (2000) suggest that maintaining normotension can limit the dysfunction of livers from brain dead donors, and therefore greatly impacts the quality and success of the transplant. Increasing availability and communication of necessary information to maintain hemodynamic stability in brain dead donors, based on current research, will increase successful transplantation by minimizing recipient graft function complications related to lack of donor BP control.

Clinical Questions

This study addresses the following research questions:

- Given the negative impact of hypotension (defined as MAP less than 60 mmHg) on transplanted organs, what has been the mean MAP and duration of intraoperative hypotension during organ procurements at a hospital with a high volume of organ donors?
- Is there a dose-dependent relationship between the intraoperative administration of volatile anesthetics to brain dead organ donors and decreases in MAP?

Literature Review

Overview of the Literature Review Process

A literature review was performed using PubMed, CINAHL, and WorldCat search engines using the following terms: *brain dead organ donor, brain dea*, organ donation, intraoperative, management, anesthe*, hemodynamic, blood pressure, organ procurement, organ harvest, and surgery*. Recent relevant peer-reviewed literature, as well as pertinent historic studies, related to managing both high and low BP, and the pathophysiology, proposed mechanisms, and treatments during organ procurement surgery were reviewed. For the purposes and scope of this literature review, interventions typically done in the intensive care unit (ICU) setting, such as initial fluid resuscitation and hormone replacement such as corticosteroids and thyroid hormones, were not included in the review. Adequate resuscitation and management prior to the operating room (OR) are key for optimizing hemodynamic stability. Even with such interventions to optimize hemodynamics prior to surgery, the BP variations intraoperatively often pose the most frequent and significant challenges for the anesthesia provider and have the potential to greatly impact the successful transplantation of organs in recipients.

Conceptual Framework

This study is guided by the Neuman's system model (see Appendix B) for nursing created by Dr. Betty Neuman. The Neuman's system model's core philosophy is rooted in basic survival factors (Neuman, 2002). The response pattern to stressors is a key element of this theory. Neuman describes a normal line of defense, which is the baseline level of wellness. The model goes on to describe maintenance of the baseline level of wellness, as well as the lines of resistance that are protective mechanisms that seek to stabilize the system after an insult and return it to the baseline level of wellness. The theory focuses on optimal system stability and variations of the optimal level of wellness. It defines the return and maintenance of system

stability after treatment for stressor reactions as reconstitution, and emphasizes prevention as an important intervention.

Neuman's systems model can be directly applied to the physiological responses demonstrated by brain dead organ donors in the OR (see Appendix C). The basic survival factors as applied to the brain dead organ donor are organ strength or weakness. The process of brain death breaches the normal line of defense, as the brain can no longer participate in maintenance of homeostasis in the body. However, some lines of resistance remain. Neuman defines lines of resistance as protective mechanisms that try to stabilize the system and reestablish wellness. The spinal cord and lower autonomic nervous system can still discharge neural activity that can have visible effects such as spinal reflexes and BP changes. These BP changes in the OR could be viewed as a line a resistance, but with the brain not being able to participate in the feedback and response functions, this line of resistance BP response becomes a dysfunctional response, therefore it must be assisted or mitigated by intervention from the anesthetist.

Pathophysiology of Brain Death

Death has been defined in the U.S. through the Uniform Determination of Death Act (UDDA):

[A]n individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards. (National Conference of Commissioners of Uniform State Laws, 1980, p. 3)

The 1968 Harvard criteria has been the traditionally accepted medical standard for the declaration of brain death in the U.S. It established that brain death is a permanent, irreversible

coma. First, the patient must be unreceptive and unresponsive to external stimuli and inner needs; for example, a lack of response to painful stimuli. Second, there must be no movement or breathing, either spontaneously or in response to stimuli, and an apnea test should be performed by removing the patient from mechanical ventilation for three minutes, allowing the carbon dioxide to rise in the body, and observing for absent respirations. Third, the patient must have absence of elicitable reflexes, including pupillary reflex, corneal reflex, oculovestibular reflex, oculocephalic reflex, gag reflex, and not exhibit any posturing, blinking, swallowing, yawning, vocalization, or tendon reflexes. The Harvard criteria recommend confirmation of an isoelectric electroencephalogram (EEG), and repeating all tests after 24 hours to ensure no change. Assessments and test validity require the patient not be hypothermic or have central nervous system (CNS) depressants obscuring the clinical picture (Harvard Medical School Ad Hoc Committee, 1968).

The most current criteria for the diagnosis of brain death are the 2010 American Academy of Neurology (AAN) guidelines (see Appendix A). The AAN guidelines are the most recent, comprehensive, evidence-based information available regarding the diagnosis of brain death, and aim to provide the standard for brain death diagnosis. Universal acceptance of the AAN guidelines for brain death diagnosis in all U.S. hospitals is still lacking.

Brain death, as it is defined in the U.S., involves the permanent cessation of function and blood flow from the whole brain; however, persistence of spinal reflexes is a known, well-documented phenomenon that occurs in some brain dead patients (Anderson & Bekker, 2015; McKeown et al., 2012). Spinal reflexes can be spontaneous or elicited by noxious stimuli (Pennefather, 1994), and reflexive activity from the spinal cord is thought to be the cause of intraoperative hypertension (HTN) and increased catecholamine levels (McKeown et al., 2012).

In brain dead patients, the herniation of the brain leads to total loss of parasympathetic activity, resulting in unopposed sympathetic stimulation seen as HTN and tachycardia, and is referred to as autonomic storm (Tuttle-Newhall, Collins, Kuo, & Schroeder, 2003). Catecholamine release due to autonomic storm at the time of brain stem herniation causes organ ischemia. Systemic vascular resistance is elevated greater than the elevated perfusion pressure (Tuttle-Newhall et al., 2003). After this surge comes a massive decrease in sympathetic outflow (Pratschke et al., 1999), causing loss of vascular tone, and therefore profound hypotension leading to cardiovascular collapse in many patients (Bugge, 2009).

After brain death, although the spinal cord is not in communication with the brain, it can play a role in catecholamine release. Catecholamine release can be triggered via stimulation of the adrenal medulla, similar to spinal cord-transected, quadriplegic patients who experience autonomic dysreflexia, where uncontrolled sympathetic outflow is unopposed by the parasympathetic nervous system (Wetzel et al., 1985). Pennefather, Dark, and Bullock (1993) found significant hemodynamic changes in brain dead donors during organ procurement surgery and measured increased catecholamine levels intraoperatively. Surgical stimuli may initiate spinal reflexes and reflexive sympathetic discharge from the spinal cord alone.

Incidence of Blood Pressure Derangement in Brain Death

According to McKeown et al. (2012), hypotension occurs 81-97% of the time in brain dead donors due to the loss of sympathetic tone, diabetes insipidus-related hypovolemia from brainstem herniation, as well as the reduced coronary blood flow and myocardial stunning from excessive catecholamine discharge at the time of brain death. It is important to note that Bijker et al. (2007) found that there is not a standard definition of intraoperative hypotension. Some studies define it as a decrease in systolic or MAP below an absolute threshold and others define

it as a decrease relative to the baseline BP. Within those definitions, the degree and duration of BP decrease varies as well. This variation in definitions makes it more difficult to understand the true incidence of intraoperative hypotension and how it is associated with adverse outcomes.

Wetzel et al. (1985) documented heart rate (HR) and BP changes that occurred during surgery for organ donation in ten brain dead donors.

Elevations above baseline occurred within the first minute after incision and maximum responses were seen between five and 20 min. These peak changes in blood pressure and heart rate were reached before aortic cross clamping or the occurrence of any other surgical procedure that could be expected to mechanically elevate blood pressure or cause an increase in heart rate. (p. 126)

The mean increase in systolic BP was 31 torr and diastolic pressure increased by a mean of 16 torr. HR increased by a mean of 23 beats per minute. All donors in this study who were being maintained on vasopressor infusions prior to entering the OR were able to have dosages of those infusions decreased or stopped. Additionally, every donor demonstrated a return to baseline BP within 25 minutes of incision (Wetzel et al., 1985).

Anesthesia and Hemodynamic Responses

The work by Wetzel et al. (1985) led to experiments to test the blunting of this hemodynamic response to surgical stimulus in brain dead patients. Fitzgerald et al. (2003) found the use of fentanyl, at a dose of seven micrograms per kilogram, was not effective in suppressing catecholamine release from surgical stimulation in brain dead organ donors. Serum catecholamine concentrations rose following noxious stimuli, however there were no differences in the hemodynamics in the group that received fentanyl versus the group that received the placebo. Investigators in this study noted that serum concentrations of epinephrine, but not

norepinephrine, were actually higher in the group that received fentanyl. Epinephrine levels were highest after sternotomy demonstrating that not only do opioids lack the ability to attenuate hemodynamic responses in brain dead organ donors, but also fail to mitigate the catecholamine discharge intraoperatively (Fitzgerald et al., 2003).

Antognini and Berg (1995) investigated the extent of the brain's role in suppressing hemodynamic responses to noxious stimuli under isoflurane anesthesia. In this animal study, they were able to isolate delivery of isoflurane to the brain in one group and isolate delivery to the spinal cord in the other group. Those groups were compared to isoflurane delivered to the whole body. They found that isoflurane delivered to the whole body does prevent hemodynamic responses to noxious stimuli, but profoundly lowers the MAP. Furthermore, by comparing the brain-only and spinal cord-only groups, the researchers found that the brain has very little control over the hemodynamic response to noxious stimuli as the minimal alveolar concentration to block autonomic response (MAC-BAR) was significantly greater in the brain-only group compared to the MAC-BAR in the whole body group.

Some studies have demonstrated potential tissue protective benefits in from preconditioning with volatile anesthetics such as isoflurane and led to some use of volatile anesthetic in the brain dead donor population, but a review by De Hert, Turani, Mathur, and Stowe (2005) concluded that none of the studies “unequivocally demonstrate that the use of a volatile anesthetic regimen resulted in a clinical benefit for the patients” (p. 590).

Several guidelines, including the 1999 recommendations from the Intensive Care Society of the United Kingdom (U.K.), state that anesthesia is not necessary for brain dead donor organ procurement operation (Morgan, Morgan, & Smith, 1999). Withholding anesthesia is the

standard in many places including the U.S., but it not universal and the risks and benefits of volatile anesthetics in brain dead donors continues to require further research.

Boutin et al. (2012) analyzed the differences in brain dead donors in France who had received anesthesia versus those who had not. Anesthesia, defined as at least one dose of hypnotic agent, anesthetic gas, or opioid, was received by 62% of donors. Donors who did not receive anesthesia maintained a MAP greater than 65 mmHg more frequently than donors who received anesthesia. Additionally, no difference in maximum MAP was found between the two groups. Donors in this study who received anesthesia required more fluid challenges and vasopressors and exhibited higher heart rates (HRs) and lower BPs. Data from this study does not support the use of anesthesia to control intraoperative HTN.

Management of Hypertension

Some have argued that volatile anesthetics can and should be used in brain dead organ donors to control intraoperative HTN; however, evidence is lacking (Boutin et al., 2012). The 1999 recommendations from the Intensive Care Society in the U.K. state that although anesthesia is not necessary for brain dead organ donors, volatile agents can be used to manage HTN (Morgan et al., 1999). Available evidence suggests volatile anesthetics are a greater detriment than potential benefit due to the lowering of BP and therefore decreased end organ perfusion.

Intraoperative HTN can be transient due to increases in catecholamines from sympathetic stimulation, thus most recommendations for treatment of HTN in brain dead organ donors suggest administering short-acting agents to control HTN. The risk of organ damage with HTN occurs when the BP exceeds the upper limit of autoregulation. Powner, Darby, and Kellum (2004) recommend conservative treatment of HTN. Initial HTN interventions should include decreasing or stopping vasopressor infusions. They suggest initiation of antihypertensive therapy

after MAP has been greater than 95 mmHg for 30 minutes, with a goal of MAP less than 90 mmHg, but above 65-70 mmHg. Additionally, the authors recommend labetalol 20 milligrams IV bolus every 20 minutes times two doses titrated to the goals above. If MAP is still not within the goal parameters, a nicardipine infusion is recommended starting at five milligrams per hour and titrated for the goals above, up to a maximum infusion rate of 15 milligrams per hour.

Although Anderson et al. (2015), acknowledges HTN related to autonomic storm can be managed with nitroprusside or esmolol, they state that autonomic storm during brain herniation is not an issue in the OR after time has elapsed since herniation, diagnosis of brain death, and consent for donation. The authors fail to address anesthetic management of HTN intraoperatively in their narrative review of anesthetic considerations in organ procurement surgery.

Likewise, Arbour (2005) also recommends treating autonomic storm with esmolol and nitroprusside. Most donor management literature focuses on interventions during and after brain death declaration in the ICU and neglects the intraoperative phase. Donor management guidelines for the ICU can be extrapolated to the OR; however, it can be argued that the physiology issues present when treating autonomic storm at the time of brain death differ from the physiology issues of treatment of intraoperative HTN in the brain dead organ donor. The principles of choosing drugs with short onset and duration as well as ability to titrate (Arbour, 2005) may be helpful in either situation.

Management of Hypotension

More studies are available regarding management of hypotension in brain dead donors compared with management of HTN. The literature is heavily focused on the ICU management rather than intraoperative management, but significant crossover exists. Literature pertaining to fluid management goals in the ICU, hormone replacement protocols, and corticosteroids were

not included in this review as those interventions are typically completed during donor management in the ICU. Proper fluid resuscitation to euvolemia is the standard for organ procurements, and without adequate fluid resuscitation, intraoperative management options may be less successful.

Traditionally, cerebral blood flow autoregulation between a MAP of 60 and 160 mmHg has been used as a benchmark for intraoperative BP management, with the knowledge that things like chronic HTN can shift this curve. Most tissues in the body are able to autoregulate blood flow to some extent (Butterworth, Mackey, & Wasnick, 2013). Ono et al. (2013) found that acute kidney injury was independently associated with excursions of MAP below the lower limit of cerebral blood flow autoregulation. Additionally, Rhee et al. (2012) found that renal blood flow decreased incrementally below baseline perfusion pressure much earlier than cerebral blood flow decreased in the setting of hemorrhagic shock. Failure to correct hypotension can lead to acute kidney injury (Lange & Souter, 2015).

Hemodynamic management should focus on the goals of restoring euvolemia, maintaining adequate perfusion pressure, and optimizing cardiac output (Lange & Souter, 2015). Literature reviewed recommended maintaining hemodynamic stability with a goal of a MAP of 60-90 mmHg.

When hemodynamic instability in the brain-dead donor is not corrected, kidney dysfunction is enhanced and immune activation occurs faster and is more profound. The observed changes may predispose the graft for additional ischemia/reperfusion injury during the transplant process and hence accelerate rejection of the graft after transplantation. (van der Hoeven et al., 2003, p. 1874)

Additionally, van der Hoeven, et al. (2000) states that progressive liver dysfunction is significantly worse in rats that were hemodynamically unstable (defined as MAPs of 55 ± 5.3 mmHg one hour after brain death and 52 ± 9.9 mmHg six hours after brain death) with increased immune activation also being present in these situations.

After proper fluid resuscitation, if MAP is less than 65 mmHg, dopamine has traditionally been the first-line vasopressor recommended for management of hypotension in brain dead organ donors (Bugge, 2009). Dopamine may offer protective effects against ischemia-reperfusion injuries and inflammation by enzyme induction of heme-oxygenase-1 and other enzymes. Bugge (2009) found that catecholamine use in donors may have some benefit in four-year graft survival rates for kidney transplantation. Norepinephrine increased the incidence of initial non-function in heart recipients, but did not negatively affect liver grafts. The author notes that the study was retrospective therefore causality could not be determined. Bugge (2009) also indicates use and avoidance of specific vasoactive medications in donors are varied and lack evidentiary consensus, as there is a lack of randomized controlled trials.

Mukadem et al. (2005) demonstrated catecholamine use (defined in this study as dopamine at 2.5 mcg/kg/min or greater, epinephrine, or norepinephrine) was associated with worsening gas exchange after lung transplantation. Zaroff et al. (2002) proposed a strict protocol for limiting the maximum dosages of catecholamines in brain dead donors in order to facilitate better outcomes for heart transplants as high-dose catecholamine infusions have been thought to cause downregulation of beta adrenergic receptors, depletion of norepinephrine and high-energy phosphates in the myocardium. Silva et al. (2002) found that primary graft failure for heart transplants was not increased in when donors had been maintained on high-dose catecholamine

infusions in order to maintain a MAP 70-100 mmHg, suggesting that organ perfusion pressure is important than adherence to maximum suggested dosages.

Studies have shown successful hemodynamic management with both norepinephrine and vasopressin after adequate fluid resuscitation and dopamine infusion (Bugge, 2009). Practice of vasopressor management varies widely since there is a lack of evidence to recommend use or avoidance of any one vasopressor over another other than based on clinical presentation of the donor (Westphal et al., 2012).

Studies establishing and examining the BP alterations encountered in brain dead donors during organ procurement are decades old. This study provides an update on intraoperative BP derangements in brain dead organ donors. Additionally, much of the available evidence to potentially support the argument for use of volatile anesthetics in brain dead organ donors is extrapolated from animal studies. This pilot study examines the effects of volatile anesthetics on BP during procurement surgery for brain dead organ donors.

The evidence table (Table 1) provides a summative overview of the main studies reviewed in the literature review section regarding the available evidence about the intraoperative blood pressure variations and the effects of anesthesia in brain dead organ donors.

Methods

Research Design

This study employed a retrospective chart review to analyze intraoperative BP management of brain dead organ donors. MAPs were collected every minute. Presence or absence of the administration of volatile anesthetic gas in the OR was collected. Type of volatile anesthetic administered and end-tidal concentrations of the volatile anesthetic gas were also

collected. The study was designed to examine intraoperative hemodynamic stability and further investigate the effects of volatiles anesthetic gas on brain dead donors during organ procurement.

Sampling and Setting

Institutional review board (IRB) approval from both DePaul University as well as Advocate Christ Medical Center (ACMC) was obtained prior to data collection. Standard Health Insurance Portability and Accountability Act (HIPAA) regulations were followed to protect donor and donor family anonymity as described later in the data collection section. Intraoperative records were reviewed from organ donor procurement surgeries from May 1, 2015 through April 30, 2016 at ACMC, in Oak Lawn, Illinois. This yielded 28 individual cases.

ACMC is a level one trauma center in the near southwest suburbs of Chicago. This facility has been the focus of media attention in recent years due to the high volume of traumas and the high rates of violence in certain parts of Chicago. ACMC was chosen as the study site because it regularly encounters a high number of organ donors.

Study

Inclusion criteria

- All brain dead organ donors age 15 and older who reached the OR at ACMC between May 1, 2015 through April 30, 2016

Exclusion criteria

- Donations after cardiac death
- Donors that cardiac arrest prior to reaching the OR and therefore no organs are procured
- Brain dead organ donors age 14 and under

Instruments for Data Collection

Data was collected from the intraoperative records at ACMC which used the Cerner SurgiNet charting system at the time of this study. BPs were automatically saved to the intraoperative anesthesia record from the patient monitor. The standard procedure for BP monitoring for brain dead organ donors at ACMC and by the local OPO is to monitor BPs from an existing arterial line, typically placed in the femoral artery. MAPs recorded for this study were taken from the arterial line pressure at one minute intervals and automatic BP cuff readings when available. Data collected includes:

- MAPs documented in the anesthesia record at one minute intervals
- Total number of minutes in the OR (defined as starting at first recorded BP to last recorded BP before aortic cross clamp)
- Administration and end-tidal concentrations of volatile anesthetic gas such as sevoflurane, isoflurane, and desflurane

Ethical Considerations

Federal regulation 45 C.F.R. §46.102 (US Department of Health and Human Services, 2009) defines a human subject as a "living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information" (p.4). Research involving deceased human subjects does not meet the criteria for research with human subjects according to the law. Patients who are declared brain dead meet the medical and legal criteria for death.

Although the subjects in this study do not meet the criteria for human subjects, it was still essential to protect their private health information. The medical record numbers (MRNs) were the initial identifiers of the cases to determine if the donor met inclusion criteria for this study. This information was protected as described below in the data collection section. Sensitive

details surrounding the medical history and manner of death were not included in this chart review. No identifiable information, such as the date of the surgery, age, or date of birth was recorded for this study.

Data Collection

The data gathered in this chart review included MAP BP readings, as well as use of volatile anesthetic gas and their end-tidal concentrations. Patients should not be able to be identified from this information; however, patients were initially be identified by MRN by the medical records department at ACMC. One Excel spreadsheet was made with the MRN and assigned subject number without any other potential patient identifier. The data sheet was stored in a password protected spreadsheet on a password protected laptop computer that is locked in a safe in the primary investigator's (Alison Karmanian) home office when unattended. A second Excel spreadsheet was used to store the data collected on MAPs and volatile anesthetic gas with only the subject number identifying the patient. The data collection spreadsheet did not have any information that could identify the subject and consisted of gathering data that already existed; therefore, the study was exempt from the Common Rule (US Department of Health and Human Services, 2009). The MRN, nor any other identifiable patient information, was not disseminated to committee members or included in the study and report in compliance with HIPPA rules.

Results

Twenty-eight cases met the inclusion criteria, and data was analyzed using International Business Machines (IBM) SPSS version 24 (IBM, 2017). Statistical significance was set at p value of ≤ 0.05 for all inferential statistics.

Mean MAP was calculated for each donor. Mean MAPs ranged from 61.04 to 99.34 mmHg with a mean of $M= 84.51$ mmHg (Figure 1). Twenty-two donors (78.6%) received

volatile anesthetic gas at some point in the anesthesia record. Six donors (21.4%) received no volatile anesthetic gas. Mean end-tidal concentrations of volatile anesthetic gas in the 22 donors who received volatile anesthetic gas ranged from 0 to 1.25% with a mean end-tidal concentration of $M= 0.39\%$ (Figure 2). Sevoflurane was used in 17 donors, and isoflurane was used in 5 donors.

Mean MAP in donors that did not receive volatile anesthetic gas was $M= 78.49$ mmHg ($SD= 9.78$ mmHg). Mean MAP in donors that received volatile anesthetic gas was $M= 86.16$ mmHg ($SD= 7.02$ mmHg). Equal variances of the groups were examined using the Levene's test, and revealed homogeneity. Independent sample t test revealed a statistically significant difference between mean MAPs of the two groups ($t= 2.182$, $p= 0.038$).

The Spearman's rho correlation coefficient (r_s) was used to determine the relationship between mean MAP and mean end-tidal concentration of volatile anesthetic gas in donors in this study because mean end-tidal concentrations were not normally distributed. There was no statistical significance ($p=0.414$) found for the weak negative linear correlation ($r_s= -0.184$) between mean end-tidal concentration and mean MAP.

Discussion

This single-center pilot study at a large teaching hospital and transplant center that performs a high volume of organ donors was conducted to determine mean MAP and duration of intraoperative hypotension during organ procurement operations. Available literature on recommendations for MAP goals in organ donors suggest that a MAP between 60-90 mmHg is optimal (Kotloff et al., 2015, McKeown et al., 2012, Powner, 2005, Powner et al., 2004, Westphal et al., 2012, Zaroff et al., 2001). Mean MAPs for donors in this study during the organ procurement operation ranged from 61.04 to 99.34 mmHg with a mean of 84.51 mmHg.

On average, BP of donors was managed in a way that MAPs fell within this optimal range. In the 28 donors included in this study, no donor demonstrated an average MAP below 60 mmHg. Five donors did have an average MAP greater than 90 mmHg, indicating that intraoperative hypertension is a more prevalent problem than intraoperative hypotension.

The majority of donors (22 out of 28, or 78.6%) in the study received volatile anesthetic gas at some point during the organ procurement. Available literature states that anesthetics, such as volatile anesthetic gas, are not necessary for this procedure as donors are brain dead (Boutin et al., 2012, Morgan et al., 1999). It was found in this study that administration of volatile anesthetic gas during organ procurement is a very common occurrence at this medical center. Although published data and rationale on using volatile anesthetic gas in this population is limited, the rationale of blocking sympathetic blood pressure response to incision is commonly cited (Antognini & Berg, 1995, Elkins, 2010, Yoo et al., 2008, Young & Matta, 2000). The clinical dose of volatile anesthetic gas needed to suppress this response in 50% of patients is referred to as the minimum alveolar concentration to block adrenergic response (MAC-BAR) (Barash et al., 2013). MAC-BAR is estimated at 50% higher than minimum alveolar concentration (MAC) (Barash et al., 2013). The MAC of sevoflurane is 1.8% end-tidal concentration, and the MAC of isoflurane is 1.17%, which makes MAC-BAR for sevoflurane 2.7% and MAC-BAR for isoflurane 1.76%. The highest mean end-tidal concentration of volatile anesthetic gas for a donor in this study was 1.25% which falls well below MAC-BAR for either volatile anesthetic gas used in this study (sevoflurane was used in 17 donors, and isoflurane was used in 5 donors).

Mean MAP was higher in donors who received volatile anesthetic gas ($86.16 \text{ mmHg} \pm 7.02 \text{ mmHg}$) than in donors who did not receive it ($78.49 \text{ mmHg} \pm 9.78$). Volatile anesthetic

gases all share a common side effect of causing dose-dependent hypotension via peripheral vasodilation (Barash et al., 2013). Therefore, it would be natural to expect donors who received volatile anesthetic gas to display lower mean MAPs, but this is not what was found in this study. It could be inferred that volatile anesthetic gas was being used to assist in controlling BP in donors who exhibited high BP intraoperatively during procurements. Volatile anesthetic gas is very convenient and easy to start, stop, and titrate, and anesthesia providers are likely most comfortable with this method of augmenting high blood pressure as this is often a first-line agent used for controlling an increasing BP in the operating room for most standard surgical cases.

An independent samples *t* test between donors who received volatile anesthetic and those who did not determined that the difference in mean MAPs between the two groups was statistically significant ($p= 0.038$).

The Spearman correlation coefficient (r_s) was also performed and determined that there the weak negative relationship between mean MAP and end-tidal concentration of anesthetic gas was not statistically significant. Interestingly, as noted above, low means were more related to low end-tidal concentrations of volatile anesthetic gas, contrary to what the literature states about the dose-dependent hypotensive effects of volatile anesthetic gas. This seems to indicate that anesthesia providers may be implementing use of volatile anesthetic gas more in donors that are demonstrating intraoperative HTN than those who are not.

Other medications that affect BP were not recorded as part of this study which poses a significant limitation. Due to the physiological processes that occur during and after brain death, vasopressor support with infusions is common. Additionally, anesthesia providers commonly administer intravenous boluses of vasopressors to titrate BP to ideal levels. Antihypertensive agents could also be administered in the operating room and would confound the BP variability.

In addition to use of these infusions and boluses of medications that can alter BP, availability of this information in the electronic anesthesia medical record is dependent on the user accurately recording the drug, dose, and time of administration. In the future, smart pumps and medication scanning in the operating room may help improve the accuracy of medication administration intraoperatively.

The MAP and end-tidal concentrations of volatile anesthetic gas are automatically recorded from the equipment directly in the electronic anesthesia record. In this specific electronic anesthesia record system, this data is able to be changed by the user in a different screen. Additionally, aberrant readings from the arterial line which records the blood pressure may be automatically documented on the record (such as when blood is being drawn from the line or when the line is being flushed). The transducer of the arterial line must be calibrated correctly in order to obtain accurate readings of arterial BP. There is not a way to verify that this was done in the cases examined for this retrospective chart review. When recordings from the arterial line were not available in the anesthesia record, non-invasive blood pressure cuff MAP values were used instead. If systolic BP and diastolic BP were documented in the record, but the MAP value was not present or was clearly aberrant (greater than the systolic BP value), MAP was calculated by the primary investigator of the study.

During data collection, different patterns of volatile gas administrations were observed including the use of volatile anesthetic gas only around incision time, as needed, throughout the entire procedure, choice of volatile anesthetic gas (sevoflurane and isoflurane were both used), and use of no volatile anesthetic gas. Provider preference may have an impact on the use of anesthetic gas and potentially the pattern of use, but the anesthesia providers for the cases were not recorded as part of this study.

Several other details may impact the intraoperative blood pressure of brain dead organ donors including medical conditions such as cardiogenic shock or supportive therapies such as intra-aortic balloon pumps or extracorporeal membrane oxygenation, co-morbidities, age, and cause of death. With only 28 donors identified for this study, collection of any of the above information could potentially identify a particular donor and therefore, these details were deliberately excluded from data collection, despite their potential significance.

Patients were identified for this study through the billing department of the hospital which keeps a log of all organ donor cases. Identification of appropriate candidates was entirely dependent on the accuracy of this list.

Additional intraoperative event time would be helpful to collect in future studies including incision time, sternotomy time, and aortic cross-clamp time.

Future studies should be done comparing recipient outcome data to intraoperative BP and the use of volatile anesthetic gas. More detailed data may be able to determine which organs may be more sensitive to the effects of low or high BP during organ procurement and may provide some insight on autoregulation of blood flow to organs in brain dead patients. Future prospective studies may benefit from observation and data collection of vital signs and medication administration in real time to minimize documentation errors.

Conclusion

This retrospective review of records among brain dead organ donors aged 15 and older demonstrated that intraoperative HTN is more prevalent than intraoperative hypotension. Volatile anesthetic gas is often being used at this medical center during organ procurements at relatively low concentrations. There was a statistically significant difference ($p= 0.038$) between mean MAPs in donors who received volatile anesthetic gas versus those who did not, and there

was no significant relationship found between mean MAP and end-tidal concentration of volatile anesthetic gas.

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Table 1

Evidence-based Table on the Intraoperative Blood Pressure and Effect of Volatile Anesthetic in Brain Dead Organ Donors

Author/ Year	Design/ Method/ Sample/ Setting	Key Findings	Appraisal Relevant to the DNP Project
Bugge (2009)	Review	<ul style="list-style-type: none"> -sustained hypotension associated with impaired graft function -80-90% require vasopressor or inotropic support -vasoactive medication use not based on randomized controlled trials; widely divergent opinions on best to use and avoid -adequate coronary perfusion pressure may be more important than avoiding high-dose catecholamines -dopamine is traditional first choice pressor -dopamine may induce protective enzymes (HO-1) to guard against ischemia/ reperfusion injury and inflammation -dopamine maximum of 10 mcg/kg/min lacks good evidence -dopamine should be titrated to target hemodynamic effect (due to individual differences in pharmacodynamics) with the limitation of tachycardia -after fluid resuscitation and dopamine, both norepinephrine and vasopressin have been used successfully -vasopressin good for DI and decreases catecholamine use -norepinephrine in mammals increases coronary and RBF -norepinephrine is related to primary graft dysfunction and decreased right ventricle contraction and 1-year survival for heart transplant (retrospective, therefore not causal) -volatile anesthetics still experimental, but may protect heart from ischemia/ reperfusion injury 	<ul style="list-style-type: none"> -review evaluates current practice against current research -HD management plan describes order of interventions and discusses HD monitoring options
Mukadam et al. (2005)	Retrospectively analyzed, prospectively collected data of 60 lung donors and recipients; categorized to treatment or	<ul style="list-style-type: none"> -catecholamine use was associated with worse gas exchange after transplantation-difference not related to ischemic time, preservation technique, or recipient donor -donors requiring catecholamines may have had more severe AS and therefore more pulmonary injury and inflammation. -if catecholamines were needed for CV 	<ul style="list-style-type: none"> -different organs respond differently to catecholamines with some gaining protection and others demonstrating worsened outcomes- a balance that must be struck with donor

	control group by what they received and compared PaO ₂ /FiO ₂ ratios	function, it could exacerbate left atrial pressure	management
Boutin et al. (2012)	Multicenter retrospective study of records of BD patients; data collected includes extended criteria donor status, resuscitation duration and procedures, period of brain death, cold ischemic time, type of anesthesia, hemodynamic and ventilatory parameters, and impact of anesthesia on renal graft	-62% of donors in study received anesthesia -donors who did not receive anesthesia maintained a MAP >65 more frequently with no difference in maximum MAP -those who received anesthesia required more fluid challenges, (especially with colloids) and pressors, had lower MAPs and higher HRs -persistence of partial spinal regulation in BP and temperature -reports increased HR and BP in 24% of subjects who received no anesthesia -tissue protective effects of opioids are not justified by research, and there is very limited info on the tissue protective effects of volatile anesthetic agents	-anesthesia → hypotension → poor graft function -anesthesia showed no difference in maximum MAP -the use of anesthesia to control intraoperative HTN is not supported by the data in this study -anesthesia increases incidence of hypotension and does not control HTN
Young and Matta (2000)	Expert opinion	-different definitions of brain death in different countries (whole brain versus brain stem) -Intensive Care Society of U.K. 1999 recommendations say anesthesia not necessary for BD donors, but HTN can be managed with nitroprusside or a volatile agent -argues for anesthesia for hemodynamic response to surgery and persistence of higher brain & spinal cord function in some donors & inability to test reticular formation	-different definitions may impact physiology and therefore donor management, so management recommendations cannot necessarily be generalized to the international community
Kotloff et al. (2015)	Consensus statement; multidisciplinary, multi-institutional task force divided in subcommittees; available literature comprised of mainly observational studies and case series (low quality evidence)	-HD management recommendations: • hypovolemia frequently present at BD and should be corrected quickly • HD monitoring tools are helpful in assessment of volume status and response to therapy. • PAC, CVC, or noninvasive monitors should be considered for serial & continuous measurement -fluid resuscitation guidelines: MAP ≥60, UO ≥1cc/kg/hr, EF at least 45%, lower vasopressor dose (e.g. dopamine ≤ 10mcg/kg/min) -goal directed fluid therapy with goal of euvoemia recommended for entire	-their literature review revealed low quality evidence therefore paper is termed consensus statement versus guidelines -ICU recommendations can likely be extrapolated to OR management -euvoemia -specific parameters for goal-directed therapy and recommendations for HD monitoring -use of vasopressin associated with increased

		<p>management phase</p> <ul style="list-style-type: none"> -HES should not be routinely used due to issues with AKI, coagulopathy, trapping in hepatic reticuloendothelial system, and is associated with delay graft function/ failure -low molecular weight HES may be safer, but not currently recommended -crystalloid & colloids ok -dopamine is the traditional first-line vasoactive agent; insufficient data to recommend others over dopamine -dopamine has protective effects -vasopressin is alternate 1st line agent; additional pressor for refractory shock -norepinephrine, phenylephrine, and others may be used in severe shock (dobutamine, dopamine, and epinephrine for primary pump dysfunction; norepinephrine and phenylephrine for vasodilatory shock/low SVR) -if HD goals still unmet and/or EF <45%, HRT is recommended 	<p>rate of organ recovery</p> <ul style="list-style-type: none"> -recommendations for which vasoactives for which scenarios
Barash et al. (2013)	Textbook	<ul style="list-style-type: none"> -BD donors present many challenging management issues because collected experience in a single center is usually small, and research in brain-dead human subjects is sparse -there is solid evidence that desmopressin is better than norepinephrine for maintaining quality of donor hearts -mainstay of donor management is maintenance of euolemia; CVP monitoring standard (maintained 6-12); PCWP <12 when PAC used -goals of volume resuscitation and HR are to minimize pressors as high-dose dopamine associated with renal graft failure 	<ul style="list-style-type: none"> -vasopressin better than norepinephrine for hearts -CVP 6-12 -POAP when available <12 -goal: minimize use of pressors → balance good end-organ perfusion by using pressors only when necessary to minimize deleterious effects
Anderson et al. (2015)	Narrative review	<ul style="list-style-type: none"> -intraoperative management may affect recipient outcomes -dramatic loss of sympathetic tone can result in HDI -evaporative loss -incisional blood loss -polyuria secondary to DI -AS not encountered in OR, but managed with nitroprusside and esmolol -avoid HES -arterial pulse pressure variation can guide fluid therapy -if lung procurement, colloid preferred 	<ul style="list-style-type: none"> -dopamine 5 mcg/kg/min improves blood flow to renal, mesenteric, and coronary vascular beds → enhances organ perfusion -dopamine versus norepinephrine; evidence lacks superiority of one over the other -avoid high-dose alpha agonists → decreased blood flow and O₂ delivery
McKeown et al. (2012)	Review	<ul style="list-style-type: none"> -increasing consensus in donor management guidelines, but lacking controlled evaluation of many of the specific components of donor management -optimal treatment combinations not established and more research needed 	<ul style="list-style-type: none"> -hormonal resuscitation as discussed in the UNOS critical pathway for the organ donor in 1999 showed a 1% increase in organs retrieved from BD

		<ul style="list-style-type: none"> -incidence of hypotension in donors: 81-97% -Crystal City Consensus Conference Cardiac Recommendations -Canadian multidisciplinary forum on donor management: HR 60-120, SBP >100, MAP ≥ 70 -rule of 100s (SBP, UO, PaO₂, Hgb) -vasopressin 0.5-2.4 units/hr may decrease catecholamine requirements -high-dose norepinephrine (>0.05mcg/kg/min) should be avoided if possible -multicenter clinical trial underway to determine if fluid management protocol via pulse-pressure variation can increase viability of lungs and other organs -vasopressin recommended as 1st line agent by Canadian guidelines -HR looked good when initial studies were compared to historic controls, but randomized studies failed to show benefit -in one study, untransplantable hearts were resuscitated during surgery and improved -CV response is generated and modifiable at the level of the spinal cord alone -spinal reflexes can occur spontaneously or with surgical stimulus → NMB -surgical manipulations can cause CV instability -several randomized donor intervention studies are in progress 	<p>donors, but a 19.5% increase in hearts transplanted</p> <ul style="list-style-type: none"> - pilot study donors were younger and less likely to have had strokes and other comorbidities; more data needed
Elkins (2010)	Literature review	<ul style="list-style-type: none"> -treatment of AS with emolol, nicardipine, and urapidil in 2006 study -Arbour (2005) recommends esmolol and nitroprusside as effective and short-acting agents for HTN -BD causes decreased CO and increased SVR -thyroid supplementation improved CO and SVR → increased tissue perfusion & oxygenation; decreased lactic acidosis -CV stimulation is believed to involve a reflex arc to the adrenal medulla and may be increased by excitation of spinal cord below the lesion -1.5% isoflurane 20 minutes prior to ischemia (animal study by Hashiguchi et al. (2005)); significantly lower BUN and creatinine at 24 and 48 hours after transplantation/ reperfusion -isoflurane, xenon, nitrous oxide at 0.43% MAC suppress effects of TNF-α on certain gene and protein expression that can damage endothelium 	<ul style="list-style-type: none"> -pathophysiology similar to autonomic dysreflexia; uncontrolled sympathetic outflow -catecholamines trigger inflammatory response and ischemia → acute rejection -more research needed on ischemic preconditioning in donors - literature suggests strongly that AS causes deterioration of organs, therefore preventing sympathetic surge intraoperatively due to surgical stimulation could increase likelihood of successful transplant
Fitzgerald et al.	Randomized,	-use of fentanyl 7 mcg/kg was not effective	-opioids have shown to

(2003)	placebo-controlled, double-blinded study (n=17)	<p>in suppressing the catecholamine release, following painful surgical stimulation in BD organ donors</p> <ul style="list-style-type: none"> -catecholamine concentrations rose following painful stimuli -no differences in hemodynamics between the fentanyl and the placebo group -epinephrine concentrations, but not norepinephrine, were higher in the fentanyl group, reaching significance following sternotomy 	not be effective in preventing catecholamine release or maintaining BP control
Wetzel et al. (1985)	Retrospective chart review of 10 donors	<ul style="list-style-type: none"> -SBP increased by a mean of 31 mmHg, DBP by 16mmHg, and HR by 23 bpm in response to surgical stimulation 	-there is significant HD response to surgical stimuli in BD patients
Antognini and Berg (1995)	Quasi-experimental (group I isoflurane to torso, group II isoflurane to cranial, whole-body administration of isoflurane)	<ul style="list-style-type: none"> -theorized that during isoflurane anesthesia, CV responses to noxious stimuli were generated in the spinal cord -at ~1 MAC, MAP changes for Group II were much smaller than MAP for the whole-body -for whole-body administration of isoflurane, MAP change was 42 ± 20 mmHg for MAC values at 1.0 ± 0.1 -MAP change for Group II was 12 ± 9 mmHg at 1.1 ± 0.4 MAC -there was decreased response in MAP to the noxious stimulus in Group II, suggesting an inhibitory response 	<ul style="list-style-type: none"> -isoflurane suppressed BP response to noxious stimuli, but this also resulted in hypotension -MAC-BAR for brain only isoflurane group substantially exceeded MAC-BAR for the whole-body group -brain only anesthesia group exhibited spontaneous movement with noxious stimuli -whole-body administration of isoflurane inhibits CV responses to noxious stimuli, but causes a substantial decrease in MAP
Powner (2005)	Review	<ul style="list-style-type: none"> -goal: maintenance of MAP > 60 -there is little evidenced-based data that ties specific hemodynamic variables with outcomes after heart transplant 	-successful titration of preload, afterload, HR, and contractility achieves optimal cardiac performance
Powner et al. (2004)	Guidelines synthesized from articles in <i>Progress in Transplantation</i> that outlined treatment issues in donor care	<ul style="list-style-type: none"> -HTN: conservative treatment recommendations; goal: MAP <90, but >65-70 -therapy should start at MAP>95 x 30 minutes or more -hypotension (MAP<60): different kinds of shock; in BD, loss of vasomotor centers in brain → vasodilation; decreased cardiac contractility; hypovolemia due to DI; treatment goal: MAP 65-75 	<ul style="list-style-type: none"> -concrete parameters and recommendations for HD normal values and treatment -specific drug recommendations
Zaroff et al. (2001)	Consensus statement/ expert opinion	<ul style="list-style-type: none"> -adjust inotropes to maintain MAP ≥ 60 -target dopamine or dobutamine < 10mcg/kg/min 	-norepinephrine and epinephrine should be tapered off rapidly in favor of dopamine and dobutamine
Van der Hoeven et al.	Randomized controlled trial	-the hypotensive group remained hypotensive after brain death with MAP 55	-dysfunction of the potential donor liver can

(2000)		<p>± 5.3 after 1 hour and 52 ± 9.9 after 6 hours</p> <p>- Cited Koo et al. (1999) who found similar activation of adhesion molecules in human cadaveric kidneys before reperfusion</p>	<p>be reduced to some extent by maintaining normotension</p> <p>-both progressive liver dysfunction & infiltration of neutrophils can cause increased immunogenicity of the potential donor organ, decreased organ viability, & increased primary graft dysfunction, acute rejection, and lower graft survival rates</p>
Pratschke et al. (1999)	Peer-reviewed, published overview	<p>-early HTN phase and late normotensive or hypotensive phase (loss of autonomic tone)</p>	<p>-both initial and late circulatory changes can cause severe ischemic damage and worsen transplant outcomes</p> <p>-both the ischemia and the reperfusion cause tissue injury</p> <p>-brain dead organs have higher immunogenicity than living donors (if both are normotensive)</p> <p>-ischemic insults happening near the time of organ transplantation are risk factors for late failure for the transplant</p>
Tuttle-Newhall et al. (2003)	Monograph	<p>-causes of HDI: hypovolemia (trauma or DI), decreased vascular tone, myocardial depression</p> <p>-clinical experience has demonstrated that normalization of HD parameters with volume replacement, inotropes, and careful administration of vasoconstrictors is associated with good transplant outcomes (immediate allograft function)</p> <p>-BD terminates PNS activity resulting in unopposed SNS stimulation (autonomic storm)</p> <p>-loss of baroreceptor function causes uncoupling of ANS and CV function causing the subsequent normotensive or hypotensive state</p> <p>-unopposed vasodilation and impaired myocardial function (injury during autonomic storm and severe catecholamine depletion)</p> <p>-α agonist may be appropriate due to low SVR resulting from sympathectomy, but should be avoided whenever possible</p>	<p>-HDI in the donor can cause organ dysfunction after transplantation</p> <p>-increased vascular resistance that exceed perfusion pressure causes end organ ischemia in rats (Herijgers et al., 1996)</p> <p>-recommends pressor therapy guided by PAC or TEE</p>
Pennefather, Dark, and	Prospective observational	<p>-dopamine can cause potentially harmful decrease in hepatic mitochondrial redox</p>	<p>-procurement causes significant HD changes</p>

Bullock (1993)	study in 14 brain dead patients (10 thoracic/ abdominal donors and 4 abdominal only donors)	<p>state and renal function in recipient can be impaired by high-dose dopamine in donor</p> <ul style="list-style-type: none"> -serial plasma catecholamine concentrations measured in donors who did not receive dopamine (could not measure due to interference when dopamine was used- 9 patients) -consistent biphasic response in 1st 30 minutes: early increase in SVR and PAWP -by 30 minutes, SVR, PVR, MAP, PAWP, and CVP decrease, and HR and CI increase -two patients suffered a precipitous drop in SVR and PAWP likely due to dilation which caused significant decrease in CI and MAP- IVF bolus restored CI and MAP in both patients -intermittent surgical manipulation affected accuracy of HD measurements -increased SVR and PAWP at 30 minutes and before thoracotomy suggests increased myocardial contractility perhaps due to endogenous catecholamines -vasoconstriction theories: spinal vasoconstrictor reflex, reflex spinal stimulation of adrenal medulla, residual brain stem function (U.K. study- not whole brain death declaration model) -vasodilation theory: late decrease in SVR due to vasodilation from epinephrine secretion 	<p>that may alter organ perfusion</p> <ul style="list-style-type: none"> -organ perfusion may be impaired by inotropes -suggests using PAC to minimize use of inotropes
Rhee et al. (2012)	Observational study- animals	<p>-renovascular autoregulation can be monitored using the renovascular reactivity index (RVx)</p> <p>-autoregulation is mediated by vascular reactivity, which is defined by Lee et al. (2009) as low-frequency diameter changes in resistance vessels in response to changes in ABP</p>	<p>-renovascular autoregulation, as measured by RVx, is impaired before cerebral autoregulation during shock in piglets</p> <ul style="list-style-type: none"> -BP does not necessarily indicate renovascular compromise -renovascular autoregulation is lost before changes in BP occur -although clinically BP is used as indicator for renal perfusion, results here show that BP does not accurately reflect RBF -renovascular autoregulation is similar to cerebrovascular autoregulation -kidney is more dependent on CO whereas brain is perfusion-dependent

RBF decrease from baseline	Perfusion pressure
75%	60
50%	45
25%	40

CBF decrease from baseline	Perfusion pressure
75%	30
50%	25
25%	15

			-shock state results from this study may be different than shock from vasoplegia and other causes
Ono et al. (2013)	Prospective observational study	-cerebral autoregulation during CPB monitored by generating a cerebral oximetry index -lower limit of cerebral autoregulation determined for 348 patients -AKI developed within 7 days in 121 patients	-average MAP during CPB did not differ -patients who developed AKI had higher MAP at the limit of autoregulation and duration and degree to which MAP was below the autoregulation threshold (mmHg x min/hr of CPB) -MAPs below the lower limit of autoregulation were associated with development of AKI
Westphal et al. (2012)	Guidelines constructed by experts after extensive literature review	-MAP > 65 mmHg or systolic > 90 mmHg -excessive use of pressors can cause arrhythmias, worsen hypotension (dobutamine), or cause intense vasoconstriction causing ischemia to organs -β agonist therapy may be helpful in low CO states causing hypoperfusion -vasopressin can be used as a pressor and DI treatment; may help stabilize BP and wean off catecholamine infusions	-drug choice should be based on physiological principles because there are no randomized studies for best choice of pressor -no consensus regarding maximum catecholamine use
Bijker et al. (2007)	Observational, retrospective cohort study of non-cardiac surgery patients in the Netherlands	-incidence of intraoperative hypotension according to different threshold values was calculated, and the effect of a defined minimal duration of a hypotensive episode was studied	-no widely accepted definition exists of intraoperative hypotension, therefore there is generalizability of studies associating poor outcomes with intraoperative hypotension

*Abbreviations in table defined: CO (cardiac output), DI (diabetes insipidus), AKI (acute kidney injury), CPB (cardiopulmonary bypass), ABP (arterial blood pressure), RBF (renal blood flow), CBF (cerebral blood flow), SVR (systemic vascular resistance), PVR (pulmonary vascular resistance), PAWP (pulmonary artery wedge pressure), CVP (central venous pressure), HD (hemodynamic), HDI (hemodynamic instability), HR (heart rate), CI (cardiac index), IVF (intravenous fluid), BD (brain death), PAC (pulmonary artery catheter), MAP (mean arterial pressure), kg (kilogram), BP (blood pressure), AS (autonomic storm), SNS (sympathetic nervous system), PNS (peripheral nervous system), ANS (autonomic nervous system), CV (cardiovascular), TEE (transesophageal echocardiogram), HTN (hypertension), HRT (hormone replacement therapy), EF (ejection fraction), bpm (beats per minute), BUN (blood urea nitrogen), mcg (micrograms), min (minute), SBP (systolic blood pressure), UO (urine output), PaO₂ (partial pressure of oxygen in arterial blood), Hgb (hemoglobin), HES (hydroxyethyl starch), FiO₂ (fraction of inspired oxygen)

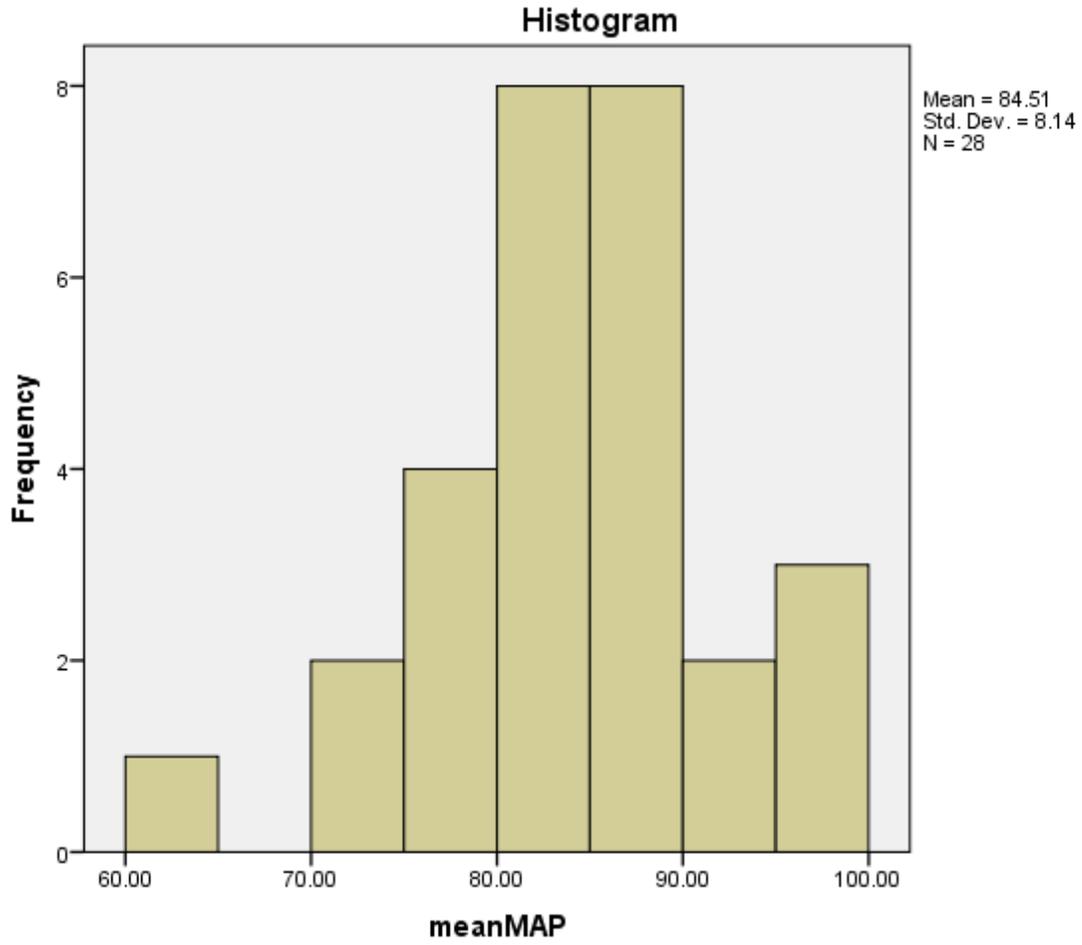


Figure 1. Frequencies displayed of the mean MAP for each case.

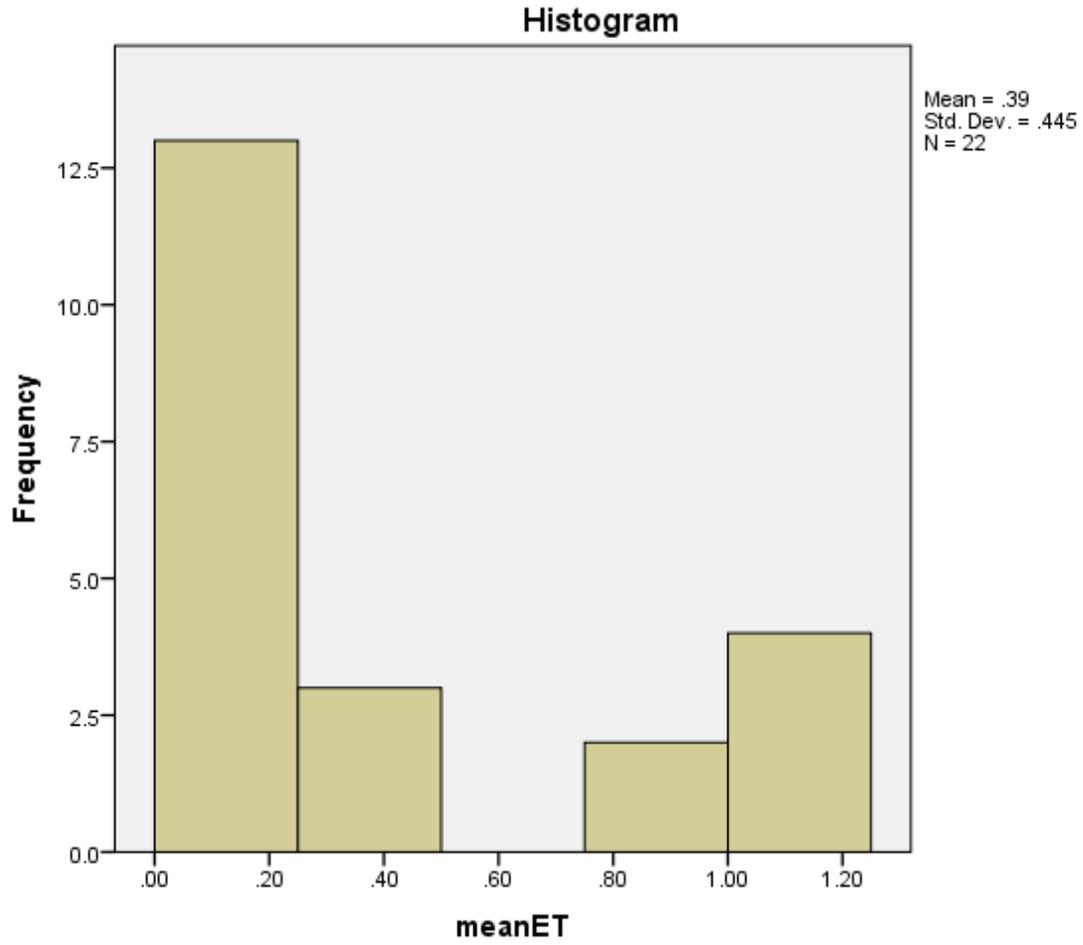


Figure 2. Frequencies displayed of the mean end-tidal concentration of volatile anesthetic gas for cases in which volatile anesthetic gas was used.

Appendix A

2010 American Academy of Neurology Guidelines for Diagnosis of Brain Death

Checklist for determination of brain death

Prerequisites (all must be checked)

- Coma, irreversible and cause known
- Neuroimaging explains coma
- CNS depressant drug effect absent (if indicated toxicology screen; if barbiturates given, serum level 10 g/mL)
- No evidence of residual paralytics (electrical stimulation if paralytics used).
- Absence of severe acid-base, electrolyte, endocrine abnormality
- Normothermia or mild hypothermia (core temperature 36°C)
- Systolic blood pressure 100 mmHg
- No spontaneous respirations

Examination (all must be checked)

- Pupils nonreactive to bright light
- Corneal reflex absent
- Oculocephalic reflex absent (tested only if C-spine integrity ensured)
- Oculovestibular reflex absent
- No facial movement to noxious stimuli at supraorbital nerve, temporomandibular joint
- Gag reflex absent
- Cough reflex absent to tracheal suctioning
- Absence of motor response to noxious stimuli in all 4 limbs (spinally mediated reflexes are permissible)

Apnea testing (all must be checked)

- Patient is hemodynamically stable
- Ventilator adjusted to provide normocarbia (PaCO₂ 34 – 45 mmHg)
- Patient preoxygenated with 100% FiO₂ for 10 minutes to PaO₂ 200 mmHg
- Patient well-oxygenated with a PEEP of 5 cm of water
- Provide oxygen via a suction catheter to the level of the carina at 6 L/min or attach T-piece with CPAP at 10 cm H₂O
- Disconnect ventilator
- Spontaneous respirations absent
- Arterial blood gas drawn at 8 –10 minutes, patient reconnected to ventilator
- PCO₂ 60 mmHg, or 20 mmHg rise from normal baseline value

OR:

- Apnea test aborted

Ancillary testing (only 1 needs to be performed; to be ordered only if clinical examination cannot be fully performed due to patient factors, or if apnea testing inconclusive or aborted)

- Cerebral angiogram
- HMPAO SPECT

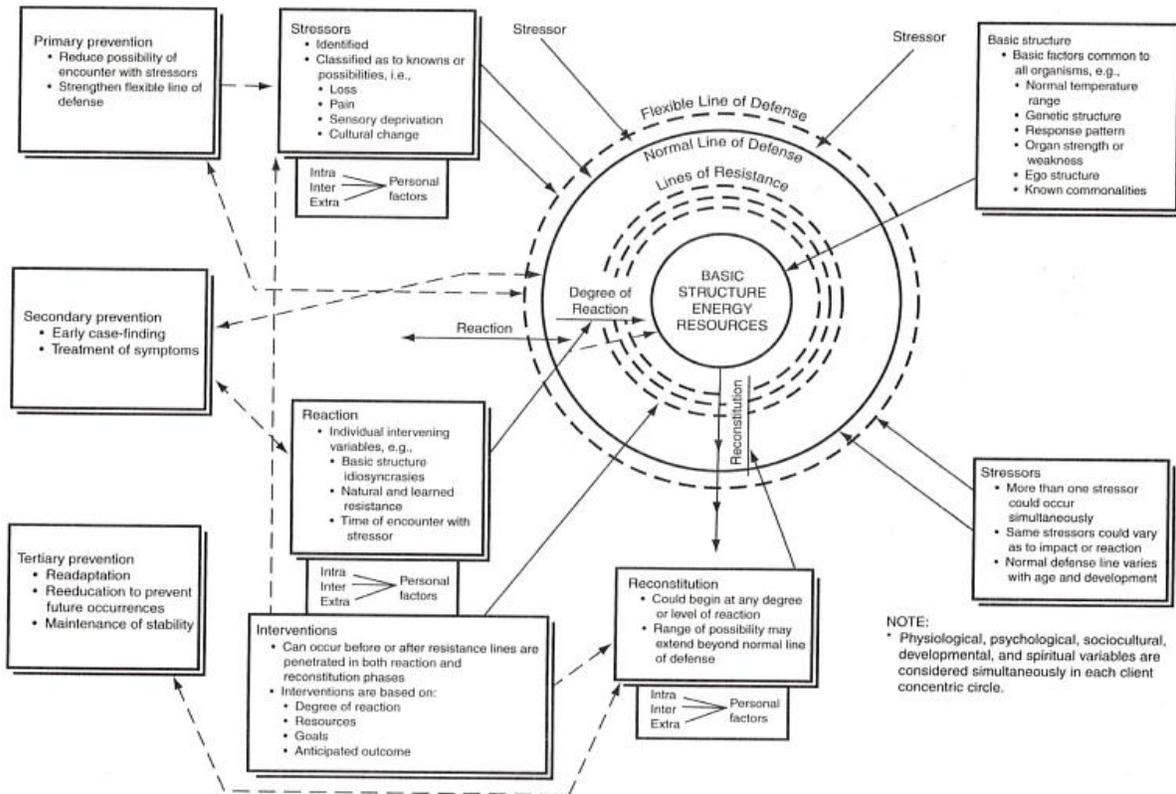
- EEG
- TCD

Time of death (DD/MM/YY) _____

Name of physician and signature _____

Appendix B

Neuman's Systems Model



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Appendix C

Neuman's System Model Applied to Brain Dead Donor

