INTRODUCTION
Perhaps one of the greatest achievements in medicine to date, organ transplantation has transformed the lives of thousands – bringing life to those who would surely have died without it. This achievement is dependent upon a generous gift from another person. From one deceased donor up to 55 lives may be saved or improved.1 With progressive advances in the trauma system, emergency physicians (EPs) are faced with more severely injured trauma patients, including the potentially brain-dead. The purpose of this three-part series is to present the components of determining brain death, to discuss the pathophysiology unique to brain-dead patients and to outline an algorithm based on that physiology to improve the care of the brain-dead patient. Rather than selectively neglect the brain-dead patient, active management while the patient is still in the emergency department (ED), specialty consultation and critical care can significantly enhance the likelihood of successful organ donation, turning a tragic loss into a rewarding patient encounter.

The majority of transplanted organs come from brain-dead or cadaveric donors. As most of these donors enter the healthcare system through the ED as either trauma patients with brain injuries or medical patients with acute intracranial hemorrhage, EPs are often involved in the diagnosis, referral, and initial stabilization of these patients. When these injuries would not benefit from neurosurgical or neurologic intervention and are deemed to be non-survivable, they are “devastating brain injuries.” The EP’s goal shifts to maintaining hemodynamic stability to diagnose brain death, should it occur. Furthermore, we must prepare the family for devastating news and allow them to begin the grieving process. EPs and trauma surgeons are often involved in discussions of end-of-life care and intensive care management of critical illness and injury. Therefore, both groups have the ability to impact organ donation, transplant frequency and success.

Table 1. Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Motor</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Purposeful; follows commands</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Localizes to pain</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Withdraws to pain</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Decorticate posture</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Decerebrate posture</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>No movement</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Verbal</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Oriented</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Confused</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Inappropriate</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Incomprehensible</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Nonverbal</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Open spontaneously</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Open to voice</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Open to pain</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>No eye opening</td>
<td></td>
</tr>
</tbody>
</table>

Total Score: 3-15

Table 2. Brainstem Reflexes

<table>
<thead>
<tr>
<th>Reflex</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pupillary response to light</td>
<td></td>
</tr>
<tr>
<td>Corneal reflexes</td>
<td></td>
</tr>
<tr>
<td>Caloric responses</td>
<td></td>
</tr>
<tr>
<td>Gag reflex</td>
<td></td>
</tr>
<tr>
<td>Coughing reflex</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Apnea Test Sequence (Derived from reference 9 and UCI Declaration of Brain Death Policy and Form - see Figure 2)

1. Preoxygenate the patient with 100% FiO₂
2. Ensure the patient is not hypocarbic via ABG
3. Disconnect the ventilator, but supply oropharyngeal oxygen
4. Monitor the patient for any signs of respiration
5. Obtain ABGs at selected intervals (q3-4 min)
6. Stop the test and return to mechanical ventilation if
   • hemodynamic instability occurs, or
   • the patient exhibits attempts to breathe, or
   • the pCO₂ is >60 mmHg or rises >20 mmHg above baseline in the setting of an arterial pH < 7.3

*FiO₂ fraction of inspired oxygen; ABG, arterial blood gas; pCO₂, partial pressure of arterial carbon dioxide

Organ Donor and Transplantation

Dr. Joseph Murray performed the world’s first transplant at Brigham and Women’s Hospital in 1954, and since then over 400,000 transplants have been performed. In 2007 there were 21,403 transplants performed in the United States (U.S.) alone. In medically suitable patients, transplantation for end-stage organ failure is the standard of care. The most commonly needed and transplanted organs, in descending order, are the kidney, liver, heart, lung, and pancreas. Kidney transplants made up 60% of all transplants in 2007 in the U.S. and have been shown to improve quality of life and to be cost-effective compared to hemodialysis.

To comprehend the potential impact of organ donation, several statistics are relevant. The five-year survival rates for patients on the transplant waiting list compared to those that are transplanted are 80.3% vs. 91% for pancreas, 66.5% vs. 92% for kidney, and 37.7% vs. 48% for lung. Two-year survival rates for heart transplantation wait-listed patients range from 44-70%, depending on the severity of heart failure, while the five-year survival after heart transplantation is 73%. Similarly, the one-year survival rate for patients awaiting liver transplantation based on severity ranges from 0-60% and the five-year survival after liver transplantation is 73%. It has been estimated that an average of 30 life-years are saved per organ and tissue donor, based on 2002 statistics, and 55 life-years would be saved if all organs were maximally utilized.

Despite this potential, there are currently 98,161 people on the United Network for Organ Sharing (UNOS) waiting list, 77,758 patients went without transplant in 2007, and approximately 7,000 died waiting.

There are several strategies to address the mismatch between available and needed organs. Education programs increase awareness of transplant needs and thereby increase the number of people who choose to donate, while prevention efforts lessen the burden of chronic diseases that require a transplant. Additionally, UNOS has an extended criteria donor program, which matches high-risk patients with advanced age or chronic diseases such as Hepatitis with high-risk donors. Expanding the donor pool from brain-dead donors to living donors and donors after cardiac death also helps to close

Table 4. Additional Confirmatory Testing for Determination of Brain Death

Cerebral angiography
The contrast medium should be injected under high pressure in both anterior and posterior circulation.
No intracerebral filling should be detected at the level of entry of the carotid or vertebral artery to the skull.
The external carotid circulation should be patent.
The filling of the superior longitudinal sinus may be delayed.

Electroencephalography
A minimum of eight scalp electrodes should be used.
Interelectrode impedances should be between 100 and 10,000 Ω
The integrity of the entire recording system should be tested.
The distance between electrodes should be at least 10 cm.
The sensitivity should be increase to at least 2 µV for 30 minutes with inclusion of appropriate calibrations.
The high-frequency filter setting should not be set below 30Hz, and the low-frequency setting should not be above 1 Hz.
Electroencephalography should demonstrate a lack of reactivity to intense somatosensory or audiovisual stimuli.

Transcranial Doppler ultrasonography
There should be bilateral insonation. The probe should be placed at the temporal bone above the zygomatic arch or the vertebrobasilar arteries through the suboccipital transcranial window.
The abnormalities should include a lack of diastolic or reverberating flow and documentation of small systolic peaks in early systole. A finding of a complete absence of flow may not be reliable owing to inadequate transtemporal windows for insonation.

Cerebral scintigraphy (technetium Tc 99m hexametazime)
The isotope should be injected within 30 minutes after its reconstitution.
A static image of 500,000 counts should be obtained at several time points: immediately, between 30 and 60 minutes later, and at 2 hours.
A correct intravenous injection may be confirmed with additional images of the liver demonstrating uptake (optional).
**Clinical Algorithm – Management of Adult Patients with Devastating Brain Injuries**

**Goal:** To maintain hemodynamic stability in patients with devastating brain injuries.

**Initial Steps of Management**
- **Penetrating and/or blunt trauma to the brain or devastating stroke.**
- **Evaluated by Neurosurgery and/or Neurology.**
- **Deemed to be non-survivable with no benefits from neurosurgical intervention.**
- **Still requires resuscitation by Trauma/Critical Care Services-consult to be obtained during course of treatment.**
- **Patient should weigh greater than or equal to 100 lbs.**

**Note:** All patients with devastating brain injury have the potential to be organ donors. However, organ donation should not be discussed with the family unless directed by the attending M.D.

**Abbreviations**
- **ABG:** Arterial blood gases
- **CBC:** Complete blood count
- **DIC:** Disseminated intravascular coagulation
- **CPP:** Cerebral perfusion pressure
- **Hb:** Hemoglobin
- **HCT:** Hematocrit
- **H & H:** Hematocrit & hemoglobin
- **HFP:** Hepatic function panel
- **IOP:** Intracranial pressure
- **MAP:** Mean arterial pressure
- **ND:** Non-dipper
- **PCWP:** Pulmonary capillary wedge pressure
- **SBP:** Systolic blood pressure
- **SVR:** Systemic vascular resistance
- **UOP:** Urine output
- **ABG:** Arterial blood gases
- **CBC:** Complete blood count
- **DIC:** Disseminated intravascular coagulation
- **ARBG:** Arterial blood gases
- **CBC:** Complete blood count
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- **PCWP:** Pulmonary capillary wedge pressure
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- **SVR:** Systemic vascular resistance
- **UOP:** Urine output

**Notes:**
- **Avoid hypotension and hypoxia in all head injury patients.**
- **Patient can go from hypertension to hypotension rapidly.**
- **To maintain hemodynamic stability in patients with devastating brain injuries.**
- **Call one Legacy to refer patient within one hour of being intubated and having a GCS < 5.**
- **Continue maintenance fluids and correct lab abnormalities.**
- **End points of resuscitation should include normalization of base deficit, lactate, CVP 6-10 mmHg and/or PAOP 8-15 mmHg, and minimal use of pressors.**
- **Rules of 100’s: Goal - SBP > 100 mmHg, UOP > 100 ml/hr, PaO2 > 100 or FiO2 < 0.3.**
- **Maintain fluids; either NS or LR, adjust as indicated.**

**Follow Up**
- **Continue to fluid resuscitate with 5% Albumin (if serum albumin < 2.0), Blood products (if indicated) and/or Normal saline until MAP > 70.**
- **Double dopamine to max 20 mcg/kg/min or norepinephrine to max of 20mcg/min if q 5 minutes until MAP > 70.**
- **If require 10 mcg/min Dopamine or 10mcg/min norepinephrine, add vasopressin gtt at 2.4 units/hour.**

**Refer to Hormone Replacement protocol see next page**

**Abnormalities**
- **Cardiac index < 2.5:** Add Dobutamine 2.5 mcg/kg/min and titrate to an index of 2.5.
- **Cardiac index > 4:** Add phenylephrine (20 to 200 mcg/min) or norepinephrine (1 to 20 mcg/min) and titrate to a MAP > 70.
- **Cardiac index 2.5 - 4:** Add epinephrine (1 to 20 mcg/min) or norepinephrine titrate to MAP > 70.

**CAUTION:**
- **Avoid hypotension and hypoxia in all head injury patients.**
- **Patient can go from hypertension to hypotension rapidly.**

**Rules of 100’s**
- **Goal - SBP > 100 mmHg, UOP > 100 ml/hr, PaO2 > 100 or FiO2 < 0.3.**
- **Maintain fluids; either NS or LR, adjust as indicated.**

**Patient MAP > 70**

**Yes**
- **Continue to fluid resuscitate with 5% Albumin (if serum albumin < 2.0), Blood products (if indicated) and/or Normal saline until MAP > 70.**
- **Double dopamine to max 20 mcg/kg/min or norepinephrine to max of 20mcg/min if q 5 minutes until MAP > 70.**
- **If require 10 mcg/min Dopamine or 10mcg/min norepinephrine, add vasopressin gtt at 2.4 units/hour.**

**No**
- **Continue maintenance fluids and correct lab abnormalities.**
- **End points of resuscitation should include normalization of base deficit, lactate, CVP 6-10 mmHg and/or PAOP 8-15 mmHg, and minimal use of pressors.**
- **Rules of 100’s: Goal - SBP > 100 mmHg, UOP > 100 ml/hr, PaO2 > 100 or FiO2 < 0.3.**
- **Maintain fluids; either NS or LR, adjust as indicated.**

**CVP > 10 and/or PAOP (wedge) > 17**

**Yes**
- **Cardiac index < 2.5:** Add Dobutamine 2.5 mcg/kg/min and titrate to an index of 2.5.
- **Cardiac index > 4:** Add phenylephrine (20 to 200 mcg/min) or norepinephrine (1 to 20 mcg/min) and titrate to a MAP > 70.
- **Cardiac index 2.5 - 4:** Add epinephrine (1 to 20 mcg/min) or norepinephrine titrate to MAP > 70.

**No**
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- **Double dopamine to max 20 mcg/kg/min or norepinephrine to max of 20mcg/min if q 5 minutes until MAP > 70.**
- **If require 10 mcg/min Dopamine or 10mcg/min norepinephrine, add vasopressin gtt at 2.4 units/hour.**

**Start vasopressin at 2.4 units/hour, and replace UOP > 200 ml with ½ NS ml for ml every hour.**

Figure 1. University of California Irvine Medical Center Devastating Brain Injury Pathway

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the gap. Finally, this series of articles focuses on improving premortem care of brain-dead donors, which decreases the number who succumb to cardiovascular collapse, and increases the number and function of viable organs procured per donor.10

In the first part of this series, we examine the concept and definition of brain death and provide an overview of the organ donation process. We will outline the clinician’s role in determining brain death and introduce our Devastating Brain Injury Algorithm, Figure 1, which is the basis of this series.

BRAIN DEATH

The concept of brain death has caused great controversy in medicine and politics. It is debated by ethicists, law professors, government agencies and healthcare workers.8-11 First introduced by Mollaret and Goulon in 1959, brain death was originally described as a persistent vegetative state or permanent coma.12 After 1959, the definition evolved until 1968 when a Harvard Medical School ad hoc committee created the current definition, which was later affirmed by the Uniform Determination of Death Act in 1981.12,13

In general, brain death is the irreversible loss of all brain function. Most agree that complex mental abilities alone do not singularly constitute being alive, lest those in a vegetative state or with severe cerebral malformations be inappropriately declared devoid of life.14 Ultimately, the brainstem controls brain function and is responsible for regulating breathing, heart rate, and reflexes such as gagging or coughing when the airway is obstructed, withdrawal from pain, and pupillary function. Without a functioning brainstem, life cannot exist. Therefore, diagnosing brain death requires the absence of brainstem function.

To establish a diagnosis of brain death, the clinician must first identify the underlying causes and determine that they are irreversible.12 Trauma, stroke, cerebral hypoxia, intracranial hemorrhage, tumors, meningitis, and encephalitis are all well-known causes.15 All confounding factors must be eliminated, such as hypothermia (< 35°C), hypoxia, intoxication by legal or illegal drugs, shock/hypotension, and severe electrolyte disturbances.12 Figure 2 shows the brain death declaration form and instruction sheet used at our institution.

The clinical brain death assessment is usually made in the intensive care unit (ICU), but if delayed in the ED, patients may warrant a brain death exam before admission. This evaluation involves three steps: verifying unconsciousness, documenting absent brainstem reflexes, and performing the apnea test. To verify unconsciousness, a Glasgow score of 3 is required (Table 1). The five brainstem reflexes that should be assessed in adults are shown in Figure 3 and Table 2.12 If all brainstem reflexes are absent, an apnea test is performed. The patient should have a pCO2 within the normal range and be pre-oxygenated with 100% FiO2. The apnea test ensures the patient has lost the drive to breathe and confirms the diagnosis of brain death.

An overview of the procedure and an example of our institution’s brain death declaration protocol can be found in Table 3 and Figure 2, respectively. Criteria for a positive apnea test include: no attempt to breathe while disconnected from the ventilator (as oxygen is still delivered to the airway), a pCO2 greater than 60mmHg or a rise greater than 20mmHg above base-line, and an arterial pH less than 7.3. It usually takes 5-10 minutes of apnea for the pCO2 to meet criteria, and we recommend drawing blood gasses every three minutes until either brain death is confirmed or the patient becomes hemodynamically unstable, at which point the patient should be reconnected to the ventilator. Some institutions recommend that the clinical exam, including the apnea test, be performed twice, six hours apart for adults and as much as 48 hours apart for neonates, but second assessment remains controversial.9,12

If the patient is hemodynamically unstable and would not tolerate even a few minutes off the ventilator for fear

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**Table 1: Neurological Examination and Reflexes**

<table>
<thead>
<tr>
<th>Reflexes Tested</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shivering/rooting</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Oculovestibular reflex absent (pt in C-spine precautions)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pupils fixed and dilated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Corneal reflex absent</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ommatropin reflex absent (pt in C-spine precautions)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Motor response to noxious stimulation absent</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Table 2: Apnea Test**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Code</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 mmHg for age or 20 mmHg over baseline</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>pH &lt; 7.30</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>pCO2 ≥ 60 mmHg OR &gt; 20 mmHg over baseline</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Figure 1:** University of California Irvine Medical Center Brain Injury Algorithm, Figure 1, which is the basis of this series.
of causing cardiopulmonary arrest, other confirmatory tests may be used (Table 4). The most common in the U.S. is cerebral angiography. If the carotid arteries cut off at the base of the skull and there is no blood flow within the calvarium, the patient is brain dead. Recently, clinicians have used magnetic resonance or computed tomography angiograms in lieu of more invasive traditional angiography.

Electroencephalography (EEG) is well-validated and frequently used to confirm brain death with absent electrical activity. The disadvantage of EEG is that devices in the ICU may cause artifacts, leading to spurious results. Other tests include transcranial Doppler ultrasound to assess cerebral blood flow and nuclear imaging to assess uptake of tracer in the brain. The latter is preferred for secondary confirmation in our institution. None of these confirmatory tests replaces the clinical exam.

Since children are more resilient than adults, a longer time between assessments has been advocated. Additionally, many institutions require other confirmatory tests, in addition to the apnea test, in children less than one year of age. Deciding who is qualified to determine brain death is another variable. Some centers advocate that at least two clinicians concur on the diagnosis of brain death and that at least one of those clinicians be a neurologist or neurosurgeon. Beyond these minor differences, the declaration of brain death is otherwise similar worldwide.

Once declared brain dead, the patient may become an organ donor with family consent or advanced directive. This may be verified by living wills or, in some states, by registration when obtaining a driver’s license. Brain death can be a challenging concept for a patient’s family, and it is important to equate brain death with the layperson’s understanding of bodily death, which usually means that the heart has stopped. The essential connection between brain function and conscious thought may not be obvious to laypersons, and should be stated explicitly.

It is imperative to separate end-of-life discussions surrounding brain death and the withdrawal of medical support from conversations about organ donation, to avoid any perceived conflict of interest. It is recommended that healthcare providers NOT approach family about organ donation without first consulting with their local organ procurement organization (OPO). In general, representatives from the OPO who are formally trained to talk with families about organ donation make the first, formal approach after end-of-life discussions have taken place. Healthcare providers with a close relationship to the family may be involved in the process as well.

Donor Management

The goal prior to and after the determination of brain death is to maintain perfusion of vital organs. This is, at times, as much the responsibility of the EP as the intensivist. After a family consents to donate organs, the OPO assumes care of the donor, both medically and financially, but physician involvement is still important to perform procedures and provide expert critical care advice. The brain is so central to bodily homeostasis, that once dead, it wreaks havoc on all other organ systems. Preserving organs is quite challenging in the face of brain death, and it is not uncommon to lose donors to the spiral of hormonal and cardiovascular collapse.

Recently, studies have proven that aggressive donor
management (ADM) can improve the quantity and quality of donated organs from brain dead donors.\textsuperscript{4,17-19} After a dedicated team of physicians assumed responsibility for the management of all potential organ donors at the Los Angeles County / University of Southern California Medical Center, there was an 82% increase in the number of organ donors and a 71% increase in the number of organs recovered.\textsuperscript{4} Furthermore, organizing the care of the brain-dead donor into an evidence-based clinical protocol has been shown to both decrease donors lost to cardiovascular collapse, as well as increase the number of organs procured per brain-dead donor.\textsuperscript{17}

The intensive care of the brain-dead donor does increase overall cost of care, but there is no cost to the donor’s estate or family.\textsuperscript{20} The cost-effectiveness of transplantation has been well established and has been most extensively reviewed for kidney transplantation.\textsuperscript{3,20-24} Furthermore, it is imperative to remember that the care of the donor potentially benefits eight patients with end-stage organ failure, and many more who will benefit from tissue donation.\textsuperscript{3,25} Traditionally, 75% of U.S. transplantations have been paid by Medicare.\textsuperscript{25} The transplanted patient or the patient’s insurance company pay for the remaining 16% and 9%, respectively.\textsuperscript{22} Costs incurred while caring for the brain-dead donor are ultimately distributed amongst the patients receiving the donated organs and are usually covered through insurance or Medicare/ Medicaid.\textsuperscript{26}

CONCLUSION

The active participation of all healthcare providers involved in the care of patients with severe neurologic insults preserves the option of organ donation for patients and their families. This care often begins in the ED. Recently, our institution implemented a Devastating Brain Injury Pathway—an evidence-based protocol designed to improve care of this unique population. The primary purposes of the pathway are to maintain hemodynamic stability by providing comprehensive critical care in order for brain death to be diagnosed, should it occur; to give families time to come to the hospital and grieve; and to preserve the opportunity of donation for patients and their families. It is imperative to explicitly state that the primary purpose is not to improve the number of organs that can be transplanted, as this would represent a potential conflict of interest for the physician caring for the injured patient. However, the pathway does represent sound neurologic critical care that will improve perfusion to the brain and has the potential to turn a devastating brain injury into a salvageable one. If a patient does regress to brain death, organ perfusion will be maintained should the patient’s family decide to donate. In the next two reviews we will discuss the pathophysiology of brain death that causes so many donors to be lost to cardiovascular collapse (part 2) and the resuscitation and management of these donors to preserve the maximum amount and function of organs per donor (part 3).

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REFERENCES


