Introduction

Organ transplantation is an effective treatment for end-stage organ failure. Increased public awareness, improved efficiency of the donation process, greater expectations for transplantation, expansion of the donor pool and the development of donor management protocols have led to unprecedented organ procurement and transplantation ***(Dahlman et al., 2006).***

Most organ donors have brain stem death (BSD). The demand for organs continues to far outweigh the supply, and more than 17 patients die each day while waiting for a transplant. Further understanding and characterization of the progression of critically ill patients toward BSD is necessary ***(Wood and Coursin, 2007).***

Brain stem death is a clinical syndrome defined by the absence of reflexes with pathways through the brain stem – the "stalk" of the brain which connects the spinal cord to the mid-brain, cerebellum and cerebral hemispheres in a deeply comatose, ventilator-dependant patient ***(Roy, 2008).***

Optimization of physiological parameters is an integral part of the management of all ICU patients, but is especially important in potential organ donors. Of further importance is the optimal timing of organ procurement. There is a perception that once BSD occurs, extracranial organ dysfunction rapidly follows. In the past,

retrieval of organs for transplantation occurred as soon as possible after declaration of BSD. Recent evidence suggests, however, that a compromise between optimization of organs and avoidance of deterioration is needed ***(Salim et al., 2005).***

Aim of the Study

The aim of this work is to study the management of organs of patients with brain stem death to optimize their physiological condition till transplantation.

Chapter (1):
Anatomy and Physiology of brainstem

The adult human brain stem emerges from two of the three primary vesicles formed of the neural tube. The mesencephalon is the second of the three primary vesicles, and does not further differentiate into a secondary vesicle. This will become the midbrain. The third primary vesicle, the rhombencephalon, will further differentiate into two secondary vesicles, the metencephalon and the myelencephalon. The metencephalon will become the cerebellum and the pons. The myelencephalon will become the medulla ***(Osborn, 1994)***.

The brainstem is the posterior part of the brain, adjoining and structurally continuous with the spinal cord. The brain stem provides the main motor and sensory innervation to the face and neck via the cranial nerves. Though small, this is an extremely important part of the brain as the nerve connections of the motor and sensory systems from the main part of the brain to the rest of the body pass through the brain stem. This includes the corticospinal tract (motor), the posterior column-medial lemniscus pathway (fine touch, vibration sensation and proprioception) and the spinothalamic tract (pain, temperature, itch and crude touch). The brain stem also plays an important role in the regulation of cardiac and respiratory function. It also regulates the central nervous system, and is pivotal in maintaining consciousness and

regulating the sleep cycle. The brain stem has many basic functions including heart rate, breathing, sleeping and eating. It is usually described as including the medulla oblongata (myelencephalon), pons (part of metencephalon), and midbrain (mesencephalon). Less frequently, parts of the diencephalon are included ***(Castillo et al., 1992)***.

Midbrain:

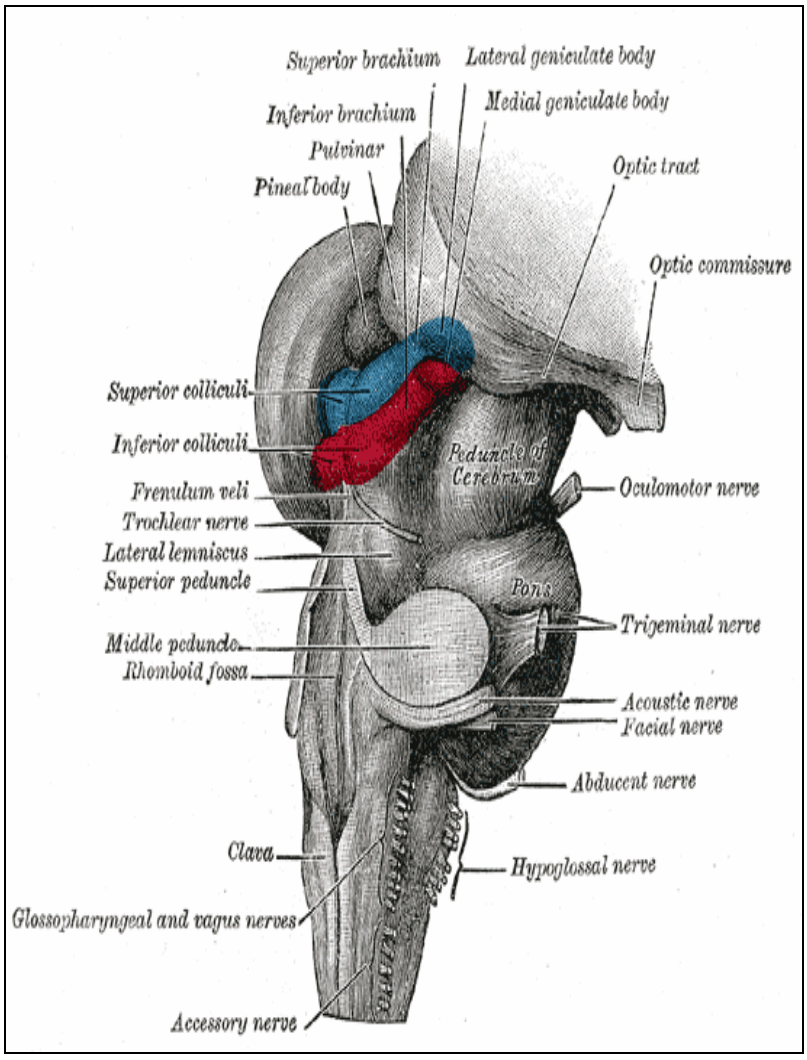

Figure (1): Hind-and mid-brains: Postero-lateral view ***(Osborn, 1994).***

The midbrain is divided into three parts. The first is the tectum, which is "roof" in Latin. The tectum includes the superior and inferior colliculi and is the dorsal covering of the cerebral aqueduct. The inferior colliculus, involved in the sense of hearing sends its inferior brachium to the medial geniculate body of the diencephalon. Superior to the inferior colliculus, the superior colliculus marks the rostral midbrain. It is involved in the special sense of vision and sends its superior brachium to the lateral geniculate body of the diencephalon. The second part is the tegmentum and is ventral to the cerebral aqueduct. Several nuclei, tracts and the reticular formation are contained here. Last, the ventral side is composed of paired cerebral peduncles. These transmit axons of upper motor neurons ***(Osborn, 1994)***.

Internal structures:

- **Periaqueductal gray:** The area around the cerebral aqueduct, which contains various neurons involved in the pain desensitization pathway. Neurons synapse here and, when stimulated, cause activation of neurons in the nucleus raphe magnus, which then project down into the dorsal horn of the spinal cord and prevent pain sensation transmission.
- **Occulomotor nerve nucleus:** This is the nucleus of Cranial Nerve (CN) III.
- **Trochlear nerve nucleus:** This is the nucleus of CN IV.
- **Red Nucleus:** This is a motor nucleus that sends a descending tract to the lower motor neurons.

- **Substantia nigra:** This is a concentration of neurons in the ventral portion of the midbrain that uses dopamine as its neurotransmitter and is involved in both motor function and emotion. Its dysfunction is implicated in Parkinson's Disease.
- **Reticular formation:** This is a large area in the midbrain that is involved in various important functions of the midbrain. In particular, it contains lower motor neurons, is involved in the pain desensitization pathway, is involved in the arousal and consciousness systems, and contains the locus ceruleus, which is involved in intensive alertness modulation and in autonomic reflexes.
- **Central tegmental tract:** Directly anterior to the floor of the 4th ventricle, this is a pathway by which many tracts project up to the cortex and down to the spinal cord.

(Osborn, 1994)

Medulla and pons:

Ventral view:

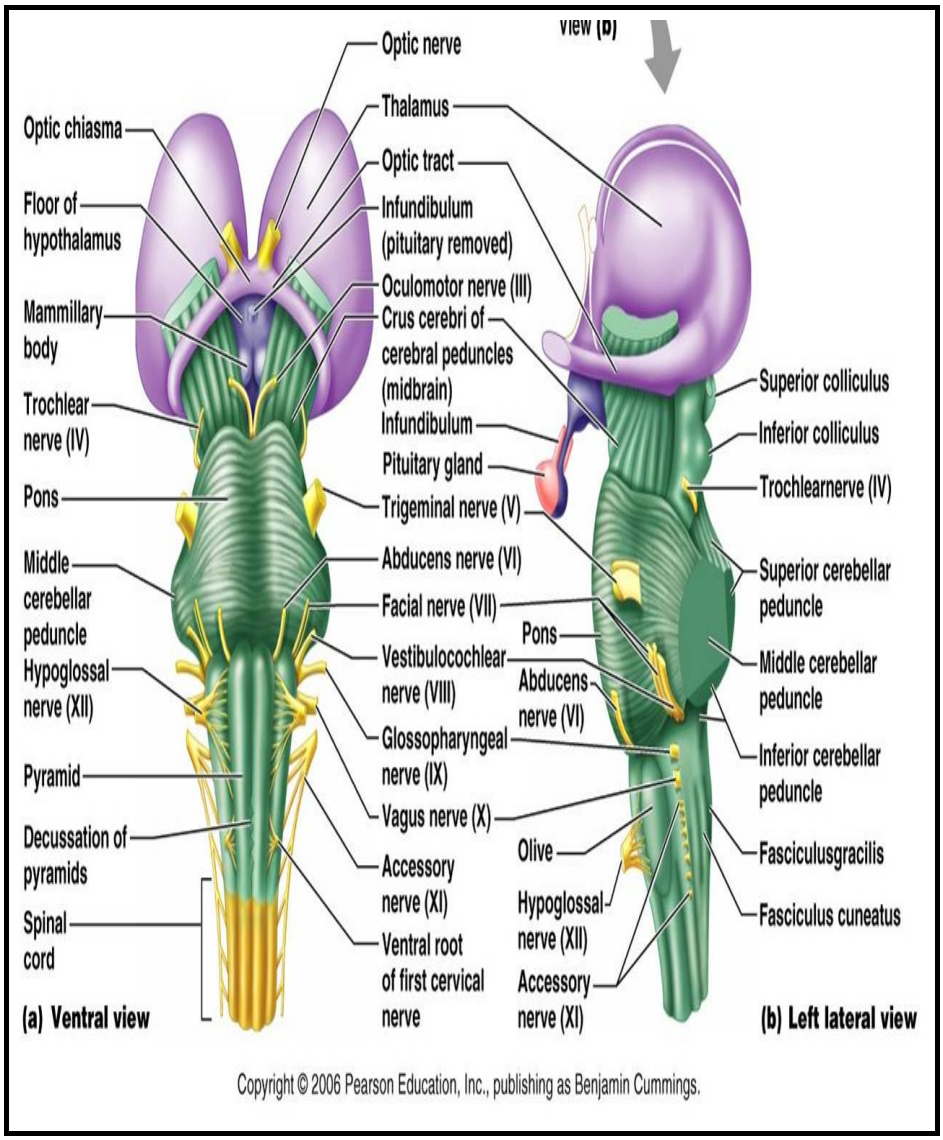

Figure (2): Ventral view of Medulla and pons ***(Barkovich, 2005).***

In the medial part of the medulla is the anterior median fissure. Moving laterally on each side are the pyramids. The pyramids contain the fibers of the corticospinal tract (also called

the pyramidal tract), or the upper motor neuronal axons as they head inferiorly to synapse on lower motor neuronal cell bodies within the ventral horn of the spinal cord.

The anterolateral sulcus is lateral to the pyramids. Emerging from the anterolateral sulci are the CN XII (hypoglossal nerve) rootlets. Lateral to these rootlets and the anterolateral sulci are the olives. The olives are swellings in the medulla containing underlying inferior nucleary nuclei (containing various nuclei and afferent fibers). Lateral (and dorsal) to the olives are the rootlets for cranial nerves IX (glossopharyngeal), CN X (vagus) and CN XI (accessory nerve). The pyramids end at the pontomedullary junction, noted most obviously by the large basal pons. From this junction, CN VI (abducens nerve), CN VII (facial nerve) and CN VIII (vestibulocochlear nerve) emerge. At the level of the midpons, CN V (the trigeminal nerve) emerges. At the rostral pons, CN III (the occulomotor nerve) emerges at the midline. Laterally, CN IV (the trochlear nerve) emerges out of the dorsal rostral pons, wrapping around towards the ventral pons ***(Barkovich, 2005)***.

Dorsal view:

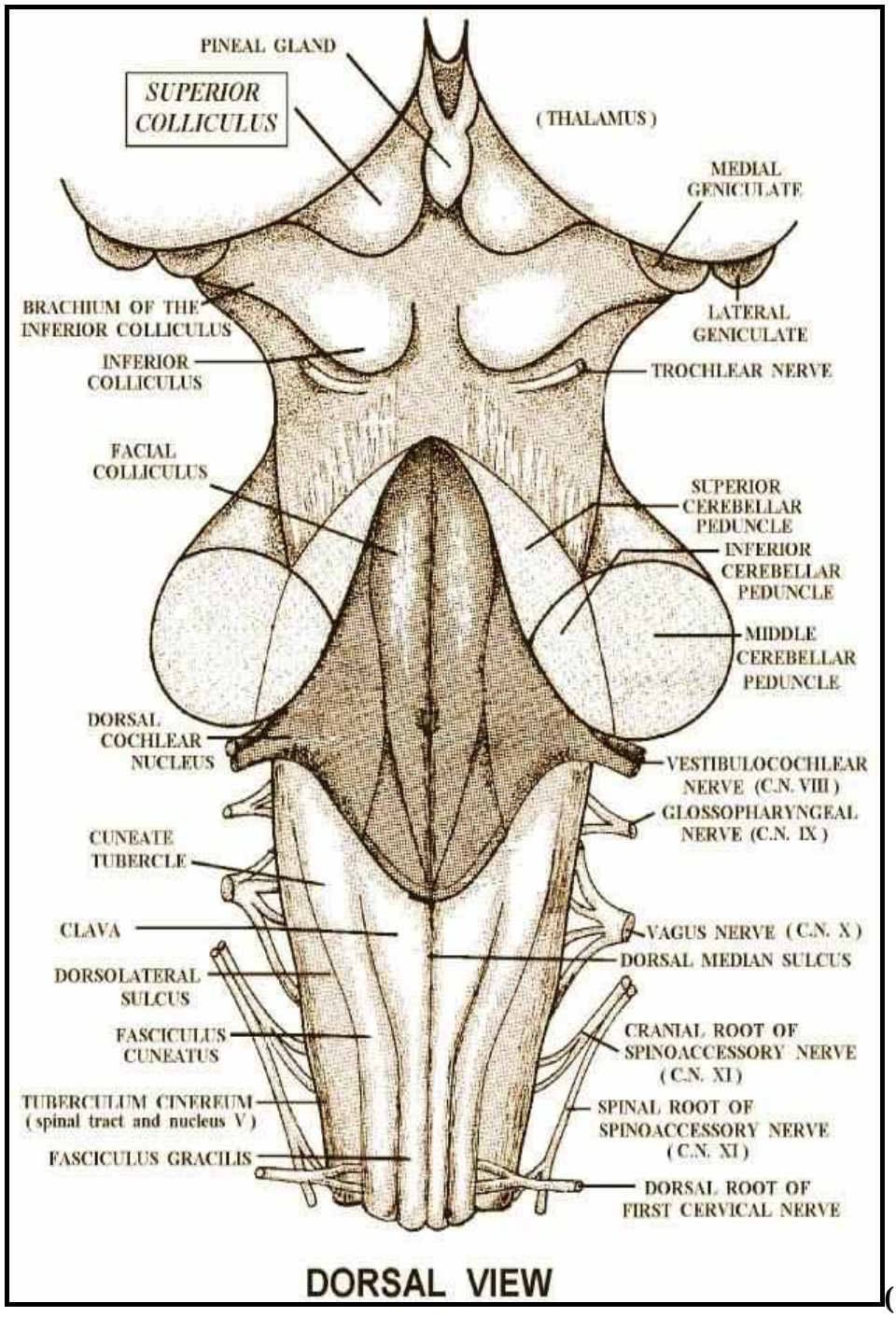

Figure (3): Dorsal view of Medulla and pons ***(Barkovich, 2005).***

The most medial part of the medulla is the posterior median fissure. Moving laterally on each side is the fasciculus gracilis, and lateral to that is the fasciculus cuneatus. Superior to each of these, and directly inferior to the obex, are the gracile and cuneate tubercles, respectively. Underlying these are their respective nuclei. The obex marks the end of the 4th ventricle and the beginning of the central canal. The posterior intermediate sulci separates the fasciculi gracilis from the fasciculi cuneatus. Lateral to the fasciculi cuneatus is the lateral funiculus.

Superior to the obex is the floor of the 4^{th} ventricle. In the floor of the 4th ventricle, various nuclei can be visualized by the small bumps that they make in the overlying tissue. In the midline and directly superior to the obex is the vagal trigone and superior to that it the hypoglossal trigone. Underlying each of these are motor nuclei for the respective cranial nerves. Superior to these trigones are fibers running laterally in both directions. These fibers are known collectively as the striae medullares. Continuing in a rostral direction, the large bumps are called the facial colliculi. Each facial colliculus, contrary to their names, do not contain the facial nerve nuclei. Instead, they have facial nerve axons traversing superficial to underlying abducens (CN VI) nuclei. Lateral to all these bumps previously discussed is an indented line, or sulcus that runs rostrally, and is known as the sulcus limitans. This separates the medial motor neurons from the lateral sensory neurons. Lateral to the sulcus limitans is the area collectively known as the vestibular area, which is involved in special sensation. Moving rostrally, the

inferior, middle, and superior cerebellar peduncles are found connecting the midbrain to the cerebellum. Directly rostral to the superior cerebellar peduncle, there is the superior medullary velum and then the two trochlear nerves. This marks the end of the pons as the inferior colliculus is directly rostral and marks the caudal midbrain ***(Barkovich, 2005)***.

Spinal cord to medulla transitional landmark: From a ventral view, there can be seen a decussation of fibers between the two pyramids. This decussation marks the transition from medulla to spinal cord. Superior to the decussation is the medulla and inferior to it is the spinal cord ***(Barkovich, 2005)***.

Physiology of the brainstem:

There are three main physiological functions of the brainstem:

1. The first is its role in conduction. That is, all information relayed from the body to the cerebrum and cerebellum and vice versa, must traverse the brain stem. The ascending pathways coming from the body to the brain are the sensory pathways, and include the spinothalamic tract for pain and temperature sensation and the dorsal column, fasciculus gracilis, and cuneatus for touch, proprioception, and pressure sensation (both of the body) (the facial sensations have simiar pathways, and will travel in the spinothalamic tract and the medial lemniscus also). Descending tracts are upper motor neurons destined to synapse on lower motor neurons in the ventral horn and intermediate horn of the

spinal cord. In addition, there are upper motor neurons that originate in the brain stem's vestibular, red, tectal, and reticular nuclei, which also descend and synapse in the spinal cord.

2. The cranial nerves 3-12 emerge from the brainstem.

3. The brainstem has integrative functions (it is involved in cardiovascular system control, respiratory control, pain sensitivity control, alertness, awareness, and consciousness). Thus, brain stem damage is a very serious and often life-threatening problem.

(Castillo et al., 1992)

Chapter (2):
Brain Death Insult and Criteria of Brainstem Death

Brainstem death is the irreversible cessation of all functions of the brainstem ***(Dyer, 2006)***.

Historical background:

Traditionally, both the legal and medical communities determined death through the end of certain bodily functions, especially respiration and heartbeat. With the increasing ability of the medical community to resuscitate people with no heart beat, respiration or other signs of life, the need for a better definition of death became obvious. This need gained greater urgency with the widespread use of life support equipment, which can maintain body functions indefinitely, as well as rising capabilities and demand for organ transplantation ***(Murray, 1990)***.

Mollaret and Goulon (1959) introduced the term ***coma dépassé*** (irreversible coma) in describing 23 comatose patients who had lost consciousness, brain-stem reflexes, and respiration and whose electroencephalograms were flat.

Harvard Medical School published a pivotal 1968 report to define irreversible coma. The Harvard criteria gradually gained consensus towards what is now known as brain death. In the wake of the *1976*, *Karen Ann Quinlan* controversy, state

legislatures moved to accept brain death as an acceptable indication of death ***(Lock, 2002)***.

Both the legal and medical communities use "brain death" as a legal definition of death. Using brain-death criteria, the medical community can declare a person legally dead even if life support equipment keeps the body's metabolic processes working. The first country to adopt brain death as a legal definition of death was *Finland* in *1971*. In the *United States*, *Kansas* enacted a similar law earlier. Since then laws on determining death have been implemented in all countries with active organ transplantation programs ***(Randell, 2004)***.

Medical criteria:

A brainstem-dead individual has no clinical evidence of brainstem function upon physical examination. This includes no response to pain and no cranial nerve reflexes. Reflexes include pupillary response (fixed pupils), oculocephalic reflex, corneal reflex, no response to the caloric reflex test and no spontaneous respirations.

It is important to distinguish between brainstem death and states that may mimic brainstem death (e.g., barbiturate intoxication, alcohol intoxication, sedative overdose, hypothermia, hypoglycemia, coma or chronic vegetative states). Some comatose patients can recover, and some patients with severe irreversible neurological dysfunction will nonetheless retain some lower brainstem functions such as spontaneous respiration. Thus, anencephaly, in which there is no higher brainstem present, is