

Pathophysiologic Changes after Brain Death and Organ Preservation: the Intensivist's and Anesthesiologist's Role

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Abstract

Organ transplantation is considered as a definitive surgical therapy for the end-stage organ failure patients, in order to improve the life quality and patients' survival. Organ donation may be considered only after the death or brain death is medically and legally confirmed, unless a living donation is being considered. The physician must know the pathophysiology of brain death, in order to ensure organ function is preserved. The physician must deal with brisk hemodynamic changes, endocrine and metabolic abnormalities, and respiratory complications. General measures are maintaining blood pressure and tissue oxygenation, fluid therapy to correct volume status, hormonal supplements, normoglycemia, respiratory care, and major organ function preservation.

The Brain Death Definitions and Limitations

It is well known that the death of the human beings' brain is considered as the most important hallmark of death. Several terms and definitions regarding brain death are available [1-6], but two definitions are mainly accepted and used. These two definitions are the "whole brain death" and the "brainstem death". The "whole brain death" is a clinical scenario that includes complete, irreversible, and definitive loss of brain, and brainstem functions. The second term so-called "brainstem death" is generally used in the UK, and is based in irreversible cessation of all brainstem functions [6] leading first to unconsciousness and respiratory arrest and, then to cardiac arrest [6,7]. There are several controversies related to the term brain death. Some authors find the "whole brain death" term as a limited one, and at the same time insert the term "higher' brain death" which includes neocortical loss of consciousness, awareness, and memory [8,9]. So using this definition a vegetative state may be diagnosed and the patient be wrongly declared dead [10]. The concept of "whole brain death" is universally accepted.

Brain Death Diagnosis

Brain death diagnosis [11] includes a medical history suggestive for brain death, clinical examination, and imaging tests. It is logical that brain death may be a result of acute central nervous system catastrophe (cerebrovascular accident), severe cranial trauma, or multitrauma. The physician must exclude all anesthetic and muscle relaxant drugs effects, hypothermia, endocrine deficiencies, especially hypothyroidism, severe electrolyte and acid-base abnormalities. Clinical diagnosis is based on a triad of coma, brain stem function cessation, and apnea. The examination of brainstem function includes pupils (no bright light reflexes, mid-position, no ocular movement, and no deviation of the eyes during cold water irrigation in the ear), and lack of pharyngeal and tracheal reflexes (no coughing during suctioning in trachea). Apnea determination is another important indicator which is generally considered positive if arterial partial pressure of carbon dioxide (PaCO₂) can be increased over 60 mmHg after 8 minutes following disconnection from the ventilator. Often confirmatory tests are required. These tests may confirm the diagnosis and help the physician and the patient's relatives make a decision about donation. These tests include conventional angiography, electroencephalography, and transcranial Doppler ultrasonography, technetium-99 m hexamethylpropyleneamineoxime brain scan. If these tests find no cerebral vascularization, no cerebral metabolism, and no isotope uptake, then the diagnosis of brain death can be made. After the

diagnosis is made the physician must deal with possible organ donor management issues, while the patient's relatives are going to make a decision for organ donation.

Pathophysiology of Brain Death

Organ donors are generally healthy patients, who suffered brain death due to massive head trauma, gunshots, or cerebrovascular disease. Brain death leads to catastrophic pathophysiological events that present a big challenge to ICU physician and the anesthesiologist as well. The increased intracranial pressure may lead to an increased arterial blood pressure in order to ensure an adequate cerebral perfusion pressure. If the cerebral perfusion pressure cannot support cerebral cell oxygen demands, then pontine ischemia can generate the so-called Cushing's reflex. The Cushing's response is manifested with bradycardia and hypertension [12]. The ischemic damage includes progressively the entire brain producing an autonomic storm characterized with hypertension, tachycardia, and intense peripheral vasoconstriction. It is reported that the levels of catecholamines (adrenaline, noradrenaline, and dopamine) are greatly increased [13-15]. This clinical scenario is often enriched with myocardial dysfunction secondary to increased oxygen consumption, arrhythmias, and increased myocardial contractility.

After this hypertensive phase, hypotension may follow as a result of sympathetic outflow loss secondary to irreversible destruction of brainstem vasomotor nuclei [16,17]. The blood pressure is determined by cardiac function, peripheral vascular tonus, and volume status. The later hypotension may be the result of catecholamine depletion, decreased cardiac output, myocardial dysfunction, intense peripheral vasodilatation, hypovolemia, electrolyte disorders, and endocrine

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changes. The catecholamine depletion and loss of sympathetic outflow induce a decreased cardiac output, and an impaired preload and decreased after load. Myocardial dysfunction may also be multifactorial including the result of the autonomic storm, calcium uptake, hypothermia, hypoxemia, reduced triiodothyronine (T3) level, reduced cortisol, and catecholamine induced cardiomyopathy. The autonomic storm induces myocardial ischemia (increased wall stress, hypertension, tachycardia, and increased oxygen consumption), depletion of beta receptors, and catecholamine induced myocardial dysfunction [18]. The increased calcium uptake secondary to increased catecholamine levels can induce myocardial cell death. Hypovolemia may be a result of volume depletion, use of diuretics, bleeding, third space sequestration, and increased urinary loss related to diabetes insipidus.

Severe arrhythmias are often encountered. Atrial and ventricular dysrhythmias, and different conduction blocks may be due to electrolyte disturbances, acid-base status, hypothermia, decreased myocardial contractility, catecholamine use, and increased intracranial pressure. The decreased sympathetic outflow induces peripheral vasodilatation and temperature loss. Hypothermia reduces heart rate and myocardial contractility, contributing to hypotension as well. Hypothermia may be related to loss of hypothalamic temperature regulation, large volumes of fluids administration, and opened cavities during surgery, and finally endocrine abnormalities. Hypothermia can also induce coagulopathy, hemolysis, and leftward shift of the oxyhemoglobin dissociation curve.

Several endocrine disorders can be evidenced after brain death has occurred. The most important changes are hypothalamic-pituitary abnormalities and decreased thyroid function. These endocrine changes induce several hemodynamic and metabolic problems. Posterior hypothalamic-pituitary deficiency is manifested as diabetes insipidus, because of reduced Antidiuretic Hormone (ADH) production. There has recently been reported an incidence of diabetes insipidus in up to 85% of brain dead donors [19]. The reduced antidiuretic hormone level causes polyuria, hypovolemia, hypotension, and hypovolemic hypernatremia [20]. Brain death is often associated with reduced Adrenocorticotrope Hormone (ACTH) level, which is the primary mechanism for a decreased cortisol level. Low cortisol level is another probable cause of hypotension after the sympathetic outflow is lost. After brain death has occurred, the levels of triiodothyronine (T3) may be decreased. The reduced T3 levels [21-24] are often associated with hypotension, decreased cardiac output, anaerobic metabolism, and elevated blood lactate. The United Network for Organ Sharing (UNOS) reported that administration of "triple therapy" (including T3 or T4 combined with steroids and vasopressin) showed a significant improvement in 1-month survival rate of transplanted organs compared to those donors not receiving triple therapy [21,22].

Pulmonary complications are often multifactorial. The patients are generally intubated and mechanically ventilated. A nasogastric or nasojejunal tube is often inserted and enteral nutrition is taking place. There is an increased risk for aspiration and ventilator associated pneumonia. Beside that new protocols of mechanical ventilation are focused on minimizing the complications of acute lung injury as a result of barotraumas. After brain death, the hypertensive phase can induce pulmonary edema as the inflammatory cocktail that is generated can increase the pulmonary capillary permeability. The consequences of brain death on gas exchange and lung function may be profound. Brain death is associated with systemic inflammation. The autonomic storm causes an acute increase of left atrial pressure, increased pulmonary capillary pressure and pulmonary edema [24,25]

The intensivist must deal with donor renal protection in order to

optimize the graft function. It is well-known that if donor Mean Blood Pressure (MAP) remains under 50mmHg acute kidney injury may occur [26]. Adequate treatment of hypotension and volume correction is a crucial component of ICU treatment. Hypotension is associated with delayed graft function, acute tubular necrosis, and graft rejection. The hypotension phase after brain death can deteriorate the hepatic function and that of all major organs. Hypotension, hypovolemia, bleeding, massive transfusions, brain death induced inflammation, and ischemia/reperfusion injury are important mechanisms that can cause hepatic dysfunction. The accumulation of leukocytes in the hepatic microcirculation may cause apoptosis of Kupffer cells and induce depletion of glycogen stores. Administration of glucose and insulin may improve glycogen storage and preoperative glucose blood level control [27,28] post-brain death as well as maintain glucose blood level control.

Organ Donor Management

The medical history often reveals no previous medical problems, and examination must evidence any possible damage or trauma of organs targeted for donation. There are several issues the anesthesiologist or intensivist must deal with.

Hemodynamic status is a significant issue that the anesthesiologist must deal with it. Several aspects need to be discussed. The first is the volume restoration. The main problems regarding the fluids are the type, and the desired hemodynamic goals. It is generally accepted that the donor may be hypovolemic. This hypovolemic state may be assessed using central venous or pulmonary artery occlusion pressures, pulse pressure variation, urine output, hematocrit, and serum sodium level. A central line, possibly a pulmonary artery catheter, and echocardiography, are often used to judge the volume status. The fluids are divided in colloids and crystalloids. Crystalloids are not expensive, but can extravasate, leading to peripheral and interstitial edema.

The colloids are expensive, can deteriorate the coagulation system, and cause allergy and the main advantage is less extravasation and better vascular bed filling. For lung and pancreas procurement colloids are preferred over crystalloids because of less incidence and severity of edema. The combination of crystalloids and colloids seems the most logical strategy. Hemodynamic goals are to maintain the Mean Arterial Pressure (MAP) 60-80 mmHg, systolic blood pressure over 100 mmHg, heart rate less than 100 bpm, the filling pressure 8-10mmHg, measured by either central venous catheter, systemic vascular resistance 800-1200 dyne/cm/sec⁻⁵, and urinary output 100 ml.hr⁻¹ (over 1ml.kg⁻¹.h⁻¹). If lung retrieval is planned, the surgeons may require lower filling pressures to prevent intra-alveolar or interstitial lung fluid accumulation [29]. If hematocrit falls below 25%, then blood transfusion may be indicated. The Crystal City Consensus Conference for management of cardiac donors reported that achieving euvoolemia, and optimizing cardiac output with the minimum of beta-adrenergic agonists, were the most important goals [30].

The second step is vasopressor or inotropic drugs administration. The use of vasopressors to maintain donor stability has recently been reported to improve organ viability, leading to an increased recipient survival rate [31]. Dopamine is the most used drug, but dobutamine may be used as well [32]. Noradrenaline increases mean arterial pressure due to peripheral vasoconstriction, whereas adrenaline can increase both myocardial contractility and blood pressure. Often these drugs can be combined in order to preserve renal and visceral blood flow. Vasopressin may also be used to supplement the decreased anti-

diuretic hormone's blood level and to counteract the vasodilatory shock in the intensive care unit [33-36]. Bradyarrhythmias may be treated using isoproterenol, epinephrine, or temporary pacing, because of resistance to atropine.

Hormonal resuscitation with insulin, corticosteroids, triiodothyronine, vasopressin, and methylprednisolone can improve hemodynamic state and reduce the need for vasopressors. The advised treatment regimen is composed by a bolus dose of 4 µg T3 followed by a continuous infusion of 3 µg/h, ADH 1 U loading dose and an infusion of 1.5 U/h or desmopressin (DDAVP) 2 U/12 h, insulin as needed to maintain normoglycaemia, adrenaline 0-0.5 µg/h and intermittent hydrocortisone 5 µg/kg [22,30,37,38].

Ensuring euolemia and renal perfusion are the most important physiological measures in order to prevent renal failure and enhance the availability for kidney procurement [39]. Ronco et al. [40] confirmed that the loss of auto regulation of renal blood flow usually occurs when the mean arterial pressure falls below 75 to 80 mmHg. Although it has been recommended that MAP should not be increased over 65 to 70 mm Hg, maintaining a MAP of 65 mm Hg may be inadequate in order to prevent renal damage in elderly patients, or in patients suffering from diabetes [41]. It is of great importance to avoid both hypovolemia and hypervolemia [42]. Pharmacological preservation of renal function is realized by loop diuretics and mannitol. Both drugs are thought to decrease renal oxygen consumption by their effect on Na/K-ATP. It is known that this pump in order to be fully functional consumes energy, so blocking the pump may reduce the energy consumption [42]. Decreased renal oxygen consumption prevents the renal cortex becoming fragile in the course of ischemia. Mannitol may increase renal blood flow and also be a free radical scavenger [43].

Pulmonary care is another major issue. Rigorous pulmonary toilet is important to prevent atelectasis and pneumonia. The intensivist must set the ventilator parameters to adequately ventilate the patient and prevent acute lung injury. If lung retrieval is planned inspired fraction of oxygen (FiO₂) must be the lowest possible value in order to ensure adequate oxygenation [arterial partial oxygen pressure (PaO₂) over 100 mmHg, and saturation over 95%]. Adequate ventilation and prevention of ventilator-induced lung injury is attained by a combination of low tidal volume, increased respiratory rate, and Positive End-Expiratory Pressure (PEEP). Several ventilation options may be available, both guided by End-Tidal Carbon dioxide concentration in expired air (ETCO₂) and blood gases and by maintaining a low peak airway pressure [44,45]. The ventilator settings are based on low tidal volume (6-8 ml/kg), respiratory rate 12-18 min, and PEEP (8-10 cmH₂O). Adequate ventilation means realizing PaO₂ over 100 mmHg, PaCO₂ 35-45 mmHg, and pH 7.35-7.45.

Conclusion

The management of brain dead patient is a challenge for the ICU physician and the anesthesiologist. The multidisciplinary team must have a good understanding regarding the adverse pathophysiological changes that occur in a brain dead organ donor. Understanding these abnormalities assist the physician in taking the right decisions to enhance the potential organ graft function and increase the organ supply.

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