

**Management of a potential donor with brain death (Part 2)**

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*After the diagnosis of brain death has been made, the donor management is a continuation of the previous intensive care. The paper reviews the brain death donor management standards established on the basis of a physiologically justified active approach.*

*The main elements of the donor management protocol include the invasive monitoring of the central and peripheral hemodynamic parameters, the correction of hemodynamic impairments and hypothermia, the use of hormonal therapy, an adequate mechanical lung ventilation.*

*An active or even aggressive brain death donor management allows the control and correction of pathophysiological processes, thereby increasing the number and improving the functional state of donor organs.*

**Keywords:** brain death donor, brain death donor management, transplantation, intensive care.

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The 1<sup>st</sup> part of our review covered the pathophysiology and clinical manifestations of brain death (BD). In the 2nd part, we present the principal guidelines for the management of donors with brain death (DBDs). These guidelines are based on the recommendations of the American and Canadian consensus conferences [1, 2], the relevant guidelines established in the UK,

Australia and New Zealand [3, 4], Spain [5], Ireland [6], the Guidelines of Moscow Center for Organ Donation, and National Clinical recommendations of the Russian Transplant Society [7, 8], as well as on our own clinical experience.

Compliance to the standards of donor management is essential to optimize the multi-organ functions while the donor is in the Intensive Care Unit (ICU) in order to improve the further transplant outcomes. In the intensive care course it is possible to normalize reversible organ dysfunctions and to assess the dynamic changes in a number of clinical laboratory parameters. This period may take 24 to 72 hours.

Basic standard monitoring (vital signs should be assessed every hour):

- ECG;
- Core temperature;
- Invasive blood pressure (BP) (crucial when considering the administration of catecholamines and vasopressors and the need for frequent blood gas and electrolyte measurements);
- CVP (central venous pressure);
- SpO<sub>2</sub>;
- EtCO<sub>2</sub>;
- Urine catheter;
- Nasogastric tube.

**Laboratory monitoring:**

- Arterial blood gases, electrolytes, glucose should be measured every 4 hours;
- Complete blood count (CBC) every 8 hours;
- Blood urea and creatinine every 6 hours;

- ALT (alanine aminotransferase), AST (aspartate aminotransferase), bilirubin (total and direct), INR (international normalized ratio), APTT (activated partial thromboplastin time) every 6 hours;
- Urinalysis.

### **Hemodynamic monitoring and therapy for hemodynamic impairments**

Hemodynamic management targets:

- Heart rate (HR) 60-120 beats/min;
- $160 \geq$  systolic BP  $\geq$  100 mm Hg;
- MAP (mean arterial pressure)  $\geq$  70 mm Hg;
- Fluid resuscitation in the amount necessary to maintain normovolemia: CVP = 6-10 mm Hg (8-15 cm of H<sub>2</sub>O);
- If arterial BP  $\geq$  160/90 mm Hg, then:
  - Primarily discontinue catecholamines and vasopressors;
  - Esmolol: 100-500 mcg bolus administration, infusion at 100-300 mcg/kg/min (labetalol is possible considering a longer half-elimination period);
  - Sodium nitroprusside: 0.5-5.0 mcg/kg/min (nitroglycerin is possible);
- Blood lactate assessments every 2-4 hours;
- S<sub>v</sub>O<sub>2</sub> (mixed venous oxygen saturation) should be assessed every 2-4 hours, the target value being S<sub>v</sub>O<sub>2</sub>  $\geq$  60%.

#### **Agents for hemodynamic support:**

- Dopamine  $\leq$  10 mcg/kg/min;
- Vasopressin  $\leq$  2.4 U/hr (0.04 U/min);

- Norepinephrine, epinephrine, phenylephrine. (Use with caution at doses  $> 0.2$  mcg/kg/min).

**Indications for pulmonary artery catheterization:**

- LVEF (left ventricular ejection fraction)  $< 40\%$  (according to echocardiography);
- Dopamine infusion  $> 10$  mcg/kg/min (or another catecholamine in equivalent dose);
- The need for vasopressor support (non including vasopressin if a part of hormone therapy);
- Escalation of hemodynamic support.

The main objective in DBD hemodynamic support is to maintain an adequate circulating blood volume (CBV) and the cardiac output (CO) to keep an adequate perfusion pressure and an optimal oxygen delivery to organs and tissues that is essential for the transplanted donor organ viability and functions. The cases of post-transplant acute tubular kidney necrosis are more common when the donor's systolic BP  $\leq 80-90$  mm Hg. The liver is also an organ highly susceptible to ischemia, as evidenced by a high rate of unsuccessful transplantations from donors with a systolic BP not exceeding 89 mm Hg. Therefore, it is crucial to maintain the systolic BP over 100 mm Hg for adequate perfusion of all organs because one of the main tasks in DBD management is to correct hypotension [5].

The CBV increase with achieving the CVP at a normovolemia level is the measure of top priority. Although the CVP and pulmonary capillary wedge pressure (PCWP) values are very close to each other, in a situation that arises in terms of left ventricle dysfunction, the CVP may be low,

despite the high PCWP values [9]. In the recent years, more attention has been paid to  $S_{vO_2}$  monitoring.

$S_{vO_2}$  is a very dynamic measure of the cardiac output, tissue perfusion and oxygenation. This parameter should be measured by the blood sampled in the pulmonary artery (PA). It is not adequate to sample blood from superior vena cava (SVC) or the right atrium (RA) for the  $S_{vO_2}$  measurement because the maximally deoxygenated blood from the coronary sinus will not be fully admixed and  $S_{vO_2}$  will be commonly overestimated. Peripheral venous blood sampling reflects the perfusion and oxygenation of peripheral tissue, and its saturation is not a good indicator of the cardiac output. A low  $S_{vO_2}$  indicates inadequate tissue oxygenation. The lower is  $S_{vO_2}$ , the more severe is this deficit.  $S_{vO_2}$  lower 40% indicates a pre-terminal state. However, a normal  $S_{vO_2}$  does not always equate with an adequate oxygen delivery: a regional hypoperfusion, left-to-right shunts, and carbon monoxide poisoning may give falsely reassuring normal  $S_{vO_2}$  readings. A high  $S_{vO_2}$  is most commonly caused by readings being taken from overwedged PA catheter [1].

### **Fluid and electrolyte balance**

Maintaining the water and electrolyte balance in DBD is a complicated task in the situation of severe losses of free fluid and electrolytes. Hypovolemia, hypernatremia, hypocalcemia, hypomagnesemia, hypokalemia, and also hypophosphatemia contribute to the development of cardiovascular failure with its complications such as arrhythmia, myocardial dysfunction, and a sudden cardiac arrest.

The most important and frequent are the losses associated with polyuria (antidiuretic hormone deficit, hyperglycemia, cold diuresis).

Excessive infusion of glucose-containing solutions may cause hyponatremia and hyperglycemia with subsequent development of intracellular dehydration and polyuria. In addition, CBV replacement with high-concentration sodium solutions in patients with high blood plasma osmolarity due to hyponatremia can rapidly lead to an intractable hypernatremia which is a predictor of a poor liver graft function.

CBV replacement should be performed with isotonic crystalloid solutions (0.9% sodium chloride solution, Ringer's solution) and colloids, 5 mL/kg body weight every 5-10 minutes, until achieving a systolic BP of 100 mm Hg or CVP above 12 cm of H<sub>2</sub>O. Rehydration should be provided carefully with maximum control of hemodynamic parameters to avoid a pulmonary edema and congestive heart failure. No randomized trials to investigate the colloid superiority over crystalloids, and vice versa, have been performed. Blood components, crystalloids, albumin have been widely used for circulating volume replacement, achieving a moderate hemodilution, improving tissue oxygenation and microcirculation, and reducing the risk of microembolism. Nevertheless, many authors have not recommended dextran, and a more recently used hydroxyethyl starch due to the risk of renal tubular damage and post-transplant graft dysfunction.

### **Rhythm disorders**

Episodes of arrhythmia have been reported in 20-30% of donors. Sinus tachycardia is the most common, followed by sinus bradycardia; atrial fibrillation occurs in 10% of cases. Bradycardia is often identified in the course of BD progression, usually within Cushing's syndrome. Since the dual core of brainstem is affected in brain death, atropine has no effect on the vagal tone, so the drugs to be administered should produce a positive

chronotropic effect directly on the heart. Isoprenaline in a dose of 1-3 mcg/min is considered the most appropriate, as well as other agents such as dopamine, dobutamine and epinephrine.

Ventricular and atrial arrhythmias are secondary, as a rule, and may be caused by an electrolyte imbalance, hypothermia, ischemia, myocardial ischemia, administration of inotropes. The top priority is to eliminate the cause of their occurrences, and if that is not enough, amiodarone is considered the drug of choice [10].

Hypothermia often becomes a trigger factor for the development of refractory ventricular arrhythmias. A prolonged QT interval can lead to a polymorphic ventricular tachycardia in "torsades de pointes" form. In this case, the drugs inducing the QT interval prolongation should be discontinued, the electrolyte imbalance be corrected, particularly hypokalemia, a 25% magnesium sulfate should be given intravenously in a dose of 2 g for 10 minutes. A pacemaker use should be considered to prevent a recurrent rhythm disturbance [11].

### **Body temperature monitoring**

Body temperature monitoring should be one of the main components of the DBD management. At BD progression, the donor becomes poikilothermic per se. Hypothermia is associated with reduced enzyme activities resulting in an impaired Na-K pump function that leads to an increased membrane potential, a reduced automaticity, and to bradycardia. Since this bradycardia is not mediated by the recurrent laryngeal nerve, it is refractory to atropine. An impaired repolarization may be manifested by the intraventricular conduction delay, the expansion of the QRS complex, the ST-segment depression or elevation, and T-wave inversion, the prominent J-

wave (hypothermic or Osborn wave), the atrial fibrillation, and even by the ventricular fibrillation at a body temperature below 30 °C [12, 13]. The renal function is also impaired. The first renal response to cold exposure is the increased renal function and urine output due to an increased renal blood flow in terms of peripheral vasoconstriction. With the enhancing hypothermia, the renal blood flow is decreasing, glomerular filtration falls, the sodium concentration gradient maintenance and the reabsorption of sodium become impaired, the urine concentration is reduced that lead to the development of cold diuresis. At body temperature of 27-30°C, an acute renal failure develops. Hypothermia affects the hepatic blood flow, metabolic and excreting liver functions. Coagulopathic disorders occur. Hypothermia increases the hemoglobin affinity for oxygen (a leftward shift of the HbO<sub>2</sub> dissociation curve), which adversely affects the oxygen delivery to tissues.

**Nutritional support:**

- Continuing intravenous glucose infusions;
- Enteral nutrition should be initiated or continued (as tolerated);
- Parenteral nutrition: if it has been initiated, it should be continued;
- Insulin infusions to achieve a target plasma glucose level of 8.4 mmol/L.

**Target values of water-and-electrolyte balance:**

- Urine output: 0.5-3 mL/kg/h;
- Plasma Na<sup>+</sup>: 130-150 mmol/L;
- Normal ranges for blood plasma K<sup>+</sup>, Ca<sup>2+</sup>, Mg<sup>2+</sup>, phosphates.

## **Diabetes insipidus**

- Clinical signs:
  - Urine output  $> 4$  mL/kg/h;
  - Plasma  $\text{Na}^+ > 145$  mmol/L;
  - Plasma osmolarity  $> 300$  mOsm/L;
  - Urine osmolality  $< 200$  mOsm/L.
- Therapy (titrated to reduce the urine output to  $\leq 3$  mL/kg/h):
  - Vasopressin infusion at  $\leq 2$  U/hr and (or)
  - Intermittent DDAVP (desmopressin) 1-4 mg intravenous bolus every 6 hours (should be titrated to urine output).

## **Combined hormonal therapy**

### Ingredients:

- Tetraiodothyronine (T4): 20 mcg intravenous bolus, followed by 10 mcg/h intravenous infusion;
- Vasopressin: 1 U intravenous bolus followed by 2.4 U/h intravenous infusion;
- Methylprednisolone: 15 mg/kg or 1 g intravenously every 24 hours.

### Indications:

- LVEF  $< 40\%$  (according to echocardiographic readings);
- Unstable hemodynamics, including shock unresponsive to the restored normovolemia and requiring a vasopressor support with the infusion of dopamine  $> 10$  mcg/kg/min or another vasopressor agent.

The use of thyroid hormones in DBD is largely based on animal experimental studies and small human series [14, 15]. In 22 studied DBDs, the levels of thyroid stimulating hormone, T3, and T4 were below normal ranges in 85%, 55% and 90% of subjects, respectively. D.Novitsky et al. and

L.C.Garcia-Fages et al. showed in their studies that the use of T3 led to a brief stimulation of the increase in  $\text{Ca}^{++}$ , ATP, glucose, and pyruvate levels while reducing  $\text{CO}_2$  production, and normalizing the lactate level. That implied a return to an aerobic metabolism, the restoration of cell energy reserves, the improvements of donor myocardial function and hemodynamic status [16, 17].

However, other studies did not obtain such impressive results. Some authors have suggested that thyroid hormone impairments in DBD fit within the sick euthyroid syndrome. Approaches to the management of patients with the sick euthyroid syndrome have been controversial. Many studies and animal experiments have indicated that the therapeutic use of T4 (levothyroxine) and T3 (triiodothyronine) has no positive effect and may even increase mortality [14]. Four placebo-controlled studies involving 209 donors demonstrated no significant effect of thyroid hormone on the cardiac index [2, 18]. However, the use of triiodothyronine as a component of the so called hormonal "cocktails" has been recommended for hemodynamically unstable DBDs in the DBD management protocols of some countries [19].

### **Transfusion therapy:**

- To maintain a target hemoglobin level of 90-100 g/L; for unstable DBDs, the lowest acceptable level is 70 g/L;
- For platelets, INR, APTT there are no predefined targets; platelets and fresh frozen plasma are transfused if there is a clinical evidence of bleeding or the patient is planned for a procedure associated with bleeding risk.

### **Microbiology and antibiotic therapy:**

- Daily blood, urine, endotracheal tube aspirate cultures;
- Antibiotic therapy should be initiated with regard to antimicrobial susceptibility test results or as a preventive measure against presumed infection.

### **Organ-specific recommendations for presumed heart donation:**

- 12-lead ECG;
- Measuring of troponin I and T blood levels every 12 hours;
- 2-dimensional echocardiography:
  - should be performed only after normovolemia has been restored;
  - if LVEF <40%, pulmonary artery catheter should be placed and the therapy is titrated to achieve the following targets:
    - ♦ PCWP (pulmonary capillary wedge pressure) 6-10 mm Hg;
    - ♦ CI (cardiac index) > 2.4 L/min • m<sup>2</sup>;
    - ♦ SVR (systemic vascular resistance) 800-1200 dyn/s • cm<sup>5</sup>;
    - ♦ LVSWI (left ventricular stroke work index) > 15 g/kg • min;
  - Repeat echocardiography every 6-12 hours.

### **Coronary angiography**

Indications:

- History of cocaine use;
- Male > 55 years old or female > 60 years old;
- Male > 40 years old or female > 45 years old in the presence of 2 or more risk factors;
  - $\geq 3$  risk factors.

**Risk Factors:**

- Smoking;
- Hypertension;
- Diabetes;
- Hyperlipidemia;
- Body mass index (BMI) > 32;
- Family history of the disease;
- Coronary artery disease;
- Ischemia signs on ECG;
- Anterolateral regional wall motion abnormalities on echocardiogram;
- LVEF  $\leq$  40% (at 2-dimensional echocardiography).

**Precautions against coronary angiography complications:**

- Normovolemia;
- Prophylactically N-acetylcysteine should be administered intravenously at a dose of 150 mg/kg in 500.0 mL normal saline for 30 minutes immediately before coronary angiography followed by a dose of 50 mg/kg in 500.0 mL normal saline over 4 hours;
- The use of "non-ionic" isoosmolar radiocontrast agents in minimal amounts; ventriculography should be avoided.

**Organ-specific recommendations for presumed lung donation:**

- Chest X-ray every 24 hours (chest CT scan, if needed);
- Bronchoscopy and Gram staining of bronchoalveolar wash;
- Routine endotracheal tube suctioning;
- Positional rotation of the patient every 2 hours;

- Mechanical ventilation targets:
  - TV (tidal volume): 8-10 mL/kg;
  - PEEP (positive end-expiratory pressure): 5 cm H<sub>2</sub>O;
  - PIP (inspiratory pressure) ≤ 30 cm H<sub>2</sub>O;
  - Arterial blood: pH = 7.35-7.45, PaCO<sub>2</sub> = 23-45 mm Hg, PaO<sub>2</sub> ≥ 80 mm Hg, SpO<sub>2</sub> ≥ 95%;
- Recruitment maneuvers in hypoxemia:
  - ♦ Periodic increases in PEEP up to 15 cm H<sub>2</sub>O;
  - ♦ Short sustained inflations of the lungs (PIP up to 30 cm H<sub>2</sub>O for 30-60 seconds).

Maintenance of adequate tissue oxygenation in DBD demands a careful choice of the mechanical ventilation method and modes considering the fact that 15% of all donors develop an acute respiratory distress-syndrome (ARDS) or acute lung injury [20]. In the initial stages of BD progression, the donors under 30 years old may experience a neurogenic pulmonary edema due to an abrupt increase in circulating catecholamines during a "catecholamine storm".

No randomized studies have been conducted that would define an advantageous mechanical ventilation method for donors to improve the further lung transplant survival. However, recently published reviews have recommended the use of a pressure-controlled ventilation mode rather than the volume-controlled one [21].

Ideally, PaO<sub>2</sub> should be maintained above 100 mm Hg at a minimum concentration of inspired oxygen (FiO<sub>2</sub>) and the minimum end-expiratory pressure in order to protect against atelectases. The CO<sub>2</sub> production in DBD is low due to an absent cerebral blood flow, a decreased muscle tone and sympathetic tone that allow the normocapnia to be maintained by using

lower volumes of mechanical ventilation than those used in a conventional mechanical ventilation [22].

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