Transplantologiya – 2014. - № 3. – P. 23–31

Management of a potential donor with brain death (PART 1)

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The lack of donor organs is the main factor limiting organ transplantation. Currently, the majority of transplants are taken from brain-dead donors. In most cases, the brain death is associated with a severe physiologic instability that may deteriorate the donor organ function prior to the excision or lead to the loss of the donor. An active or even aggressive management of a donor allows the control and correction of pathophysiological processes in donor organs, thus increasing the number and improving the functional condition of donor organs.

An aggressive management strategy for a potential donor with brain death requires changing both the approach to intensive care, and the philosophic aspect in the evaluation of this work. Despite the development and implementation of various protocols of brain-dead donor management, an optimal combination of objectives, monitoring, specific therapy has not been worked out yet.

Keywords: brain-dead donor, brain-dead donor management, transplantation, intensive care.

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Transplantation is entirely dependent on the availability of viable donor organs that is reflected in a well-known thesis "no organ, no

transplantation". There is a marked disproportion between the number of available donor organs and the number of potential recipients [1-4].

Living donors, particularly those of liver transplants, have made a significant contribution to the increase of available donor organs. Increasingly apparent is becoming the augmentation of donor pool from the number of those who have died as a result of a circulatory arrest i.e. DCD-donors (Donation after Circulatory Death), but their portion in the total number of donors is changeable and varies significantly between the countries [1-3, 5].

In most cases, the organs used for transplants are taken from the donors deceased as a result of a brain death, i.e. DBD-donors (Donation after Brain Death). It is possible to obtain up to 8 donor organs from a DBD-donor (average 3.9-4.2 donor organs from a single donor), which is significantly higher than that from a DCD-donor (average 2.5-2.9 donor organs from a single donor) [3]. In addition, DBD-donors are the only source for a heart transplant. However, the most significant advantage of DBD over DCD lies in the possibility to maintain and correct the functional condition of donor organs. From the moment of signing the brain-death determination statement, a unique process for the modern medicine begins that is termed "a donor conditioning" in Russian literature, and "a donor management" in English literature. The ideology of this process is based on the fact that the patient has been pronounced dead on the basis of diagnosing the brain death (BD) as a complete and irreversible loss of all brain functions, but the cardiac function is maintained and the mechanical ventilation (MV) is continued. BD is equivalent to a human death. In this regard, directed therapeutic measures aimed at saving the human life and restoring health are discontinued. At the same time the patient with a

diagnosed BD is considered a potential organ donor if no absolute contraindications exist [6].

Unfortunately, making a BD diagnosis is not a widely-spread practice in Russia. However, BD as the cause leading to death, has been observed in 12.3% of patients who die in the ICU having traumatic brain injury (TBI), acute stroke, brain tumors, brain hypoxia of various origin (long-term cardiovascular resuscitation, drowning, strangulation asphyxia, etc.) [7]. So there is no doubt, every critical care physician has faced with such conditions many times. However, the resource of potential deceased organ donors has been inefficiently used in Russia, and is far from implementation. This is determined primarily by an outdated form of post-mortem organ donation system. Local Executive Authority Regulations on organ donation in the field of healthcare are advisory by nature and are not backed by Federal Laws and Health Ministry Directives.

At best, an actually dead patient will be transferred to a symptomatic therapy, and at worst, will continue using the entire arsenal of an intensive care unit.

A potential DBD-donor management aimed at the organ excision is independent from the organ transplantation activities and performed by the ICU staff. The complex of measures to identify and maintain functions in a deceased person is a more complicated and labor-consuming task than providing a standard intensive care in critically ill patients.

Within the course of a BD development, and subsequently, when the BD diagnosis has been made, the human organs and tissues may have dysfunctions of varying degrees that require a timely correction. If the severe BD-caused homeostasis impairments have not been timely corrected, the organ dysfunction becomes irreversible which ultimately leads to the loss of

donor organs for transplantation. Up to 25% of organs from potential DBD-donors may be lost due to an irreversible circulatory arrest [8] in conditions of inappropriate and inadequate correction of BD-caused disorders.

Over the past 20 years, the causes leading to BD have significantly changed. More rigorous measures in transport legislation, improvements in motor vehicle design, advances in the treatment of traumatic brain injury have led cerebrovascular conditions to the first place among BD causes, that, in turn, is reflected in an older age, more common comorbidities, and obesity among the patients with a diagnosed BD.

This resulted in extending the indications for excision of donor organs from so-called marginal donors or donors with expanded criteria. Transplantation from so-called high-risk donors is associated with an increased mortality among recipients, primary dysfunctions, a graft loss [9-11], but the high mortality on the Waiting lists for the organ transplantation of the heart, lung, or liver does not permit to refrain from using the donors. The key to a successful outcome in transplantation from expanded-criteria donors lies in an individual-based assessment of the donor and appropriate selection of the recipient [9, 10, 12, 13].

Pathophysiology of brain death.

Clinical manifestations

Brain death is rather a process than an event. It is not just a functional loss of the brain as an organ; it is rather a process that causes a negative impact on other organs and body systems. During BD, a number of various physiologic changes occur in a human body. Without treatment, the acute abnormalities lead to a rapid deterioration of the heart function and to a cardiac arrest, even despite an undertaken mechanical ventilation. Besides,

there exists a systemic inflammatory response, abnormalities in fluids, electrolytes, and endocrine disorders that adversely affect donor organ functions.

An appropriate donor management in the period from the moment of BD diagnosis to the organ excision and conservation is a major factor determining the outcome of DBD-donation. In rare cases, patients with BD are maintained in this condition for a long period. This may be related to the prolongation of pregnancy [14] or relatives' insisting on the treatment continuation [15].

Severe mechanical brain injuries, severe hemorrhage, cerebral anoxia trigger similar mechanisms of brain damage. Pathophysiological mechanisms leading to BD may be represented in the form of a diagram (see Figure) [16].

An intracranial pressure (ICP) elevation and cerebral compression cause the venous congestion and the medulla oblongata ischemia leading to the stimulation of brain-inherent vasomotor centers and to an increased blood pressure (BP), reduced heart rate (HR), and breathing impairments. The classical description of the physiological nervous system response to these events was given by H.U.Cushing [17, 18]; subsequently it was termed Cushing's reflex (triad). This response can be considered as a compensatory factor to ensure sufficient blood supply to medulla oblongata. However, the compensatory potential is limited. As long as the elevation in ICP does not exceed the compensatory increase in BP, there are no severe brain stem impairments affecting the vital functions. At this stage, the situation is still reversible. Otherwise, the symptoms of decompensated brainstem mechanisms emerge and the responses from other body systems occur. Important to note that during the cerebral blood flow discontinuation and the

onset of brain tissue necrosis, the rate of irreversible destruction of brain tissue differs in different brain parts [16, 19]. On the ischemia spreading over medulla oblongata, an increased activation of the sympathetic nervous system (SNS) occurs with the release of catecholamines, a pronounced vascular spasm, hypertension, tachycardia, an increased cardiac output, an increase in peripheral vascular resistance [20]. This response is termed a catecholamine storm (autonomic storming, sympathetic storm, sympathoadrenal crisis) [21-23]. It is the stage when the BD occurs. Having reached the upper cervical spinal cord segments, ischemia causes the sympathetic denervation with the loss of vasomotor tone and the collapse development i.e. the spinal shock. Hypotension causes the hypoperfusion of all organs, including the heart, which may quickly result in the loss of the donor. [24]

Clinical manifestations of BD are diverse and not necessarily seen in all donors. The symptoms are individual and may depend on the age, the premorbid disorder, the initial injury, the fulminant course of events, the patient's treatment in each case (Table 1).

Hemodynamic impairments

BD is characterized by two hemodynamic phases. The first one, a hyperdynamic phase, mentioned above is termed "a catecholamine storm". The catecholamine storm develops in 50% of patients with BD [25]. It is characterized by a sudden acute onset, and a severe arterial hypertension and tachycardia with a variety of cardiac arrhythmias developing within few minutes. The catecholamine storm may last from several minutes to several hours. This is the final attempt of a patient's body to maintain an adequate level of the cerebral perfusion. The systolic blood pressure can go up to 250-

300 mm Hg, and the heart rate can exceed 150 beats per minute. The intensity of the reaction and the degree of internal organ involvement depend on the rate at which the BD is progressing. In experimental animal models, the degree of blood adrenaline increase was closely related to the rate of intracranial pressure elevation. Among DBD-donors, the myocardial damage occurs in 20-35% of cases [26], and echocardiographic signs of myocardial dysfunction are seen in 40% [27].

The second hemodynamic phase, a hypodynamic phase, occurs actually after the herniation of medulla oblongata and is characterized by a severe hemodynamic collapse due to the endogenous catecholamine reduction, by an acute fall of the sympathetic tone, vasodilatation, and the decrease in a total peripheral resistance (a spinal shock, a neurogenic shock). Inotropic and chronotropic functions lead to the arterial hypotension and bradycardia accompanied by an organ hypotension and hypoperfusion requiring the administration of cardiotonics and vasopressors. The condition worsens with a hypovolemia, both an absolute one (caused by the restricted fluid therapy during the cerebral edema treatment; the consequence of trauma and blood loss, polyuria resulted from an inadequate secretion of antidiuretic hormone and an active use of diuretics; osmotic diuresis in hyperglycemia and hypernatremia), and an effective hypovolemia (the increase in the bloodstream).

Lungs

Lung is a very vulnerable organ in donors. Lung injury, aspiration, pneumonia, iatrogenic injuries (MV-associated ones, hyperhydration, pneumo- and hydrothorax), systemic inflammatory response are observed in a significant proportion of donors [28]. A severe destructive effect on the

lungs is posed by the catecholamine storm. Fifteen per cent of patients without previous left ventricular dysfunctions develop a neurogenic pulmonary edema. An avalanche release of sympathetic neurotransmitters leads to a redistribution of blood into the pulmonary circulation with a consequent increase in pulmonary capillary wedge pressure and the increased capillary permeability caused by endogenous noradrenaline. In addition, a high sympathetic stimulation reduces the left ventricular compliance (Takotsubo cardiomyopathy) [8, 28, 29].

Endocrine system, metabolic changes

Changes in the endocrine system in BD are variable in time and severity. In baboons, an abrupt increase in ICP causes a fast cessation of anterior and posterior pituitary function [30]. Individuals with the brain death often experience the loss the posterior pituitary function leading to diabetes insipidus with fluid losses and electrolyte imbalances. Owing to circulation peculiarities (a retained residual blood flow in the extradural part of internal carotid artery and its outgoing branches), the anterior pituitary function may be partially preserved [31], but, nevertheless, there may be a deficiency in thyroid hormones (adrenocorticotropic, somatotropic hormones). Altered thyroid status fits to the pattern of a so-called "euthyroid sick syndrome" [32-36] which is a characteristic of many critical states, including those non-related to a TBI-caused insult. This impedes the conversion of peripheral inactive thyroxine into active triiodothyronine (T3), that is accompanied by a compromised metabolism in the myocardium with a shift to anaerobic metabolism and a reduction of myocardial contractility.

Hyperglycemia is a common sign in BD. The insulin concentration is reduced, but may still remain within the normal range. Hyperglycemia is

highly related to a developing tissue insulin resistance that results in energy deficit. The infusion of glucose, catecholamine solutions, if inadequately controlled in the intensive care unit, may aggravate hyperglycemia contributing to the development of osmotic diuresis that exacerbates hypovolemia [21, 22, 37 [21, 22, 37].

Hypothermia

Although hyperthermia may develop during the manifestations of the catecholamine storm, a subsequent destruction of the hypothalamus leads to the loss of thermoregulation, and a hypothermia development if no measures are taken to maintain the body temperature. The absence of shivering in a patient, a decreased metabolism, a peripheral vasodilatation, a high volume fluid therapy with cold solutions, and polyuria contribute to the hypothermia development. The donor becomes poikilothermic, dependent on the ambient temperature and infused solutions. Hypothermia (<35° C) bears the risk of a myocardial depression, cardiac arrhythmias, anticoagulation, polyuria [22].

Coagulopathy

Coagulopathy is observed in 34% of patients with an isolated head injury [40] and may be caused by the following: a tissue thromboplastin release from a necrotic brain tissue [39], a widespread damage of the endothelium, hypothermia, hemodilution, a systemic inflammatory response. Besides the problems in BD-donor management, the anticoagulation may impair the function of the transplanted organ in the recipient [40] because of the fibrin deposition.

Systemic inflammatory response

Active systemic inflammatory response (SIR) is a characteristic of a severe injury and a critical illness and can be induced by a variety of factors at all stages of the disease [39]. Its severity in BD is determined by the mediators released from the damaged brain tissue, by the reperfusion injury developing in ischemic tissues, by metabolic changes during catecholamine storm, and a non-correctable cardiovascular insufficiency [41, 42]. Some authors call this process "a cytokine storm" and consider it one of key factors of the donor organ damage, the increased immunogenicity of the graft and its dysfunction after transplantation [43, 44].

An active management of patients with suspected BD is important for achieving a physiological stability required for making the BD diagnosis. Before BD diagnosis, the treatment should be focused rather on achieving the maximum chance of survival, than maintaining functions of individual organs. After BD diagnosis, the donor management should constitute a continuation of previous intensive care. It should be aimed at preserving organ and system functions, and keeping a greater number of organs eligible for transplantation [45]. While DBD-donor management aims at a multiorgan retrieval, even a single organ excision is of great value.

Requirements to the donor management are as strict as those for the previously administered treatment as there are no feedback between the body systems in the situation of BD. In this situation, a wider use of invasive techniques is possible for monitoring the donor status.

Each potential donor must be carefully examined with the maximum possible collection of medical history. Although the refinement of medical history through interviewing the relatives may be time-consuming, otherwise actions could entail disastrous consequences. Of note, A. Srinivasan et al.

reported the death of 4 recipients as a result of a rabies virus infection after the organ transplantation from a single donor [46]. Therefore, the earliest possible involvement of professionals experienced in an organ donation is required.

The DBD-donor status may be characterized as tending to an extreme instability. Hypotension, hypothermia, diabetes insipidus are often refractory to adequate correction, and may cause a decreased organ perfusion, hypernatremia, and dehydration and, finally, great losses. This has led to making attempts to standardize the DBD-donor management procedure based on goal measurements to maintain the body system physiology close to "normal" values. One of the first uniform standards of goal values was "the rule of 100" [47]: systolic blood pressure ≥ 100 mm Hg; urine output > 100 ml/h; PaO_2>100 mm Hg; Hb > 100 g/L. A later addition was "blood sugar 100% normal".

Further studies on the BD physiology promoted the implementation of innovative monitoring and treatment techniques in the clinical practice of the DBD-donor management. So, the indications to a pulmonary artery catheterization were expanded to improve the outcomes of intra-thoracic organ transplantation. With regard to the physiological aim of donor conditioning, hormone "cocktails" (methylprednisolone, vasopressin, triiodothyronine or L-thyroxine) started to be used as a standard measure in the DBD-donor management which was termed "a hormonal resuscitation" [33, 48, 49].

Standards of the DBD-donor management were first developed and implemented in the UNOS (United Network for Organ Sharing), the United States [50]. Based on current research and expert opinions, the recommended approaches to the donor management, the donor status

assessment, and the goal values of body system physiology measurements have been revised. For example, Canadian Multidisciplinary Forum on Donor Organ Management recommends maintaining the donor physiological parameters within the goal ranges as described in Table 2 [35].

The use of standards based on a physiologically justified proactive approach to the DBD-donor management called in literature "an aggressive organ donor management" (ADM) significantly increased the numbers of actual donors, and obtained donor organs, and improved their quality that resulted in an increase of transplanted donor organs [51, 52].

Table 1. **The incidence of the pathophysiological abnormalities associated with brain death**

Catecholamine storm	50%
Hypothermia	Always in no warming
Hypotension	81-97%
Diabetes insipidus	46-78%
DIC	29-55%
Arrhythmias	25-32%
Pulmonary edema	13-18%

DIC, Disseminated intravascular coagulopathy

Table 2. **Goal values of physiological parameters during an aggressive management of potential donors**

Parameter	Target values
HR	60-10 beats/min
BP	Systolic blood pressure> 100 mm Hg
	Mean arterial pressure ≥ 70 mm Hg
CVP	6-10 mm Hg
Urine output	0.5-3 ml x kg/h
Electrolytes plasma	Na^+ 130-150 mmol/L

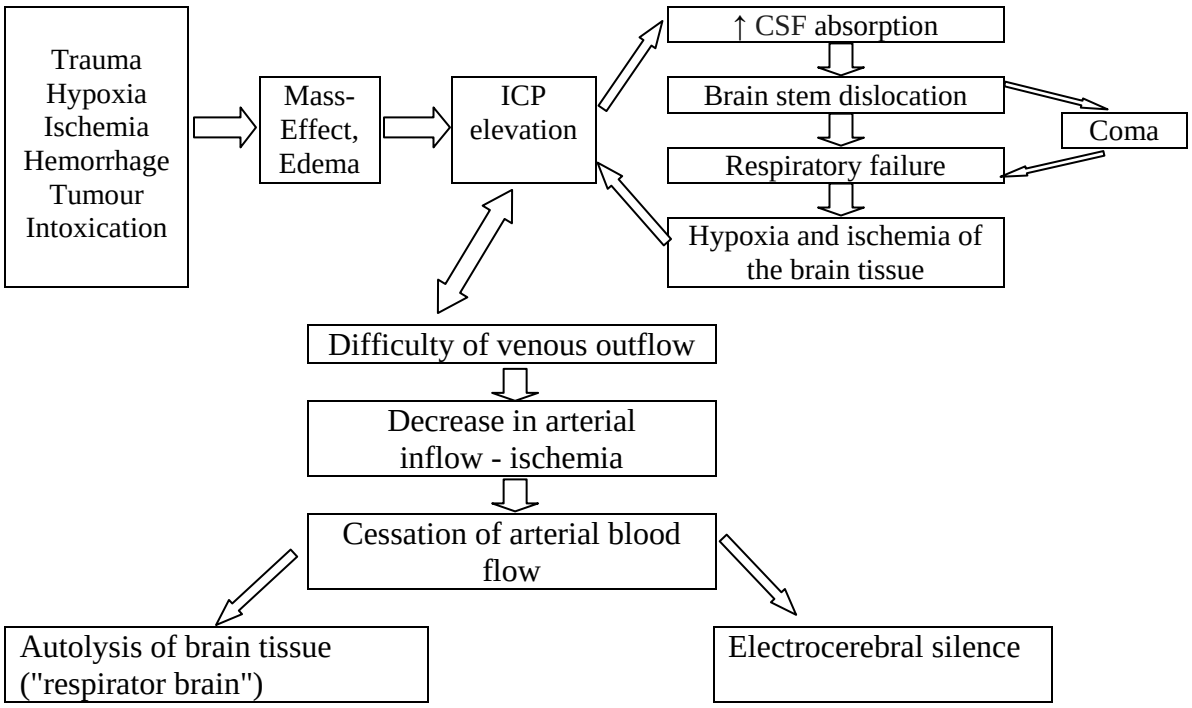
	K^+, Ca^+, Mg^+, P^+ within normal range Blood glucose 8.4 mmol/L
Arterial blood gases	pH 7.35-7.45 $PaCO_2$ 35-45 mmHg $PaO_2 \geq 80$ mm Hg $SpO_2 \geq 95\%$
If pulmonary artery is catheterized	
PCWP	6-10 mm Hg
Cardiac index	2.4 L / min/m^2
TPR	800-1200 dyn x sec/cm^5

CVP, central venous pressure

PCWP, pulmonary capillary wedge pressure

TPR, total peripheral resistance

Figure 1. **Pathophysiological mechanisms leading to brain death**.



ICP, Intracranial pressure

CSF, Cerebrospinal fluid

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