Chapter

Pathophysiological Changes and Systemic Inflammation in Brain Dead Organ Donors: Effect on Graft Quality

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Abstract

Transplantation is the definitive treatment of end-stage organ disease. As the shortage of suitable organs poses its main limitation, the active management of potential organ donors becomes increasingly more important. The majority of solid organs are still obtained from donors after confirmed brain death. Brain death is the complete and irreversible cessation of all brain functions, and triggers a variety of severe pathophysiological changes in cardiovascular, hormonal and metabolic status that can result in organ damage. Moreover, brain death is associated with massive inflammatory response with a cytokine storm and complement activation that increases graft immunogenicity and adversely affects graft survival. Organs from brain-dead donors are more prone to graft dysfunction and rejection when compared to organs obtained from living donors. Brain death is thus believed to be an important risk factor influencing the quality of organs before procurement.

Keywords: inflammation brain death, pathophysiology brain death, systemic inflammation brain death, SIRS, donation after brain death, brain death, organ donation

1. Introduction

Transplantation is the definitive treatment for solid organ end-stage disease. The waiting list for organ transplant is growing rapidly and the available offer of suitable organs is not sufficient enough to satisfy the needs. Within the Eurotransplant region and worldwide, the majority of transplanted organs are obtained from deceased brain-dead donors [1].

It is well known that the results from kidney grafts retrieved from living donors (both related and unrelated to recipients) are far superior to those of deceased organ donors in terms of delayed graft function, acute rejection and graft survival [2–4]. As there is a significant difference between short- and long-term survival of kidneys from living and deceased donors, the focus has recently shifted from recipient to donor and the events occurring at the time of and after brain death.

Brain death is a catastrophic event resulting in severe systemic disturbance including haemodynamic instability, inflammatory, hormonal, metabolic and hematological disorders [5]. A limiting factor for better transplant outcome in a

potential organ donor is definitely activation of the immune system that starts early, during and immediately after brain death. For this reason, brain death has become one of the key factors believed to significantly impact transplant function and survival.

Early identification of potential donors is essential to establish timely and aggressive donor management so as to provide the quantity and quality of organs available for successful donation and transplantation. Unfortunately, no standardized guidelines for the management of brain-dead donors have been implemented to this moment [6]. Nevertheless, the main goal for successful organ donation is to normalize and maintain the physiological conditions, including haemodynamic stability, adequate oxygenation, and optimal fluid and electrolyte balance. Aggressive respiratory and haemodynamic monitoring is thus essential to prevent any unnecessary loss of organs [7].

2. Brain death-related pathophysiological systemic disorders

Brain death is a complete cessation of all brain functions, including the brain stem, when the etiology of brain dysfunction is known and considered irreversible. All reversible causes must be examined and excluded. The essential criteria for brain death, according to the American Academy of Neurology (AAN), are coma or unresponsiveness, absence of brain stem reflexes, and apnea. A patient determined to be brain dead is legally and clinically dead, and can be considered as organ donor in agreement with his own and his next of kin's choice [5]. Loss of central regulation leads to severe pathophysiological alterations in haemodynamics and the respiratory, inflammatory and endocrine systems [7, 8].

2.1 Cardiovascular changes

The increased intracranial pressure following cerebral trauma, infarction or hemorrhage causes increased arterial blood pressure as an attempt to restore adequate cerebral perfusion. In case this fails, ischemia of pons generates a reflex response, known as Cushing reflex, with bradycardia and hypertension. The ischemic damage then progresses through the entire brain and results in sympathetic stimulation and a catecholamine storm characterized by hypertension, tachycardia, and severe peripheral vasoconstriction. A more explosive increase of intracranial brain pressure correlates with a higher increase in catecholamine concentrations. Consequently, a significant reduction in blood flow prevails despite increased systemic perfusion pressure, and leads to visceral and myocardial ischemia [8, 9]. Observations in brain-dead donors show evidence of myocardial ischemia on echocardiographic exam [10, 11].

The initial phase of a catecholamine storm is followed by a loss of sympathetic tonus and profound vasodilation due to ischemia of the brain stem vasomotor nuclei. Many factors contribute to hypotension, including vasodilatation, catecholamine depletion, myocardial dysfunction, relative hypovolemia, and endocrine dysfunction. Hypoperfusion further deteriorates organ integrity and, together with a catecholamine explosion, leads to deleterious consequences for potential grafts if left untreated.

2.2 Pulmonary changes

Two main complications related to brain death-induced lung injury and dysfunction are neurogenic pulmonary edema and inflammatory acute lung injury.

Donors may also have specific pulmonary damage, including aspiration, atelectasis, contusion, chest trauma, or infection [12]. Volume overload after fluid resuscitation, also due to profound hypotension, increases the risk of pulmonary edema [8].

2.3 Endocrine system, stress and metabolic responses

Diabetes insipidus secondary to posterior pituitary infarction and lack of antidiuretic hormone results in electrolyte imbalance, hypovolemia, and circulatory instability. Thyroid hormonal changes and thyroid-stimulating hormone (TSH) levels show the typical picture of euthyroid sick syndrome. Temperature regulation in the hypothalamus is affected, manifesting with initial hyperthermia followed by hypothermia. Hypothermia, additionally worsened by peripheral vasodilatation, further aggravates acidosis and increases the risk for arrhythmias and cold-induced diuresis. Due to reduced insulin concentration and peripheral insulin resistance, hyperglycaemia is common [7, 12].

2.4 Hematological changes

Damaged brain tissue is a rich source of potent platelet-activating and procoagulant molecules, which often leads to disseminated intravascular coagulation. Hypothermia, acidosis and catecholamines all affect platelets function, further contributing to coagulopathy [13, 14].

3. Strategies to maintain pathophysiological changes in organ donors

The current recommendations and guidelines for the management of a potential organ donor in the intensive care unit (ICU) are based on pathophysiological reasoning and experience gained from general ICU management strategies, and not on evidence from randomized controlled trials (**Table 1**) [17]. The protection and optimization of organ functions in order to provide for a maximum number of quality organs that can be offered for donation is the essential goal of intensive care donor management. The purpose of this paper is not to describe the management of the donor in detail, as this was already summarized recently by Meyfroidt et al. [18]. A more simplified and easy-to-remember series of goals was established a decade ago, known as the "rule of 100": systolic arterial pressure > 100 mmHg, urine output >100 ml/hr., arterial partial pressure of oxygen (PaO2) >100 mmHg, hemoglobin concentration > 100 g/L, and blood sugar 100% normal [15].

4. Activation of inflammatory system

Aseptic necrosis of brain tissue leads to the release of numerous inflammatory mediators that trigger and support massive local and systemic inflammatory response driven by both the innate and adaptive immune systems. Catecholamine storm and hypotension with hypoperfusion of organs then contribute to the additional activation of immunologic pathways [19].

One of its harmful consequences is the activation of the cytokine system, polypeptide immunomodulatory molecules that participate in both immune responses and act on cell differentiation, proliferation and activity. Several cytokines have been found in brain tissue and cerebrospinal fluid after brain death. These cytokines are then delivered into circulation through a faulty blood–brain barrier, and continue to stimulate peripheral target cells and organs [20].

	Suggested approach
General care	Manage in ICU. Central and arterial line insertion and monitoring of central venous and arterial pressure. Cardiac output monitoring preferred. Nasogastric tube insertion. Foley's catheter insertion and measurement of urine output. Reduce heat loss and actively warm, if necessary, to maintain core temperature >35°C. Actively treat infections. Frequent airway suctioning. Maintain pneumatic compression device for preventing deep vein thrombosis. Eye protection. Ulcer prophylaxis. Broad spectrum antibiotics.
Respiratory	Use 'lung protective' ventilation (lowest possible plateau pressure, tidal volumes of 6 ml/kg of ideal body weight, and moderate positive end expiratory pressure [PEEP] of 5–10 cmH2O to achieve an oxygen saturation >92%). The respiratory passage must be kept clear of any obstruction with routine measures. Avoid the administration of excessive i.v. fluids.
Cardiovascular	Goals for the management of haemodynamic status in donors: (1) to maintain normovolaemia; (2) control blood pressure (BP); (3) optimize cardiac output and maintain perfusion pressure of all organs; and (4) to minimize the use of vasoactive agents. Review fluid balance and correct hypovolaemia. Monitor cardiac output to titrate fluids and inotropic/vasopressor drugs to intended goals. At present, there are no convincing studies or consensus to demonstrate that one vasopressor is superior to another, and different drugs (noradrenaline, adrenaline, vasopressin, dopamine, and/or dobutamine) are used, depending on local practices and protocols. High doses of catecholamines (e.g., norepinephrine >0.05 μg kg^{-1} min^{-1}) should be avoided, if possible.
Fluids and nutrition	Administer maintenance fluids, preferentially crystalloids with balanced salt content (lactated Ringer's solution and half-normal saline (0.45%) are most frequently used) to avoid hypernatremia. Avoid volume overload. Correct electrolyte abnormalities to normal values. Blood glucose target concentrations 4–8 mmol/ litre. A solution of 0.9% normal saline may cause hyperchloremic acidosis, which increases renal vascular resistance. Colloids, such as hydroxyethyl starches, need to be avoided in organ donors, as they can damage renal epithelial cells and cause early graft dysfunction in the transplanted kidneys. Albumin solutions can be used to reduce the amount of fluid volume administered.
Blood and coagulation	Consider the need for transfusion. The target is to maintain the hematocrit above 30%. Maintain thromboprophylaxis, as there is a high incidence of embolisms. Coagulopathy should be treated promptly with management, including the administration of red blood cells, clotting factors, and platelets.
Systemic effects	Corticosteroids. The main purpose of using corticosteroids is not to treat adrenocortical failure, but rather to attenuate the immune responses and reduce the catecholamine requirement for maintaining BP. Methylprednisolone 15 mg kg^{-1} bolus is recommended immediately after brain death is confirmed. Triiodothyronine. Routine replacement of thyroid hormones is not recommended for all organ donors, but only if impaired cardiac performance is documented despite overall good general management and in case of patients with true hypothyroidism. Insulin. Hyperglycemia is closely associated with reduced host immune responses that result in an increased risk of infection, worsening of renal function in renal transplant recipients, as well as osmotic diuresis [16]. Hyperglycemic organ donor patients should be treated according to the local institutional guidelines used for other critically ill patients. Anti-diuretic hormone. If the patient develops diabetes insipidus, the condition can be treated by the replacement of fluid with adequate crystalloid solutions. However, if hypotension persists despite adequate volume resuscitation in the absence of other causes, treatment with vasopressin or DDAVP should be considered.

DDAVP, 1-deamino-8-D-arginine-vasopressin; PEEP, positive end-expiratory pressure.

Table 1.
Summary of the principles of donor management (adapted from Anwar et al. [7] and McKeown et al. [15]).

The up-regulated expression of cell adhesion molecules (CAMs), including selectines, vascular (VCAM-1) and intracellular CAMs (ICAM-1) on the endothelium of potential grafts plays a critical role in numerous inflammatory processes. One of their tasks is the recruitment of circulating monocytes, macrophages and polymorphonuclear leukocytes as shown in organ biopsies after organ retrieval [12, 16, 21, 22]. Therefore, unsurprisingly, increased levels of CAMs have been associated with increased mortality in transplant recipients [16].

The activation of leukocyte populations in peripheral organs further maintains an inflammatory environment by expressing CAMs and releasing proinflammatory substances, among others, tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) [16]. Especially IFN-γ induces the expression of major histocompatibility complex (MHC) classes I and II on graft cells, which potentiate the immunogenicity of organs via the T-cell recognition process. The activated organs provoke a host immune system after engraftment, resulting in severe acute or chronic rejection [23].

Complement activation has already been demonstrated in ischemia–reperfusion injury and rejection. Fragments of complement activation products have been measured in plasma and organ biopsies. Their values were higher compared to living donors [24–26].

4.1 Cytokines implicated in brain death

Increased blood levels of several cytokines, such as TNF-α, interleukin (IL)-6, IL-8, IL-1β, and IL-2R, have been observed after brain death [27, 28]. Cytokines derive mostly from T-cells and are classified into different groups according to their main function and T helper (Th) cell subtypes to which they are related.

The Th1-cell related cytokines are TNF-α, IL-1, IL-2, IL-12 and IFN-γ [29, 30]. They act early in the inflammatory cascade and stimulate and support the inflammation by mediating between different inflammatory pathways; they activate endothelial cells and cellular adhesion molecules, and contribute to T-cell maturation.

The Th2-cell-related cytokines IL-4, IL-5, IL-10 and IL-13 are not as significant and are considered to be anti-inflammatory when related to brain death and the early transplant period [19, 31, 32].

One of the most heavily implicated cytokines in brain death is IL-6, a member of Th-17 cell related mediators [33, 34]. Increased concentrations of IL-6 have been demonstrated both in plasma and organs of brain-dead donors, including the kidneys, lungs, liver and heart [34–36]. Higher values of IL - 6 are associated with worse transplantation outcomes and poorer survival of recipients [33, 37].

A significant increase in IL-8 values in the bronchoalveolar lavage fluid from brain-dead lung donors has been demonstrated and correlates with early graft dysfunction after lung transplant [38]. In addition, elevated IL-6 gene expression was observed in the preimplantation biopsies of patients who died within 30 days after lung transplant [39]. Furthermore, the levels of IL-1β and TNF-α were significantly higher in donor lungs rejected for transplantation compared to transplanted lungs [40]. The values of IL-6 and TNF-α in the myocardium of dysfunctional discarded donor hearts were higher than in transplanted donor hearts [41].

4.2 Role of complement

The complement cascade is an important part of the innate immune system and transplantation process. Activation of either the classic, alternative or lectin pathway of the complement system leads to the formation of a common terminal

cell lytic complex or C5b-9, also known as membrane attack complex (MAC). MAC induces complement-mediated lysis of cells. Proteolytic complement fragments such as C5a, C3a and, to a lesser extent, C4a, further induce acute inflammation by activating mast cells, neutrophils and endothelial cells.

Studies have shown that all three pathway types are involved in systemic inflammation secondary to brain death [24]. Complement activation products have the ability to produce proinflammatory substances, including cytokines, and act as chemotactic factors for leukocytes.

In deceased brain donors, the increased complement plasma levels of C5b9 were higher than in the plasma of living organ donors. Higher levels of C5b9 in deceased brain-dead and deceased cardiac-dead donors were associated with worse tissue damage, a higher rate of acute and chronic rejection, and inferior function after transplantation [25].

Complement activation also results in the release of anaphylatoxins C3a and C5a, potent activators of T-cells. Brain-dead organ donors had higher values of C5a in plasma compared to living donors [26].

5. Inflammation limiting strategies

5.1 Inflammation limiting strategies in organ donors

The use of methylprednisolone, alone or as part of hormonal replacement, reduces the immunological activation observed after brain death in terms of decreasing cytokine production and preventing alterations induced by proinflammatory mediators [36, 42]. In a prospective randomized study, reduced serum and graft cytokine expression and improved graft function in human liver transplantation was found/reported after methylprednisolone administration [42]. Inflammation in the heart and kidneys is also reduced. The reduction in cytokine activation is almost comparable to the levels seen in living donor transplantation [36]. Methylprednisolone use is associated with increased organ retrieval and improved short- and long-term outcome for most transplanted organs [12].

Numerous other agents and approaches are currently under investigation as part of organ protection and preservation strategies.

Among such strategies, active removal of cytokines by haemoadsorption was shown to be feasible, leading to at least a moderate fall in cytokine concentration in circulation, attenuating the inflammatory response associated with brain death [9].

Although no RCTs in humans currently exist, animal models have also demonstrated a reduced inflammatory response and improved oxygenation when using noradrenaline [43, 44].

Since glucagon-like peptide-1 (GLP1) analogues were shown to possess interesting cytoprotective effects in different liver and pancreatic disease models, these molecules were also tested in experimental transplantation models. Treatment with the GLP1 analogue exendin-4 (Ex-4) relieved brain dead-induced liver [45], renal [46] and pancreatic islet injury [47] through alleviation of inflammation and oxidative stress.

After single administration of antithymocyte globulin (ATG) to brain-dead mice, the inflammatory reaction in the myocardium showed a significant reduction in IL-2 expression and the reduction of IL-6 deposition in media cells in ATG-treated specimens compared to controls [48].

Targeting complement activation after the induction of brain death also reduced renal inflammation and improved renal function before transplantation in animal models [49]. Recently, a study by Jager et al. [50]. has shown that experimental

donor rat pre-treatment with anti-FB preserved renal function reduced renal damage and inflammation prior to transplantation. Seemingly, high-dose C1-INH treatment of brain-dead rat donors resulted in significantly lower renal gene expression and serum levels of IL-6, which reflected with improved renal function and reduced renal injury [51].

Traumatic brain injury and other inflammatory conditions are currently being treated in preclinical and clinical trials by a number of cellular therapies, among which mesenchymal stem cells (MSC) are of greatest interest due to their widespread usage and ease to isolate and culture [52, 53].

Therefore, strategies targeting cytokine and complement activation in human brain-dead donors pose as a new and promising opportunity to improve organ quantity and quality for successful organ donation and transplantation outcome.

5.2 Inflammation limiting strategies to preserve procured organs

After procurement, organs are further exposed to injury due to removal from their physiological conditions. Hypoxic injury has a detrimental effect on organ structure and function, and adds to increased immunogenicity. Prolonged ischemia, cold or warm, is a risk factor for early graft dysfunction and worse long-term outcomes. The duration and type (warm or cold) of ischemia time may also directly influence cytokine production [19]. Significant cytokine gene expression has otherwise already occurred directly after brain death. Namely, the cytokine gene expression before transplantation was shown to be even higher than during the period of acute rejection [35]. A strong association was recently identified between cold ischemia time and the levels of IL-1 and IL-8 in human liver transplants. Warm ischemia time also correlated with IL-6 and IL-10 in the same study [54].

Successful preservation strategies are key to minimize ischemic damage and the effect of reperfusion with associated increased immunogenicity after organ implantation. The current accepted standard for most solid organs is static cold storage (SCS), where the solid organ is stored on ice after removal from the donor, and then removed from the ice box at the time of implantation. However, novel technologies enable perfusion of the donated organ during the transport phase or at the recipient centre, with the option to use a variety of temperatures and different perfusates. Machine perfusion systems (hypothermic, normothermic, oxygen persufflation) represent dynamic preservational methods.

Hypothermic preservation strategies are now widely used to decrease inflammation, depress the metabolic rate of cells, and reduce the effects of ischemia [55, 56]. In the largest meta-analysis performed so far [57], hypothermic machine perfusion (HMP) was superior to SCS in deceased donor kidney transplantation (this was true for both DBD and DCD kidneys). The incidence of delayed graft function in kidneys from deceased brain donors was much lower in the group with hypothermic perfusion. Additionally, reports of economic analysis suggested that HMP can lead to cost savings in both North American and European settings.

Since very low temperatures can also have harmful repercussions on organs in terms of cytokine and reactive oxygen production [58], over the last two decades several research groups have examined the effects of increasing the temperature of machine perfusion to near-normothermic temperatures (20–33°C). Near-normothermic preservation is particularly applicable for organs of marginal donors or donors after cardiac death. In these cases, due to prolonged warm ischemia times, organ viability is negatively impacted by the subsequent cold preservation. Hence, normothermic perfusion may enhance preservation and transplantation outcomes and reduce the risk of non-functional organs [59].

6. Conclusion

Brain-dead organ donors represent the major source of organs for organ transplantation. The path from a brain-dead potential donor to a favorable graft and recipient outcome is long, and can have a cardinal impact on the quality of transplanted organs. Brain death-related systemic changes can damage the organs to the point where donation is not possible. Severe systemic inflammatory response enhances graft immunogenicity and affects graft survival and transplant outcome. Thus, immunomodulatory agents can become pivotal in donor procurement and preservation in future.

Conflict of interest

The authors declare no conflict of interest.

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