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REVIEW

What can be learned from brain-death models?

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Summary

Brain death of the donor is an important risk factor influencing graft outcome. In addition to its nonspecific effects, it potentiates graft immunogenicity and increases host alloresponsiveness. Thus brain death in addition to other unspecific injuries such as organ procurement, preservation and consequences of ischemia/reperfusion injury, contributes towards the change of an inert organ to an immunological altered graft. Prior to engraftment, brain death initiates a cascade of molecular and cellular events including the release of proinflammatory mediators leading to cellular infiltrates. Those events may affect the incidence of both acute and chronic changes, developing and contributing to reduced graft survival. Consequently, strategies to reduce the immunogenicity or the pro-inflammatory status of the graft are becoming more attractive and might even help to improve organ quality and graft function.

Introduction

Transplantation has evolved as the treatment of choice for many patients with end-stage organ disease. During the past decades and particularly during the recent years, the success rate of transplantations have progressively improved because of better understanding of organ failure, improvements in operative and perioperative care, deeper insight into the process of organ rejection and the development of more effective immunosuppressive modalities. It has been hypothesized that allografts, particularly from less optimal donors, may not be biologically inert at the time of placement, but already be programmed to initiate or amplify subsequent host responses [1]. These potentially activated organs may provoke a continuum between the inflammatory changes from initial nonspecific insults and the onset of alloresponsiveness [2,3]. Several donor-associated factors implicated alone or in combination including age, hypertension, diabetes, the systemic effects of brain death and ischemia/reperfusion [4]. This concept has been emphasized by pooled UNOS (United Network of Organ Sharing) data, which shows that the survival rates of kidneys from living unrelated and one haplotype-matched living related donor is identical despite potentially important differences in the recipients' genetic relationship [5,6]. In addition, transplanted organs from all living donors demonstrate consistently superior results to those from cadaver sources over both the short- and long-term [6].

Brain death is a rarely considered risk factor uniquely relevant to the cadaver donor, the primary source of solid organs for transplantation. Such individuals have suffered extensive and irreversible central nervous system damages secondary to trauma, hemorrhage or infarction. Virtually all experimental organ transplantation studies generally utilize young, healthy living animals as donors; in clinical practice, however, a relatively low percentage of organs are acquired from living sources. Amongst other variables, the difference between the two donor populations includes the effect of profound physiological and structural derangements, which may occur during and subsequent to brain death and prior to the actual engraftment procedure.

At the beginning of kidney transplantations in the 1950s, and subsequent attempts at placement of livers and hearts increasingly forced the consideration to use organs from heart-beating cadavers who had sustained a

central catastrophe. The use of such donors substantially reduced the ischemic insult associated with transplantation of organs from nonheart beating donors. Understanding the systemic changes, which occurred following massive irreversible brain injury, increased because of experimental studies with animals. These studies delineated the dynamics of 'autonomic storm', including chaotic fluctuations in blood pressure, hypotension, pulmonary changes, hypothermia, coagulopathies and electrolyte abnormalities [7,8]. The effects on cardiopulmonary dynamics and on hemodynamic stability of the subject usually occurs in two phases, an initial hypertensive phase associated with herniation of the brain stem, and subsequently a hypotensive phase [9,10]. A brief increase in parasympathetic tone with bradycardia is followed by profound, albeit transient sympathetic outflow, secondary to cerebral ischemia. The effects of catecholamines on the vascular resistance and the systemic cardiopulmonary parameters correlate with an increased intracranial pressure, the techniques used to produce brain death, and of the animal species investigated [11–14]. Despite a substantial rise in arterial pressure, tissue becomes ischemic from intense vasoconstriction, elevated vascular resistance, and significantly reduced local blood flow [15]. These effects on the heart lead to a sudden and massive increase in myocardial workload, oxygen consumption and other functional parameters. Oxygen supply to the heart, although increased, is insufficient to cover the enhanced demand and leads to transient global myocardial ischemia [16,17]. During the subsequent normotensive or hypotensive phase, reduced sympathetic outflow decreases peripheral vascular resistance and myocardial contractility. Impaired perfusion pressure and vascular autoregulation causes further decline in tissue perfusion and local oxygen supply. As a result, prior to removal the clinical management of brain dead donors must and maintain peripheral vascular resistance, cardiac output and perfusion pressure to minimize ischemic damage to peripheral organs.

Consequences of brain death on the endocrine system

Although most investigators accept a link between brain death and disruption of the hypothalamic-pituitary axis, there is however conflicting data about the hormonal changes occurring during and after central nervous system injury and its influence on hemodynamic parameters and organ quality [18–20]. There also is some disparity between available information on endocrine function following brain death in experimental animals and in humans [18,21]. Two different categories of hormonal changes in animal models are postulated: those associated with the autonomic storm represent a transient and massive increase in circulating catecholamines, and those associated with hypothalamic-pituitary dysfunction lead to neurogenic diabetes insipidus and a marked decrease in levels of thyroid hormones and cortisol [22]. Progressive depletion of high-energy stores have been reversed successfully in animals by a combination of T3, cortisol and insulin administration [23,24]. Novitzky *et al.* reported similar changes in human cadaver donors and suggested that hormonal changes are the major cause of mitochondrial dysfunction with impaired energy production at the cellular level [25].

However, some investigators, have demonstrated only minimal changes in humans. Data from clinical examination of 32 organ donors showed that brain death does not necessarily lead to endocrine failure: sufficient, albeit minimal, functional hormone levels can be preserved in many patients for prolonged periods [18]. An extensive survey of studies on brain-dead human donors showed that a reduction in the level of fT3 was usually documented, but that changes in other hormone levels (such as TSH, T4, and cortisol) varied [26–29]. Correlations between hormonal levels, metabolic, and hemodynamic parameters are also diverse, as are those between hormonal levels and subsequent allograft function after transplantation. These observations are in accordance with histological observations in which the pituitary gland shows varying degrees of edema, hemorrhage and coagulative necrosis. These microscopic changes correlate with previous reports, which suggest persistence of partial cerebral flow in some areas in brain-dead patients [30].

Morphological changes in donor organs after brain death

Whether and how brain death affects the quality of the organs used for transplantation, both early and late after engraftment, is a critical question. Acute morphological and functional changes in the heart have been described. As similar changes occur secondary to ischemia/reperfusion (I/R) injury, close correlation between brain death and ischemia have been postulated. For instance, hearts from healthy anesthetized baboons, stored for 48 h and then engrafted, functioned immediately [31,32]. However, those taken from brain dead animals, stored in similar fashion, did not perform adequately for several hours. In addition to functional influences, elevated levels of catecholamines may produce major morphologic changes in the heart [33,34]. Particularly involving the subendocardium of the left ventricle, the lesions include petechial hemorrhage and coagulative myocytolysis with a mononuclear cell infiltrate [35]. Contraction band necrosis occurs frequently in individuals who survived for a prolonged period after an intracranial hemorrhage. Recent

experimental investigations demonstrated that acute brain death caused by increased intracranial pressure results in a transient increase in myocardial adenosine and lactate, which indicates that oxygen demand exceeds oxygen delivery during the sympathetic storm [36]. In conclusion, in pig brain death models the sympathetic storm produced transient contractile dysfunction, consistent with ischemic injury during brain death [37,38]. Similar changes have also been noted in patients dying after acute cerebral injury and in animals following administration of exogenous catecholamines [33,34]. In addition to elevated systemic levels of these substances, brain death also increases exocytic release of norepinephrine from sympathetic nerve endings in the heart. Local nonexocytic release may also occur following depletion of high-energy phosphates [39]. As a result, myocardial necrosis may even develop in the well-perfused heart, which may not only influence host allogeneic responses, but the long-term course after transplantation. Recent clinical data seem to confirm a correlation between brain death and rejection episodes after heart transplantation. A retrospective evaluation showed that recipients where the donor sustained traumatic injuries had significantly more rejection episodes postoperatively compared with organs, which originate from donors with subarachnoid hemorrhage [40]. The modality of brain death did not significantly impact short and long-term survival after transplantation, but nevertheless appeared to influence the incidence of rejections. Furthermore, the results demonstrated that increased management time of the donor on intensive care units over 72 h is significantly associated with adverse survival trends in heart-transplant recipients [40].

Although excessive catecholamine release, secondary to suddenly increased intracerebral pressure during explosive brain death, appears to produce the above morphological alterations, such changes are significantly reduced following brain death caused by a gradual increase of intracranial pressure in experimental models [8,13]. In the latter situation, there are no changes in hemodynamic parameters other than a transient decrease in heart rate and less severe morphological changes in the myocardium. These observations support the crucial role of catecholamines on organ quality after extensive central injury. The differing course of hemodynamic instability between explosive and more gradual brain death appears to be caused by the extent and kinetics of involvement of brain stem lesions and as consequence the extent of ischemic injury following brain death.

Ischemia because of prolonged systemic hypotension, regardless of etiology, can be a major cause of kidney damage. Specifically renal function after engraftment may be affected by the cardiovascular instability surrounding the events of brain death; caused at least in part, by the marked vasoconstriction occurring during the autonomic storm. A high incidence of post-transplantation acute tubular necrosis have been observed in kidneys harvested from brain-dead donors with unstable hemodynamic status [41]. The histopathological changes in the kidney described after brain death include the immediate onset of extensive glomerular hyperemia, the development of glomerulitis, endothelial proliferation and periglomerulitis. Within 3 days, degeneration, atrophy and necrosis of tubular cells became marked. At the biochemical level, impairment of renal slice function following brain death in the pig model has been described [42]. The intracellular sodium/potassium ratios as energy-consuming mechanisms and as parameters of kidney viability were significantly reduced after brain death compared with normal anesthetized animals, demonstrating a deleterious effect of the autonomic storm, prolonged storage and/or hormonal depletion on kidney function. Again the time between onset of brain death and organ harvesting seems to correlate with changes observed in the organ and the outcome after transplantation. An experimental study in rats assessed brain death induced hemodynamic instability in addition with the duration of brain death as important factors on the function and the immunogenetic status of potential donor kidneys [43]. It seems that progressive organ dysfunction is most pronounced in hemodynamically unstable brain dead donors with prolonged periods before organ harvesting after brain death induction.

Morphological changes in the liver following brain death are even less well defined. A Japanese study on hepatic tolerance to prolonged hypotension in the brain-dead canine model supports the generally accepted view that the liver is resistant to diminished blood pressure and has a large physiological reserve [44,45]. Alternatively, it has been suggested that hemodynamic disorders may have deleterious effects not as much on the function of the liver as on its morphology. Extensive central venous congestion was observed 4 days after brain death in humans; piecemeal necrosis and periportal necrosis have also been shown to increase after day 15 [41]. It remains unclear whether these effects are caused by the condition *per se* or by supportive intensive care treatment of the patient, including the use of vasopressive agents. Nevertheless recent experimental findings show that hepatocytes in livers from brain dead donors show an altered cell membrane permeability and integrity [46]. Clinical findings in livers from brain dead donors revealed significant higher leukocyte infiltrates compared with optimal organs from brain dead donors [47]. This is in accordance with our own results, confirming that livers form brain dead donors are indeed infiltrated by immunocompetent cells before transplantation (J. Pratschke, unpublished data).

The lung is particularly susceptible to injury resulting from the rapid hemodynamic changes that occur during

autonomic storm. The elevated systemic vascular resistance can lead to increasing pulmonary capillary reserve followed by enhanced flow in the pulmonary artery. As left atrial pressure is also high, structural injury and/or pulmonary edema may develop. This can lead to deterioration in pulmonary function, sometimes resulting in the organ being unsuitable for transplantation [48].

Pancreatic function does not markedly change in brain-dead donors, if hemodynamic stability is maintained [26]. However, elevated insulin and C peptide levels have been observed, despite the presence of hyperglycemia, although increased glucagon levels are more common. Resistance of the tissue to insulin because of impaired receptor binding has been suggested. Recent experimental investigations proved, that brain death induces macrophage associated molecules in pancreatic islet cells [49].

Cytokine activation after brain death and influence on graft outcome

Recent studies investigating the relation between brain death and activation of peripheral organs, have demonstrated that an explosive increase in intracranial pressure in rats up-regulates various lymphocyte- and macrophage-derived cytokines on somatic organs [12]. Rapid activation of leukocyte populations and their associated products have been demonstrated in heart and kidney allografts from brain dead donors before and during the first days after transplantation [50,51]. Increased cellular infiltrates have been proven to be present in all other organs from brain dead donors suitable for transplantation [3,52,53]. In addition to the presence of chemokines, cytokines and adhesion molecules, major histocompatibility complex (MHC) class II antigen expression is increased, triggering a more rapid and intense host alloimmune response than that mounted against the more inert grafts from living donors.

The adhesion molecules responsible for such leukocyte-endothelial interactions have been increasingly defined. Selectins, early adhesion molecules not present on vascular cell surface under resting conditions but up-regulated rapidly after injury, appear to trigger subsequent events. After initiation of neutrophil binding, the adhesion molecule – cytokine cascade is amplified further. Adherent leukocyte populations express other classes of adhesion molecules (ICAM; VCAM; LFA-1) and release proinflammatory lymphokines (TNFα, IFN-γ). Expression of MHC class I and II molecules is increased. The up-regulation of MHC on graft cells is mediated primarily by INF-γ, itself being increased by the brain death/ischemia/reperfusion insult. Although MHC antigen expression alone does not lead to allograft rejection, it increases graft immunogenicity via the T-cell recognition process. The up-regulation of antigen expression secondary to nonspecific endothelial injury may increase the frequency of early acute rejection. Adhesion-molecules responsible for the initiation of the immunological cascade have been clearly defined in experimental brain death models on endothelial and parenchymal cells [46]. Furthermore, most experimental studies confirm a significant increase in proinflammatory cytokines and interleukins shortly after brain death induction. Those effects were associated with an increased activity of NF-kappa B, c-Jun and ATF-2 [54]. Own investigations of livers from brain dead donors with sequentially taken biopsies before organ harvesting, following the completion of donor surgery after engraftment and 1 h after reperfusion, revealed a maximal immunologic activation of the graft at the end of surgical organ harvesting procedure (J. Pratschke, unpublished data). Cytokine levels in organs from brain dead donors did not further increase after reperfusion during the engraftment procedure. Those observations are in accordance with recent findings, showing that platelet deposits and neutrophil infiltration is a more common feature in organs from brain dead donors than in those from ideal living donors [55].

In addition to an increased expression of proinflammatory cytokines and more pronounced cellular infiltrates, recent experimental investigations showed a higher rate of apoptosis in organs from brain dead donors prior to transplantation [56]. Brain death of the donor in combination with various additional injuries, such as ischemia and reperfusion injury, leads to an immunologically activated organ before transplantation. As a consequence, the survival of the activated organs in unmodified recipients is significantly reduced. This correlation was proven experimentally for hearts and kidneys as well as in recent investigations for lungs and islet cells. After liver transplantation the results with organs from brain dead donors seem to be comparable with transplants with living donor organs [57]. This is partly explained by the high regeneration capacity of the liver. One could speculate that the early results after liver transplantation are unaffected by brain death, but over the long-term a higher rate of injury of more susceptible structures, as for example the bile duct, may be observed. When immunosuppression is administered to the recipient, grafts from brain dead donors experience accelerated changes of chronic rejection in experimental investigations. Experimentally it seems to be clear, that the state of donor brain death in combination with associated ischemia, comprises important risk factors for both initial and late graft behavior [50,58].

Conclusions

The observation, that insults occurring around the time of organ transplantation become risk factors for allograft

failure, suggests that the graft injury may be programmed even prior to transplantation. Deleterious changes of endothelial surfaces and the increasing immunogenicity of somatic organs may begin promptly after massive central injury and can partly be explained by excessive catecholamine release. In addition, nonspecific events relating to circumstances surrounding donor management and the perfusion and storage of organs, may initiate an inflammatory response, which in turn may acutely increase host immunological activity. As a consequence, organs from brain-dead donors could experience increased and more severe episodes of acute rejection after transplantation.

These recent data demonstrate that organ grafts should not be considered as immunological inert. Donor risk factors, such as previous diseases and age, the cause of death, donor management, consequences of ischemia/reperfusion injury and most importantly brain death, reprogram the graft into an immunological active organ. Consequently, immunosuppression should already start in the donor. Treating the donor following confirmation of brain death seems to be a promising approach to reduce the immunological activation of the graft and to improve organ quality before transplantation [59,60].

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