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Review Article

Brain death and its implications for management of the potential organ donor

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The systemic physiologic changes that occur during and after brain death affect all organs suitable for transplantation. Major changes occur in the cardiovascular, pulmonary, endocrine, and immunological systems, and, if untreated may soon result in cardiovascular collapse and somatic death. Understanding these complex physiologic changes is mandatory for developing effective strategies for donor resuscitation and management in such a way that the functional integrity of potentially transplantable organs is maintained. This review elucidates these physiological changes and their consequences, and based on these consequences the rationale behind current medical management of brain-dead organ donors is discussed.

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TRANSPLANTATION of organs from brain-dead individuals has evolved as the treatment of choice for many patients with end-stage organ disease, but shortage of available donors limits solid-organ transplantation.[1] Improvements in donor management, surgical techniques, and perioperative care, together with more effective immunosuppressive treatments, have contributed to an increasing success rate of transplantations during recent years. It has also encouraged the use of older, more marginal, and higher risk donors without compromising the outcome of recipients. Despite this enlargement of the donor pool, the gap between supply and demand continues to widen,[2] and it has become increasingly important to maximize the number of available donors.

Assuming complete detection and support to organ donation of all potential donors, the maximal rate of organ donation is estimated to be in the range of 50 donors per million of population (pmp).[3,4] The actual donor rates, however, are much lower and vary substantially between countries. Spain is at the top end, with an annual donor rate of 30–35 pmp,[5] while most countries in Western Europe have annual donor rates between 12 and 20 pmp.

Potential donors fail to become actual donors due to mainly three reasons: (1) the family refuses consent for organ donation, (2) the donors are lost secondary to hemodynamic collapse and subsequent cardiac arrest, and (3) the donors are deemed medically unsuitable according to acceptance criteria. Standardizing organ donor care with more aggressive donor management protocols has been shown to reduce family refusal rate, to substantially decrease the number of donors lost due to circulatory collapse, and to transform some unacceptable donors into actual donors.[6,7]

Brain death induces considerable hemodynamic, hormonal, and metabolic changes, that if untreated, may result in cardiac arrest and somatic death. Early and aggressive hemodynamic management and hormonal support may delay and temporarily reverse these events of hemodynamic instability and metabolic derangements. Using a combined approach of hemodynamic and hormonal management, the Papworth program in Great Britain showed that 84% of donors well outside acceptance criteria on initial evaluation could be functionally resuscitated to yield transplantable organs.[6] Since the introduction of the Papworth program in the early 1990s, most transplantation centers have developed standardized donor management protocols focusing on hemodynamic and hormonal resuscitation.

The purpose of this review is to elucidate the physiological effects and consequences of brain death, and, based on these consequences, discuss the rationale behind current medical management of brain-dead organ donors.

Cardiovascular changes

Brain death following progressive increases in intracranial pressure (ICP) induces sequential systemic physiologic changes as the ischemia propagates from the cerebrum to the spinal cord in an orderly rostro-caudal fashion. The cardiovascular changes follow a characteristic and easily observable pattern.[8] Pontine ischemia leads to the 'Cushing reflex,' a mixed vagal and sympathetic stimulation resulting in bradycardia and hypertension. This response is followed by an unopposed sympathetic stimulation, the so-called 'sympathetic storm' as ischemia progresses downwards to the distal medulla oblongata, making the vagal motor nucleus ischemic. This period is characterized by severe hypertension and tachycardia. Completion of herniation with ischemia of the spinal cord is followed by a gradual loss of all sympathetic and hence, vascular tone, leading to progressive hypotension and cardiovascular collapse.

Cardiac function is reduced after brain death. This has, to a great extent, been attributed to catecholeamine cardiotoxicity brought about by the sympathetic storm. Myocardial damage and morphological changes following brain death are quite similar to changes that can be induced by high doses of catecholeamine infusion,[9] and they can be prevented by a total cardiac sympathectomy before the cerebral insult, indicating a substantial role of catecholeamines in triggering the myocardial injury following brain death.[10,11] Both the magnitude of the catecholeamine response and the extent of the myocardial injury seem to be correlated to the velocity of increase in ICP. In a dog model, an explosive increase in ICP resulted in a 750-fold increase in epinephrine and a 400-fold increase in norepinephrine plasma levels accompanied by extensive ischemic injury to the myocardium. A gradual increase in ICP, inducing brain death over 2 1/2 h, resulted in less increase in catecholeamine plasma levels, 175- and 40-fold increases for epinephrine and norepinephrine, respectively, and only mild ischemic injury to the myocardium.[12] Another difference was that all animals in the explosive ICP elevation group developed hemodynamic collapse within an hour after brain death, whereas all animals in the gradual ICP elevation group remained relatively stable until the experiment ended, on average 3 h after brain death. This may indicate that an explosive induction of brain death not only leads to a greater sympathetic storm, but also to a more rapid subsequent loss of sympathetic tone. In a similar dog model,[13] Sebening and colleagues demonstrated that a rapid induction of brain death led to a 40% reduction in systemic vascular resistance (SVR) after 60 min, but cardiac pump function could be preserved by volume substitution. Loss of sympathetic tone and accompanying vasodilation alter loading conditions of the heart, and Szabo and colleagues have, through a series of experiments, clearly demonstrated their roles in hemodynamic instability and cardiac dysfunction after brain death.[14–19] Vasodilation and afterload reduction result in a reduced coronary perfusion pressure, relative intravascular hypovolemia, and consequently decreased pre-load. In a canine cross-circulated heart model they showed that if loading conditions and coronary perfusion pressure were kept constant, no cardiac dysfunction occurred after brain death.[19] In an *in situ* isolated perfused, heart model, it was demonstrated that if coronary perfusion was decoupled from aortic pressure and elevated to pre-brain death levels, coronary blood flow, and myocardial contractility were also restored toward baseline levels.[17] The implications are that altered loading conditions themselves may have significant effects on contractile performance, that the myocardial injury triggered by brain death, to a great deal, may be reversed or avoided by restoring cardiac loading conditions, and that the hemodynamic collapse often observed after brain death is more a result of reduced afterload than due to primary cardiac dysfunction. The significance of reduced coronary perfusion on cardiac performance in this setting is not settled, but brain death induces endothelial dysfunction impairing endothelial-dependent vasodilatory mechanisms, and may thus contribute to the observed reduction in coronary blood flow.[20] Loss of autoregulatory reserve in coronary vessels and consequent hypoperfusion probably contributes to the deterioration of cardiac function in this hypotensive state after brain death.[19]

Pulmonary changes

The lungs are the organs most often deemed medically unsuitable, and only 10–20% of lungs from multiple organ donors are used for transplantation.[21] Although brain death has great physiological consequences, pulmonary dysfunction in the brain-dead organ donor is often associated with incidents not related to brain death per se such as

aspiration, pneumonia, contusion, and ventilator-induced injury.

Brain death-induced lung injury and dysfunction are mainly related to neurogenic pulmonary edema (NPE) and inflammatory acute lung injury.[22] The latter will be discussed later.

NPE results from brain injury or stimulation, and it can occur immediately after a neurological insult. Combat casualties in Vietnam suffering instant death after head injury had pulmonary congestion and hemorrhage at autopsy,[23] and 90% of patients who suddenly died due to intracranial hemorrhage were found to have pulmonary edema.[24] NPE is caused by hemodynamic and sympathetic mechanisms, and, during brain death, is related to the sympathetic storm, but often occurs earlier in the course, before the patient turns out to be a potential organ donor. The sympathetic storm induces systemic vasoconstriction, increasing cardiac afterload and hence left ventricle and left atrial pressures. The blood is shifted from the periphery to the central compartment, increasing pulmonary blood volume and pulmonary artery pressure. These increases in left atrial and pulmonary artery pressures result in a massive increase in pulmonary capillary pressure, and the accompanying pulmonary edema is a combined result of elevated hydrostatic pressure and structural damage to the capillary endothelium.[25] Stimulation of α-adrenergic receptors can increase the permeability of pulmonary capillaries independent of its hemodynamic effects,[26,27] but the pulmonary edema induced by this mechanism is less severe.

Both the hemodynamic response and the NPE can be prevented by α-receptor blockade and spinal cord transection, but not by adrenalectomy or β-receptor blockade, indicating that neuronal discharge of norepinephrine mediates both the hemodynamic and the local direct effect on the pulmonary capillaries.[28–30]

Endocrine changes

In addition to the changes in sympathetic activity and catecholeamine plasma levels, brain death may also cause significant endocrine changes reflecting anterior and posterior pituitary failure. Induction of brain death in animals is followed by a rapid decrease in triiodothyronine (T3), cortisol, and insulin.[31,32] The pattern in brain-dead patients seems to be somewhat different. Cortisol and insulin levels remain within normal levels in most cases, and the decline in T3 plasma levels is not uniform.[33–35] Subnormal T3 levels occur in 60–80% of brain-dead donors, but only a few (15%) reach very low values, and the decline in T3 is accompanied by a parallel increase in reverse T3. Free thyroxine is less affected and only 30–35% have subnormal values. Anterior pituitary function seems to be well preserved in most donors with normal values of thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and human growth hormone, indicating some residual function and thus perfusion of the hypothalamic–pituitary neuro-endocrine system. Thyroid hormone and TSH levels are typical for the 'sick euthyroid syndrome' that often accompanies severe brain injury, rather than a result of TSH deficiency.

Novitzky and colleagues have, in a series of experimental studies in baboons and pigs, demonstrated that parallel to the deterioration of cardiac function after brain death, there is a shift from aerobic to anaerobic metabolism in the heart and a depletion of myocardial energy stores.[32,36–38] The deterioration of cardiac function, the need for inotropic support, and the metabolic changes could be reversed by T3 supplementation.[37,38] Other studies, however, could not confirm these results,[39] and in most human studies there is no correlation between plasma T3 levels, cardiac function, and the need for inotropic support.[40–42] In a review by Powner and Hernandez,[43] it was concluded that routine replacement of thyroid hormones for all donors could not be advocated. In a recent, randomized-controlled trial, T3 administration neither changed cardiac performance nor heart retrieval rate from human brain-dead donors.[44]

Although plasma cortisol values remain within normal levels in most brain-dead donors,[34,35] the capacity to increase secretion upon ACTH stimulation seems to be reduced.[45] In a group of 37 patients with serious brain injury, 17 patients progressed to brain death. After brain death plasma levels of cortisol were significantly lower than in the patients who did not deteriorate to brain death, and 76% of the brain-dead patients did not respond to ACTH stimulation compared with 10% in the non-brain-dead group.[45] Thus, the prevalence of an attenuated adrenocortical response to physiologic concentrations of ACTH seems to be high in brain-dead patients, but its clinical implications are not settled. Corticoid treatment of brain-dead donors is routinely used by many centers, not to substitute adrenocortical failure, but to attenuate immune

responses. The rationale for this treatment will be discussed later.

In contrast to anterior pituitary function, posterior pituitary function is clinically lost in as much as 80% of brain-dead organ donors, and diabetes insipidus with electrolyte disturbances, hypovolemia, and circulatory instability may cause major problems in donor management.[34,35] In addition to the aquaretic effect, loss of vasopressin activity amplifies the systemic vasodilation induced by disappearance of sympathetic activity, and, if untreated, may rapidly result in cardiovascular collapse and somatic death.[46]

Inflammatory and immunological aspects of brain death

Increased blood levels of several cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-1β, and IL-2R are seen after severe cerebral injury and brain death, and there is an up-regulation of these cytokines in somatic organs.[47–50] Increased expression of IL-6 and TNF-α has been related to malfunction of donor hearts and prediction of right ventricular failure after human heart transplantation.[51,52] In kidney transplantation, both short- and long-term results of unrelated living transplants are superior to even well-matched cadaveric transplants,[53–55] and increased cytokine levels in the blood and kidney of brain-dead donors compared with living donors reflect this difference in outcome between living and cadaveric donation.[47] Cytokines have many effects, both synergistic and antagonistic, on the immune system. After brain death they seem to initiate an inflammatory cascade in all organs investigated, with rapid activation of leukocyte populations and adhesion molecules, such as selectins, intercellular adhesion molecule (ICAM)-1, and monocyte chemotactic protein-1, leading to increased cellular infiltrates in all organs suitable for transplantation.[56,57] Adherent leukocyte populations release proinflammatory lymphokines such as TNF-α and interferon-γ, the latter mediating the up-regulation of major histocompatibility complex (MHC) class I and II on graft cells. MHC may increase graft immunogenicity via the T-cell recognition process.[58] In the pig, Skrabal et al.[49] found an organ-specific regulation of proinflammatory molecules in the kidney, heart, and lung following brain death. Of the cytokines and cytokine-related molecules measured, IL-1β and IL-6 increased in all organs whereas TNF-α only increased in lung tissue. ICAM-1 mRNA also increased only in the lung, while only heart tissue revealed a significant increase in IL-6 receptor mRNA. These differences may account for differences in organ immunogenicity and may hence contribute to differences in outcome following transplantation.[49]

Although the up-regulation of blood cytokines is well documented, the question of origin still remains unclear, and the link(s) between brain death and a systemic inflammatory response may be formed from many sources.[59] Possible sources include affected organs as well as immunocompetent cells in the blood or the damaged brain itself. Both the sympathetic storm and the hemodynamic instability following brain death seem to be involved in these processes because they can be attenuated experimentally by α-receptor blockade during brain death avoiding the hypertensive crisis, and by norepinephrine or volume loading after brain death avoiding the subsequent hemodynamic instability.[28,60–62] Both the sympathetic storm and the subsequent hemodynamic instability may lead to hypoperfusion and ischemia in various organs and consequently activate the cytokine system. Several cytokines have been found in brain tissue and cerebrospinal fluid after brain injury and through a defective blood–brain barrier, they may reach the circulation and stimulate target cells in the blood and somatic organs.[63]

In summary, brain death is associated with the release of proinflammatory substances and inflammatory responses are detected in all organs suitable for transplantation leading to immunologically activated organs before engraftment, resulting in histological damage, decreased function, and lower graft survival compared with organs from living donors.[58,64–68]

Donor management

Most potential organ donors suffer from intracranial hemorrhage or traumatic brain injury, and their treatment will be aimed at saving their brains. This treatment often includes heavy sedation and infusions of hyperoncotic solutions with high levels of saline to reduce ICP and to improve cerebral hemodynamics.[69,70] Heavy sedation often demands infusion of catecholamines to restore cardiac output (CO) and achieve a targeted cerebral perfusion pressure. When a potential organ donor eventually becomes an actual donor, this brain-

saving therapy might have some consequences for organ quality and donor management. The therapy often includes hydroxyethyl starch (HES),[69] which can induce injury to renal tubular cells and impair early renal graft function.[71,72] Such treatment often results in hypernatremia, which is associated with an increased risk of graft dysfunction after liver transplantation.[73–75] Another effect of this osmotherapy is that it may slow down the herniation process, leading to a less pronounced sympathetic storm with less damage to solid organs and probably less immunological activation.[28]

Hemodynamic management

Keeping the donor circulatory stable is challenging, and the time from brain death to organ procurement should be as short as possible in most cases.[76] The goal is to maintain adequate circulating blood volume, and proper CO and perfusion pressure to assure optimal oxygen delivery to tissues. Depending on the degree of hemodynamic instability the donor might need fluid resuscitation, inotropic support, vasopressors, and hormonal substitution. Initial hypotension may occur in as much as 80% of donors,[77] and sustained hypotension is associated with impaired graft function.[78,79] Hypovolemia is common and fluid resuscitation is usually considered the first step in the correction of hypotension. However, hypervolemia may aggravate right ventricular dysfunction[80] and cause rapid deterioration of lung function.[81,82] The goal should therefore be to achieve normovolemia if thoracic organs are to be harvested. On the other hand, kidney function seems to benefit from a more aggressive fluid regimen,[83] making it necessary to balance the antagonistic interests of organs related to fluid resuscitation. There is no consensus on what kind of fluid is more appropriate, and both crystalloids and colloids are used, often in combination. However, in lung donors, colloid solutions are recommended to minimize accumulation of pulmonary edema and deterioration in gas exchange.[21,84] Although modern, third generation, rapidly degradable HES solutions with a low degree of substitution seem to have less toxic effects on donor kidneys,[85] these HES solutions should be avoided until more documentation is available. Administration of packed red cells to keep the hemoglobin level $\geq 100\,g/l$ (or the hematocrit $\geq 30\%$) is recommended,[21,83] but is not evidence based. Hypernatremia should be corrected to avoid liver graft dysfunction,[73–75] and it also seems reasonable to correct other electrolyte abnormalities.

Adequate fluid resuscitation is often not sufficient to restore blood pressure and CO, and approximately 80–90% of donors require additional vasoactive (inotropic and/or vasopressor) support.[86] The use of vasoactive medication is not based on randomized-controlled trials and there are widely divergent opinions concerning the best drugs to use and which to avoid. Most of the discussion is about catecholamines and their anticipated detrimental effects on the donor heart. Very high doses of catecholamines administered to experimental animals have induced damage to the myocardium similar to the changes induced by the sympathetic storm during brain death,[9–11] and the use of norepinephrine to donors has been related to primary nonfunction in heart transplantation.[87] This has led to high numbers of donors refused by cardiac surgeons exclusively due to the doses of catecholamines used.[88] However, excellent outcomes have been reported in heart transplant recipients from donors managed with high doses of dopamine and norepinehrine[89] and, as discussed previously, restoring the loading conditions of the heart after loss of sympathetic tone is essential for maintaining and improving cardiac performance after brain death. Achieving an adequate coronary perfusion pressure is probably more important than avoiding high doses of catecholamines.[90]

Dopamine has traditionally been the first choice and still defends its place in most recommendations.[83,89,90] Catecholamines have immunomodulatory effects and may attenuate the increased immunogenicity of organs following brain death, leading to improved organ survival after transplantation.[91,92] These effects are best documented for dopamine, which also stimulates the induction of protecting enzymes like heme oxygenase-1 (HO-1), rendering organs more resistant to the insults of ischemia/reperfusion (I/R) and inflammation.[92–95] There is also some experimental support that dopamine might limit pulmonary edema and inflammation in lung allografts during cold storage,[96] and pre-harvest administration of dopamine to donors is associated with faster alveolar fluid clearance in human lungs.[97] The upper dose limit for dopamine has traditionally been set to $10\,\mu g/kg/min$,[83,98] but seems rather arbitrary and lacks good documentation. There is considerable interindividual variation in dopamine pharmacokinetics,[99] and it should be titrated to achieve the targeted hemodynamic effect only limited by tachycardia.[100]

In some cases, fluid resuscitation and dopamine administration is insufficient to restore cardiac afterload, and a vasopressor has to be added. Both norepinephrine[83,89,90] and vasopressin[101–103] are recommended, and excellent results have been obtained by both. Vasopressin is effective against diabetes insipidus, and it reduces the hemodynamic need for catecholamines.[101,102] In addition to the association with primary nonfunction,[87] norepinephrine has been related to reduced right ventricular contractility and reduced 1-year survival in heart transplantation.[104] However, these data are retrospective, and no causal connection between norepinephrine and outcome has been demonstrated. On the other hand, norepinephrine has been shown to increase both coronary and renal blood flow in the normal mammalian circulation[105] whereas vasopressin had no effect.[106] At present, there are no convincing studies demonstrating that one vasopressor is superior to the other.

If the hemodynamic goals are still not reached, hormone replacement therapy is used by many centers as the very last effort.[83,98] Traditionally, a combination of a thyroid hormone, steroids, vasopressin, and insulin has been used.[6] Today, insulin therapy and blood sugar control is implemented in intensive care,[107–109] and a majority of organ donors receive insulin already before brain death. They also receive metylprednisolone to attenuate immune responses (to be discussed later), and vasopressin is often already part of the vasopressor therapy. As discussed previously, thyroid hormone administration remains controversial, but good outcomes with more transplantable organs have been obtained in circulatory unstable donors on high doses of vasoactive therapy.[110,111]

Hemodynamic monitoring

Standard ICU hemodynamic monitoring with central venous pressure (CVP) and invasive arterial pressure is generally used in all potential and actual donors. Most donors are circulatory stable with a mean arterial pressure above 70 mmHg, a CVP of 4–10 mmHg, and an adequate urine output ($\geq$ 1.5 ml/kg) on dopamine infusion,[112] and do not need further invasive monitoring. If a vasopressor (norepinephrine, vasopressin, or epinephrine) has to be added for stabilizing hemodynamics, a device to measure CO and SVR is recommended.[6,83,98,103,113] The goals are to 'normalize' hemodynamic variables[6,83,98] and use of the pulmonary artery catheter (PAC) has been the gold standard, but transpulmonary thermodilution measurements or esophageal Doppler measurements (EDM) are good alternatives.[114] In addition to CO and SVR, transpulmonary thermodilution gives continuous CO by pulse contour analysis and estimates of intrathoracic blood volume (ITBV) and extravascular lung water (EVLW).[114] ITBV is a much better estimate of cardiac pre-load than pulmonary artery occlusion pressure,[115] and EVLW is an indicator of pulmonary edema and capillary leakage. It may be elevated before changes occur in gas exchange or chest roentgenogram, and measurements and manipulation of EVLW may become important in the assessment and management of potential lung donors.[21]

EDM has been successfully used in resuscitation and optimization of unstable donors.[116,117] It is an attractive alternative to PAC because it is less invasive, easy to insert, almost without complications, and gives rapid retrieval of hemodynamic data. CO estimates are based on the assumption that 70% of CO passes through the descending aorta and may thus be overestimated in brain-dead donors who are without cerebral blood flow.

CO and SVR can also be estimated by means of echocardiography. In addition, echocardiographic assessment of donor heart function might provide valuable information about both global and regional cardiac performance, and the conditions of the valves. However, early myocardial dysfunction is often reversible, and the significance of abnormalities observed in relation to post-transplant cardiac function is not easy to assess.[118] There is clear evidence that not only hearts with mild, but also hearts with more serious wall motion abnormalities can be successfully transplanted.[118–120]

Immunosuppressive strategies

The beneficial anti-inflammatory effects of catecholeamines and the importance of avoiding hemodynamic instability after brain death have been discussed above. Insulin also has anti-inflammatory properties,[121,122] and strict blood sugar control by means of insulin infusion may contribute to reduced cytokine activation after brain death.[123] However, the main issue in this connection is the use of steroids. Administration of methylprednisolone to brain dead donors is associated with improved short- and long-term outcome for most transplanted organs.[124–129] It reduces the increase in EVLW ob-

served during donor management,[21] and it was the most significant independent predictor of successful lung donation in a multivariate analysis on lung donor variables.[129] It is also associated with significant reductions in the incidence of early graft dysfunction in heart transplantation.[124] In both experimental and clinical investigations, Pratschke and colleagues[127,128] have demonstrated that methylprednisolone reduces the immunological activation observed after brain death. In a prospective randomized study, they found that methylprednisolone reduced both serum and intragraft cytokine expression and improved graft function in human liver transplantation.[128] The I/R injury was ameliorated, and reduced rates of acute rejections were observed during follow-up. Methylprednisolone administration to brain-dead donors can reduce cytokine activation to levels almost comparable to the levels seen in living donor transplantation,[127] and should as a consequence, be given to all donors immediately after brain death. The dose often recommended is a single bolus of 15 mg/kg bwt,[83,98] whereas Pratschke and colleagues[127,128] used 250 mg as a bolus, followed by an infusion of 100 mg/h.

Pulmonary care

Optimal management of respiratory function in the brain-dead donor is not based on randomized-controlled trials. A lung-protective ventilation strategy with low pressures and tidal volumes to avoid ventilator-induced lung injury is recommended, together with a moderate PEEP of 5–10 cmH_2O.[130] An initial bronchoscopy to aspirate secretions, to detect evidence of active bronchitis or aspiration, and to obtain a bronchoalveolar lavage specimen for culture should be performed. Frequent endotracheal suctioning to keep the airways clean and physiotherapy, together with gentle lung recruitment to avoid atelectasis, is associated with increased rates of lung procurement and improved quality of organs.[21,131] As discussed previously, hypervolemia may rapidly deteriorate gas exchange, and the use of diuretics is often necessary. Another way to decrease excess alveolar fluid is inhalation of a β_2-adrenergic agonist, which may increase the rate of alveolar fluid clearance.[97] Intermittent transpulmonary thermodilution to assess and follow changes in EVLW might be useful in the management and optimization of marginal lung donors.[21] Some factors, such as persistent bilateral infiltrates, copious purulent secretions, or overt signs of aspiration, are contraindications to the use of donor lungs. On the other hand, smoking history, age, positive Gram stain, number of days on ventilator, or localized abnormality on the chest radiograph may not be associated with increased perioperative risk, and should not by themselves preclude transplantation.[103,132]

Organ procurement

All the above strategies for donor management have to be continued during organ procurement to ensure optimal organ preservation and post-transplant function. The anesthesiologist of the harvesting team often plays a crucial role in assessing the adequacy of actual fluid resuscitation and vasoactive medication in use. This assessment may be difficult to perform, especially in circulatory unstable donors without advanced hemodynamic monitoring, which often is the case. Organ preservation and the use of the different perfusion fluids for cold storage are beyond the scope of this review, but some points regarding pharmacological preconditioning will be discussed. As mentioned previously, dopamine is capable of stimulating the induction of protective enzymes like HO-1, rendering the organs more resistant to the insult of I/R[94] and should probably be continued through the procurement procedure. In addition, catecholeamines may prevent cold-induced damage to endothelial cells by scavenging reactive oxygen species (ROS) or by inhibition of ROS production.[133] Volatile anesthetics (sevoflurane, isoflurane, and desflurane) have, in several experimental and clinical settings, been shown to protect the heart from I/R injury.[134–137] Recently, isoflurane was demonstrated to have a similar effect on the rat liver,[138] and sevoflurane, in a prospective randomized study, protected the human liver from I/R injury during liver resection.[139] It is our practice to administer volatile anesthetics at least during the last 30 min before aortic cross clamping.

In summary, donor management is challenging intensive care therapy aiming at reducing the negative consequences of brain death on solid organs suitable for transplantation. To achieve this goal, adequate fluid resuscitation, intense vasoactive medication, immunosuppressive therapy, and sufficient hemodynamic and other monitoring are required.

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