Review article

TRANSPLANT International

Transplant Int (1991) 4: 186–190

Donor treatment after pronouncement of brain death: a neglected intensive care problem

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Received October 24, 1990/Received after revision February 28, 1991/Accepted February 28, 1991

Abstract. The need for cadaveric organs for transplantation is increasing. To decrease the shortage of organs, identification of potential donors and conditioning of these donors must improve. We present a review of relevant data on body and tissue alterations due to brain death and summarize the recent literature covering experimental and clinical studies on optimal donor management.

Key words: Donor management – Brain death, metabolic changes

For decades the need for organs has exceeded the number of available organs. As a result, patients must often wait a very long time to receive a suitable graft. This unwanted situation leads to increased morbidity and, at times, mortality, and places a financial burden on the health care system. The scarcity of organs is an issue that has to be dealt with in order to obtain maximal return on investment. Both doctors' and public awareness of this shortage, together with sound legislation, may increase the source of potential donors. Donor treatment will also help to solve this problem, since optimal donor conditioning, when the brain lesion is so severe that the patient's condition is hopeless and brain death is imminent, will improve the quality and increase the quantity of transplantable organs.

Here we review relevant data on body and tissue alterations due to brain death and we summarize the literature on optimal management of the donor during the agonal period. This management starts immediately after pronouncement of brain death and ends after successful completion of organ procurement.

Body and tissue alterations due to brain death – experimental data

Both changes in tissue perfusion and circulating hormone levels during and after the onset of brain death have been documented. Preceding actual brain death, body circulation is often hampered by capricious fluctuations in blood pressure caused by autonomic dysregulation. Novitzky et al. showed in several animal models that a sudden increase in intracranial pressure or a sudden onset of brain ischemia leads to a so-called autonomic storm [12, 34, 44, 67]. After a brief, initial period of excessive parasympathetic activity, evidenced by a marked bradycardia, most of the effects are caused by the sympathetic nervous system [35]. Increased catecholamines are found within minutes after induction of brain death but return to normal values after about a quarter of an hour; thereafter, they decrease to below baseline values. Significant increases in systemic vascular resistance and mean arterial pressure occur during this autonomic storm and, in a majority of animals, a short period of complete cessation of pulmonary capillary blood flow is observed, due to the fact that left atrial pressure has exceeded pulmonary arterial pressure. This may result in pulmonary edema with high protein content and interstitial hemorrhage [39]. A decrease in coronary blood flow, associated with electrocardiographic features of ischemia, is also seen during this period of tachycardia [12, 34]. Furthermore, brain death, with or without hemodynamic support of the circulation, may lead to a significant reduction in subsequent myocardial function, associated with some depletion of energy reserves [67].

Von Schiffner found in both the dog and the pig an initial increase in liver perfusion during the first 30 min after brain death; thereafter, it decreased parallel with decreasing cardiac output. Intrahepatic shunting during the initial phase is similarly increased, as reflected in temporary biochemical and electromicroscopic signs of hypoxemia [56]. Perfusion of other transplantable organs is also influenced by fluctuating catecholamine levels, leading to periods of tissue hypoxemia that are not caused by shock. Repetitive hypoxemic events may harm organs considerably, leading to early reperfusion injury in the donor. This may endanger organ viability, as reflected in impaired cellular energy metabolism and loss of cell and tissue integrity.

Furthermore, myocyte necrosis may occur, due to high levels of circulating endogenous catecholamines during this period of excessive sympathetic activity [35, 44]. In a

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later stage of brain death, various degrees of hypotension are often evident. Grundmann et al. concluded that the level of hypotension was more important than its duration [17]. Thus, inotropic and vasopressive agents, such as dopamine, dobutamine, and norepinephrine, are required to sustain blood pressure. However, this may result in acceleration of donor heart deterioration [54, 67, 69]. At a dose of 15 μg/kg per minute, dopamine impairs liver metabolism [45, 65].

While in low doses (less than 5 μg/kg per minute) dopamine has a renal vasodilating action that could protect the kidney from ischemic damage [55, 65], higher doses can result in renal and splanchnic vasoconstriction.

Cellular metabolism may also be altered by changes in levels of circulating hormones. Fluctuations in plasma levels of triiodothyronine (T3), thyroxine (T4), insulin, and cortisol have been found in many species, including man, after brain death [12–14, 16, 34, 44, 53].

Observations in the pig and in the baboon have shown reduced cellular energy stores with a reduction in aerobic metabolism, something which could be reversed by administration of T3, cortisol, and insulin [11, 38, 41, 68]. Especially when dopamine is essential for treating donor hypotension, concurrent use of T3 may preserve post-transplant renal function [49].

Administration of glucose to liver donors before organ procurement in order to optimize its adenosine triphosphate production may improve post-transplant graft function by reducing the loss of hepatocellular energy, retarding membrane damage, and fostering glycogen storage for use in the early postoperative period [48].

The effects of a fall in antidiuretic hormone levels in brain-dead cadavers are frequently and easily noticed by clinicians involved in the management of brain-dead donors by the development of the clinical picture of diabetes insipidus. Blaine et al. showed in their animal study that early, low-dose (0.002–0.010 IU/kg per minute) vasopressin supplementation by continuous i.v. infusion may improve donor management [4]. However, it can have a deleterious effect on myocardial function [67].

Clinical data on the effect of donor conditioning

A procedure as complex as multi-organ donation, performed by several surgical teams often coming from different medical centers, needs to be coordinated very carefully. A transplantation coordinator is virtually indispensable in order to prevent a conflict of interests in this situation. Threatening impairment of circulation in the organs to be donated must be treated promptly and efficiently.

It can be said that, in general, optimal circulation is guaranteed by optimal tissue perfusion and not just by optimal systemic systolic pressure.

The ultimate goal of donor management is to ensure adequate oxygen transport. In order to prevent hypotension, it is necessary to anticipate underlying causes, such as hypovolemia due to polyuria, left ventricular dysfunction, and neurogenic shock. Hemodynamic monitoring should include continuous recording of arterial blood pressure and central venous pressure. Pulmonary capillary wedge pressure, obtained via a Swan-Ganz catheter, should be measured in hemodynamically unstable donors, if possible.

Fluid management

Appropriate fluid management is the cornerstone of donor conditioning. Hypovolemia is mainly the result of a fluid-restrictive therapy to treat brain edema and will quickly develop in the presence of diabetes insipidus. Aggressive fluid resuscitation is needed, preferably guided by pulmonary pressure recording. The choice of fluid replacement used will depend on the type of fluid loss. Saline infusion should be avoided in order to minimize the hypernatremia that frequently develops in the brain-dead patient. Blood losses should be replaced with whole blood or packed cells in order to maintain a hematocrit of 30%. This maximizes oxygen supply by optimizing the balance between oxygen transport by the red cell mass and blood flow related to changes in viscosity [31, 61]. Maintenance fluids should contain dextrose to ensure the preservation of adequate stores of intrahepatic glucose [48]. Crystalloids can be given in fairly large amounts if osmotic pressure is high enough to prevent tissue edema [7, 24]. The liver and lung are especially sensitive to low osmotic pressure-mediated tissue edema. Colloids have to be given if osmotic pressure falls, but artificial plasma expanders need to be titrated in restricted amounts in order not to jeopardize kidney function. Serious tissue edema is prevented when serum albumin levels are above at least 25 g/l. Direct colloid osmotic pressure measurement, when available, delivers more precise information.

Treatment of diabetes insipidus

Clinical evidence of diabetes insipidus is found in 38%–87% of all brain-dead patients whose death results from trauma or global brain ischemia [15, 47]. Hypernatremia and hypokalemia, caused by diabetes insipidus, must be avoided, especially in the heart, where this can lead to decreased myocardial contraction. Hypokalemia has to be corrected by potassium infusion. Unfortunately, persistent hypernatremia and hypokalemia, in combination with excessive urine production, frequently arise during brain death. Some authors advise starting vasopressin infusion when urine production exceeds 5–7 ml/kg per hour. Continuous infusion of 0.1–0.4 IU/h, an antidiuretic dose, is successful in reducing excessive urine production in most cases of central diabetes insipidus [9, 21]. Iwai et al. showed that a pressor dose of vasopressin (1–2 IU/h) plays a central role in circulatory stabilization of brain-dead patients. They also demonstrated that long-term maintenance of stable circulation is possible by the combined use of vasopressin and a catecholamine [21, 23]. Circulation was maintained with a smaller dosage of epinephrine when vasopressin was given [23].

Kinoshita et al. saw no clinical or pathological changes in the kidneys after brain death when the donor was maintained with a combination of epinephrine and vasopressin [23]. Nor were pathological lesions in the liver or bio-

chemical indices altered during the first 2 weeks of brain death, except for increases in cholangitis and the serum alkaline phosphatase level [33]. However, the study by Schneider et al. indicated that kidneys from donors who received dopamine, pitressin, or both prior to nephrectomy were less than optimal. These kidneys had a higher incidence of acute tubular necrosis than kidneys from non-treated donors [57]. Yet, it is obvious that these drugs are required to maintain a great percentage of unstable donors. Thus, the optimal dose is the lowest one which is effective in minimizing vasoconstriction in the splanchnic and renal vascular bed. For this reason, some prefer 1-desamino-8D-arginine vasopressin to vasopressin, which has a prolonged antidiuretic effect and results in virtual elimination of vasopressor activity [13, 52].

Use of inotropes

After variable periods of brain death, most donors need vasopressors. Again, optimal tissue perfusion is the ultimate goal. In brain death, cardiac activity is influenced only by the sympathetic system; no acceleration of cardiac rate can be expected after intravenous injection of atropine [46, 63]. Dopamine, dobutamine, and norepinephrine are the most widely used inotropes, but several newer drugs are also presently on the market.

Dopamine at low infusion rates (less than 5 μg/kg per minute) generally causes vasodilation of the renal arterial vascular bed, and this might minimize end-organ ischemic damage. In the kidney, low-dose dopamine also has a direct tubular effect, thus stimulating diuresis. In addition to this beneficial effect on renal perfusion, dopamine appears to be a better inotropic agent than dobutamine [19, 59]. At higher doses, the vasodilatory effects are lost and perfusion decreases due to stimulation of alpha-adrenergic receptors [65]. This increases systolic blood pressure but leads to a higher rate of acute tubular necrosis and poorer allograft survival than allografts not exposed to high-dose dopamine prior to nephrectomy [50, 57, 66]. Liver perfusion is hampered with doses above 15 μg/kg per minute, despite elevated portal and hepatic arterial blood flow.

Kormos et al. concluded that 2–10 μg/kg per minute doses of dopamine can be given to cardiac donors prior to donor cardiectomy [27]. Yet, whether or not hearts are treated with dopamine, Ballester et al. concluded that there is no difference in the difficulty coming off bypass, mortality, or left ventricular function early after transplantation. However, hemodynamic stability was attained with greater difficulty in those recipients whose donor hearts had undergone dopamine treatment [1]. The latter observation could be related to the functional cardiac defect seen when the heart is exposed to the persistent action of catecholamines, something which has been related to a decrease in B-adrenergic receptor density [5].

Other inotropic agents may be necessary to support the hemodynamically unstable, brain-dead cadaver. In general, those preferred are inotropes with minimal or no peripheral vasoconstrictive effects, i.e., dobutamine or dopexamine. However, a short-term stimulation of the alpha-adrenergic receptors may be necessary in spinal shock to support perfusion pressure during fluid rehydration [19, 59]. Norepinephrine can be used in this situation, but the infusion dosage must be as low as possible [21, 23].

Hormone levels and hemodynamic function

Alterations in circulating hormone levels, especially thyroid hormone levels, have been observed by several investigators [18, 20, 25, 28, 29, 36, 40, 42, 43, 64]. The clinical relevance in relation to hemodynamic instability has, however, been questioned. Although improved hemodynamic function after T3 administration has been reported [29, 36, 40, 42], several investigators could not confirm a correlation between decreased thyroid and adrenal hormone levels and circulatory defects [16, 20, 53]. Moreover, a correlation between thyroid hormone levels and the incidence of acute tubular necrosis in renal transplants [16, 25] or dopamine requirements for heart allograft recipients, as shown in experimental and clinical experiments by Novitzky et al., has not been confirmed [28, 64]. Hormonal supplementation with cortisol and T3 should, therefore, be restricted to controlled, clinical trials [20].

Ventilation

Some donors are hyperventilated in an attempt to reduce intracranial pressure. In the brain-dead cadaver, pCO_2 can be normalized in order to prevent vasoconstriction and to obtain normal pH values. Monitoring of arterial blood gases is required to optimize both the acid-base balance and oxygen saturation. Arterial pO_2 should be kept between 9.3 and 13.3 kPa, ventilating with FiO_2 values below 0.45. Frequently, neurogenic pulmonary edema will occur, and this must be treated with the lowest possible PEEP level. However, one must bear in mind that whenever PEEP is applied, as in the case of pulmonary edema, a reduction and redistribution of cardiac output may occur, possibly jeopardizing tissue oxygenation and, thus, interfering with organ function [2, 3, 22, 30].

Hypothermia

Hypothermia often occurs during brain death. This is caused by a lack of hypothalamic regulation and by excessive amounts of cold infusion fluid during rehydration. Hypothermia may lead to bradycardia and myocardial depression. The combination of lower cardiac output, vasoconstriction, and reduction in tissue oxygen delivery may cause ischemic damage to tissues [51]. Simple remedial procedures include infusion of warmed fluids, provision of heated gases from the respirator, and application of heating blankets. More invasive measures (bladder irrigation or peritoneal dialysis) should be avoided.

Future trends

Apart from all of these rather well-established treatment modalities in brain-dead cadavers, recent experimental data have been published describing attempts to influence tissue perfusion and to prevent reperfusion damage. How-

ever, almost all of these studies have involved only renal donation, and the question remains whether conclusions drawn from these studies can be extrapolated to multi-organ donation.

Intravenous administration of allopurinol, catalase, superoxide dismutase, or other drugs, such as naloxone or chlorpromazine, prior to ischemia, hemorrhagic shock, or perfusion leads to a decreased incidence of reperfusion injury of the kidney, liver, and heart [6, 8, 60, 62]. Improved renal function after pretreatment with prostacyclin just prior to crossclamping has been observed [32]. Lidocaine infusion at a dose of 2 mg/min before and during the procurement operation also decreases the incidence of early renal dysfunction [58].

Reperfusion injury is caused by free oxygen radicals. The initial step in the generation of free radicals is the conversion of xanthinodehydrogenase into xanthinoxidase, a process that depends on the intracellular concentration of ionized calcium [10]. A calcium antagonist given prior to nephrectomy will decrease intracellular calcium and may, therefore, reduce the production of oxygen radicals. Verapamil, given prior to procurement, has indeed been reported to prevent delayed graft function of kidney transplants and to prevent myocardial injury in heart transplants in animals [26, 37]. Controlled clinical trials are urgently needed to validate the role of these experimental drug regimens in multi-organ donors.

In conclusion, the cornerstone of proper donor management is fluid management. In some cases it is possible to use only this to keep the donor stable. When drugs are needed, it means that we are dealing with an unstable donor. Careful drug treatment, guided by pulmonary arterial pressure measurement, is strongly recommended, when possible, to prevent iatrogenic tissue damage. Dopamine is, at present, the inotropic agent of choice when administered at an infusion rate less than 10 μg/kg per minute. The usefulness of new, promising inotropes in brain-dead donors has yet to be investigated. Low doses of an antidiuretic hormone (0.1–0.4 IU/h) may prove successful in treating diabetes insipidus. Large controlled, prospective studies are urgently needed to investigate the efficiency of a number of agents in preventing reperfusion damage.

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