Management of the Brain-Dead, Heart-Beating Potential Donor

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Organ transplantation is the optimal treatment for patients with end-stage disease of the kidneys, pancreas, liver, intestine, lungs and heart. While the ideal source of many of these organs is a living-related or unrelated donor, this option is not available for all patients. The alternative is transplantation from a patient who has suffered irreversible brain damage but in whom the circulation is maintained, that is, a brain-dead, heart-beating potential donor. While vital organ function, with the exception of the ability to breathe spontaneously, may be initially maintained in this setting, cardiac arrest within hours to days is inevitable.

Outcome following transplantation is directly related to the quality of the organs procured, particularly those that need to function immediately, such as the heart and liver. At the same time, the organs of potential donors are exposed to a wide variety of insults. These may be the result of the primary condition leading to brain death. For example, severe multi-trauma may result in severe brain injury. However, other organs may also be injured directly by the trauma, or indirectly as a result of hypoxia, shock, severe anemia, exposure to blood products, and infections. Although many of these insults can be avoided by the proper care of these complicated patients – procedures well known to most physicians – the process of brain death itself leads to profound changes that predominantly affect the cardiovascular and endocrine systems. If the donor is inadequately managed at this stage, a significant number of available organs may become unsuitable for transplantation. Preservation of organs requires knowledge of the changes associated with brain death.

In this article we review the clinical consequences of brain death and the management of the potential donor to maintain optimal organ function.

Consequences of brain death

The autonomic storm

Immediately after brain death, there is an initial brief period of excessive parasympathetic activity [1]. This may result in sinus bradycardia, sinus standstill, junctional escape beats, or even complete heart block; hypotension is the usual hemodynamic consequence. This is rapidly followed by a period during which large amounts of catecholamines are released from the adrenal glands and nerve endings, the so-called autonomic or catecholamine storm, the pathophysiology of which is based largely on experimental data [1,2]. The result is intense vasoconstriction of muscular arterioles, which results in a marked rise in systemic vascular resistance and mean arterial blood pressure [3]. Myocardial work and oxygen consumption are increased, cardiac output is depressed [4], and intravascular volume is redistributed to the capacitance vessels and the lungs. The acute rise in systemic vascular resistance may cause cardiac ischemia, acute mitral valve regurgitation, and elevated left atrial pressures, leading in turn to a disruption of pulmonary capillary integrity and resulting in neurogenic pulmonary edema [5]. Recovery from this phase is rapid, so that despite obvious pulmonary edema on clinical and radiographic examination, the pulmonary occlusion pressure measurement may be normal when the patient is first seen [6]. At the cellular level, decreased production of adenosine-triphosphate, a result of the intense vasoconstriction and inadequate supply of oxygen, causes loss of normal cellular pump and channel functions [5]. There is a sudden rise of cytosolic calcium that leads to the activation of enzymes such as lipases, proteases, endonucleases and nitric oxide synthetase, which may produce structural cell damage [7]. Free oxygen radicals are generated during the subsequent period of reperfusion, causing additional cell damage [4]. The manifestations of the cellular damage are widespread. In the heart, there is focal myocyte necrosis especially of the subendocardial area, a hypercontractile state of the sarcomere, and coagulative myocytolysis associated with a mononuclear cell infiltrate [8]. The lungs show hemorrhages in the alveolar wall and spaces with capillary endothelium disruption, favoring the exudation of protein-rich fluid into the lungs [6]. In the kidneys, there is a marked reduction of the glomerular capillary spaces with scattered cell necrosis [9]. Changes in the liver are less well characterized; however, the liver has large physiologic reserves and appears to tolerate hypoperfusion [10].

This period of intense catecholamine release is short-lived (typically hours) and self-limited, and thus requires no treatment. The next phase is characterized by a reduction in sympathetic

outflow [11]. The inotropic and chronotropic state of the heart is impaired, and there is failure of autoregulation due to loss of autonomic tone. The immediate consequence is a reduction in cardiac output and blood pressure with further impairment of organ perfusion and aggravation of ischemic tissue injury [11]. Heart rhythm, which may show sinus tachycardia and multifocal ventricular tachycardias during the autonomic storm [1], usually returns to sinus rhythm.

The hypothalamic-hypophyseal axis

The effects of brain death on the hypothalamic-hypophyseal axis are profound. The most frequent and almost universal manifestation is diabetes insipidus due to loss of antidiuretic hormone secretion [12]. The kidneys are unable to concentrate urine and excrete large amounts of diluted urine (specific gravity usually < 1.005; urine osmolarity < 300 mOsm/L). Polyuria may lead to hypernatremia, which is common and may be severe (>160 mEq/L), and to hypokalemia, hypocalcemia and hypomagnesemia [13]. The secretion of renin and aldosterone in response to hypotension may further aggravate the hypernatremia and hypokalemia.

Since the hypothalamus is the primary thermoregulatory control center, significant hypothermia may follow hypothalamic destruction [14]. This is aggravated by the loss of vasomotor tone. Consequences include atrial and ventricular fibrillation that may be resistant to therapy, and compromised organ perfusion as a result of depressed ventricular contractility [15]. While renal blood flow and glomerular filtration rate decrease during significant hypothermia, urine output typically increases, the so-called cold diuresis [16]. The etiology is unclear but is probably due to centralization of the blood volume. Failure to correct hypothermia may delay the certification of brain death and thus result in further deterioration of the patient.

Dysfunction of the anterior pituitary may result in low levels of other hormones, namely, cortisol, insulin and the thyroid hormones – thyroid stimulating hormone, triiodothyronine, and thyroxine [17]. The changes in all these hormones are variable [18], except for T3, for which a reduction has almost always been documented. Low T3 levels progressively inhibit aerobic metabolism and may cause mitochondrial injury [19].

Abnormalities of the coagulation system

Disseminated intravascular coagulopathy may be triggered by the release of plasminogen activator from brain-dead tissue and results in significant and sometimes uncontrolled bleeding [14]. The tendency to bleeding may be further aggravated by hypothermia and catecholamine use, both of which impair platelet function.

To manage the widespread organ dysfunction resulting from the brain death process, an appropriate setting, ideally an intensive care unit, is required with staff familiar with the clinical complex and its treatment. Adequate monitoring is essential and should include heart rate, oxygen saturation, central venous pressure, continuous core temperature and urinary output. The insertion of an indwelling arterial catheter allows for continuous blood pressure monitoring and facilitates the collection of the repeated blood sampling required to manage these complicated patients. The goals of therapy are as follows:

- *Maintenance of systolic blood pressure*. A systolic blood pressure of 100–120 mm Hg is needed to ensure adequate perfusion of essential organs. In the presence of hypotension, initial therapy should always consist of fluids, as guided by the central venous pressure. The aim of therapy is to reach a normovolemic state; more aggressive fluid resuscitation may result in congestion particularly of the liver and lungs and preclude their procurement. If required in large amounts, the fluids should be warmed so as not to cause or aggravate hypothermia. Initial fluid resuscitation may be with crystalloids, such as normal saline. However, colloids, such as hydroxyethyl starch, may also be used in recommended dosages, in view of recent studies indicating that they apparently do not impair immediate renal function in kidney transplant recipients as was initially thought [20]. Blood should be transfused if the hematocrit is <30% in the multi-organ donor (in whom there is a longer operative time and greater potential for intraoperative blood loss) or <24% in other donors. If the systolic blood pressure remains <100 mmHg despite adequate fluid therapy, inotropes are warranted. The initial agent of choice is dopamine, which should be given in increasing doses but not exceeding 15 μg/kg/minute. If blood pressure still remains low, norepinephrine should be added, starting with a dose of 0.01 μg/kg/minute and titrated against the blood pressure. While high doses of these agents may compromise organ perfusion by causing vasoconstriction, the immunomodulating effects of dopamine and noradrenaline have recently been found to improve kidney graft survival on long-term follow-up [21]. Vasopressin, which is primarily used for the treatment of diabetes insipidus (see later), also has significant pressor effects. When used in doses varying from 1 to 2 U/hour, its use in brain-dead patients has been shown to produce circulatory stabilization, permitting weaning from alpha agonists, and without adverse effects on transplant organ function [22,23]. Until more studies are available, vasopressin should be used in patients who remain hemodynamically unstable despite therapy with fluids and conventional vasopressor agents. Higher blood pressure (>150 mmHg) too may compromise organ perfusion and should also be treated. The agent of choice is nitroprusside, which has a rapid onset and offset and is therefore easily titrated.
- *Maintenance of electrolyte levels*. It is important that sodium levels be monitored frequently and fluid therapy given accordingly; elevated sodium levels have been associated with higher rates of primary organ non-function after transplantation [11]. In the presence of serum sodium levels of >136 mEq/L, 0.45% saline and 5% dextrose water should be substituted for 0.9% saline. Fluids should be given in an amount equal to urinary output plus 50 ml in order to replace insensible losses. In many donors, high intravenous replacement rates may be required (sometimes exceeding 1,000 ml/hour) before diabetes insipidus can be brought under control. The need for large volumes of dextrose-

T3 = triiodothyronine

containing fluids may result in iatrogenic hyperglycemia. In the presence of persistent polyuria (>400 ml/hour) together with other evidence of diabetes insipidus, treatment with desmopressin acetate (Minirin®, Ferring) is needed to avoid volume depletion and further loss of electrolytes. Minirin is administered as an intravenous bolus in a dose of 4 μg and may be repeated every 2 hours as needed [24]. The goal of therapy is to achieve a urine output of about 100 ml/hour. Adequate potassium supplementation is important for maintaining normal cardiac contractility and rhythm.

- *Maintenance of renal function*. This depends largely on adequate perfusion of the kidneys. If urine flow remains <100 ml/hour despite a systolic blood pressure of 10–120 mmHg and central venous pressure of 8–12 cmH_2O, furosemide should be administered.
- *Control of bleeding*. In the presence of significant bleeding, which may further contribute to hemodynamic instability, replacement of clotting factors with fresh frozen plasma and platelet transfusions may be indicated. Goals of therapy include an INR < 1.5 and platelet count > 50,000 mm^3.
- *Maintenance of body temperature*. Body temperature should range between 36.0 and 38.0°C. Hypothermia should be aggressively prevented; significant decreases in body temperature may be corrected by the use of warming blankets, the warming of intravenous fluids, and raising the room temperature. Hyperthermia also requires treatment in the form of cooling blankets and alcohol sponging.
- *Ventilatory management*. The goal of therapy is a pO_2 of at least 100 mmHg with the lowest inspired oxygen content (FiO_2) possible. Treatable causes of hypoxemia, such as pulmonary congestion, pneumothorax, and atelectasis should be excluded. If peak end-expiratory pressure is required, it should not exceed 5–10 cmH_2O, as higher levels may cause hemodynamic instability by decreasing venous return. The pH should be kept within the normal range (about 7.4) by adjusting the minute ventilation on the ventilator. Hyperventilation, which is frequently used to reduce raised intracranial pressure *before* the stage of brain death, is unnecessary and should be avoided once brain death has occurred as it may result in significant hypokalemia, hypophosphatemia and intracellular activity.
- *Management of hyperglycemia*. Hyperglycemia (blood sugar level > 250 mg/dl) is common and is ideally managed with continuous infusions of insulin according to the blood sugar level. Sometimes very high doses of insulin (>20 U/hour) are required due to insulin resistance (a consequence of the stress response and use of catecholamines).
- *Eye care*. The eyes should be kept closed and moist with the use of normal saline drops or artificial tears.
- *Hormone replacement*. A more controversial aspect of treatment is the use of hormone replacement therapy, specifically cortisol

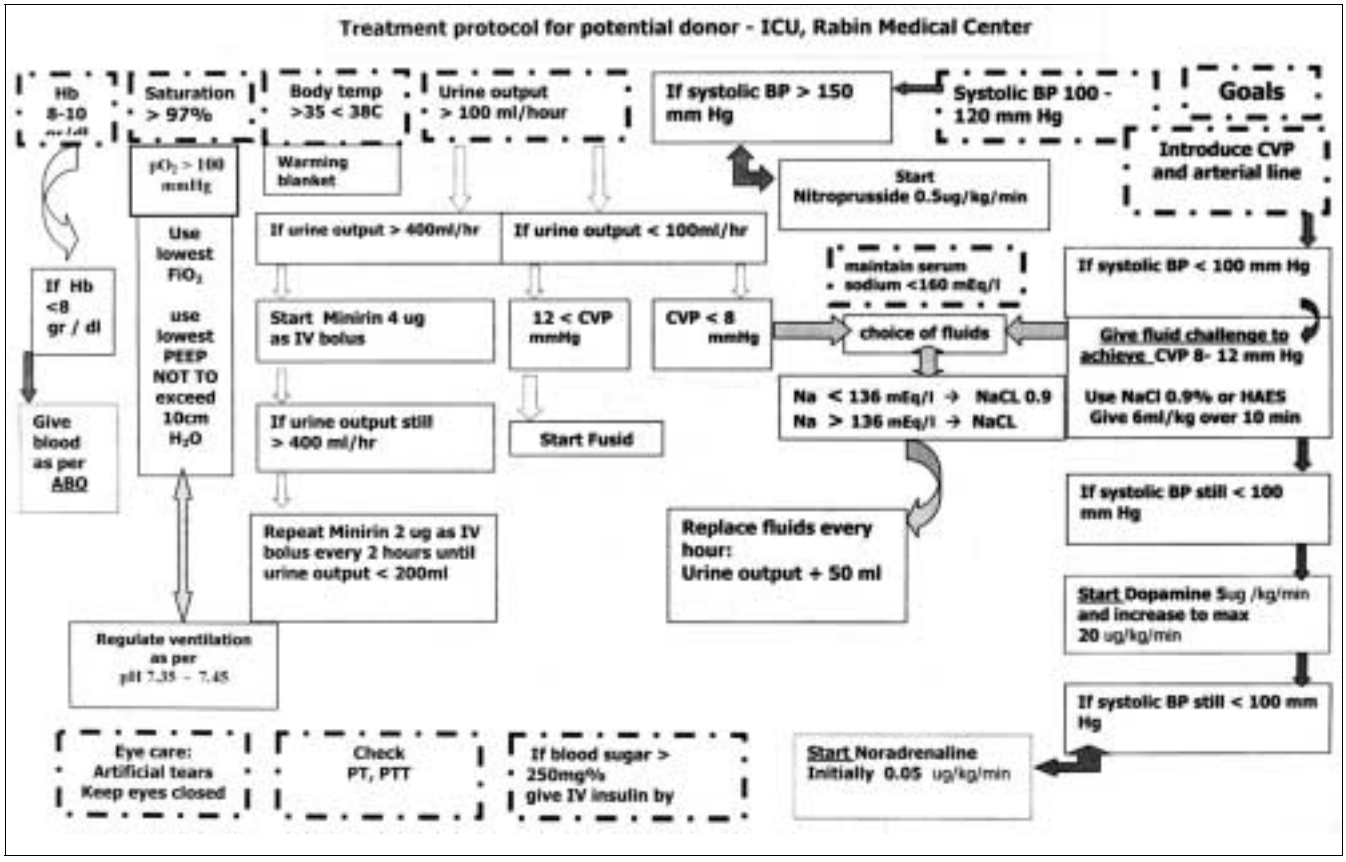

Figure 1. Treatment protocol for potential donor in the intensive care unit

and thyroid hormones. Experimental evidence suggests that the use of exogenous T3 may reverse the depressed myocardial contractility that occurs with excessive catecholamine exposure, such as after brain death [25]. Replacement therapy consisting of T3, cortisol and insulin has been shown to restore hemodynamic and biochemical abnormalities in brain-dead animals [26]. Limited studies in humans, especially with the use of T3, have led to a reduction in inotropic use in donors and possibly improved the quality of transplanted organs [27]. More studies are required before definite recommendations can be made for the routine use of hormone replacement.

A protocol aimed at simplifying the treatment of these complicated patients has been developed in our unit [Figure 1]. The flow chart is also available in Hebrew.

In addition to the management outlined above, the rapid determination of brain death is an important and positive factor in maintaining the quality of potentially transplantable organs. Conditions delaying the certification of brain death, such as significant hypothermia and hyperosmolality (usually due to hyperglycemia and hypernatremia) must be avoided.

In conclusion, the continuing shortage of donor organs demands that donor supply be maximized by optimizing donor management. In this regard, the importance of a well-trained and motivated staff cannot be overemphasized.

References

1. Novitzky D. Physiologic consequences of brain death. In: Klintmalm GR, Levy MF, eds. Organ Procurement and Preservation. Landes Bioscience 1999:31–46.
2. Shalin R, Sole MJ, Rahimifar M, Tator CH, Factor SM. Increased intracranial pressure elicits hypertension, increased sympathetic activity, electrocardiographic abnormalities and myocardial damage in rats. *J Am Coll Cardiol* 1988;12:727–36.
3. Novitzky D. Detrimental effects of brain death on the potential organ donor. *Transplant Proc* 1997;29:3770–2.
4. Pratschke J, Wilhelm MJ, Kusaka M, et al. Brain death and its influence on donor organ quality and outcome after transplantation. *Transplantation* 1999;67:343–8.
5. Novitzky D. Donor management: state of the art. *Transplant Proc* 1997;29:3773–5.
6. Novitzky D, Wilcomb WN, Rose AG, Cooper DKC, Reichart B. Pathophysiology of pulmonary edema following experimental brain death in the Chacma baboon. *Ann Thorac Surg* 1987;43:288–94.
7. Herinjgers P, Leunens V, Tjandra-Maga TB, Mubagwa K, Flaming W. Changes in organ perfusion after brain death in the rat and relation to circulating catecholamines. *Transplantation* 1996;62:330–5.
8. Pinelli G, Mertes PM, Carteaux JP, et al. Myocardial effects of experimental acute brain death: evaluation by hemodynamic and biological studies. *Ann Thorac Surg* 1995;60:1729–34.
9. Nagareda T, Kinoshita Y, Tanaka A, et al. Clinicopathology of kidneys from brain dead patients treated with vasopressin and epinephrine. *Kidney Int* 1993;43:1363–70.
10. Lin H, Okamato R, Yamamoto Y, et al. Hepatic tolerance to hypotension as assessed by changes in arterial ketone body ratio in the state of brain death. *Transplantation* 1989;47:444–8.
11. Gramm HJ, Zimmerman J, Meinhold H, Dennhardt R, Voigt K. Hemodynamic responses to noxious stimuli in brain dead organ donors. *Intensive Care Med* 1992;18:493–5.
12. Scheinkestel CD, Tuxen DV, Cooper DJ, Butts W. Medical management of the potential organ donor. *Anesth Intensive Care* 1995;23:51–9.
13. Blevins LS, Wand GS. Diabetes insipidus. *Crit Care Med* 1992;20:69–79.
14. Powers BM, van Heereden PV. The physiological changes associated with brain death: current concepts and implications for treatment of the brain dead organ donor. *Anesth Intensive Care* 1995;23:26–36.
15. Rivers EP, Buse SM, Bivens BA, Horst HM. Organs and tissue procurement in the acute care setting: principles and practice. Part 1. *Ann Emerg Med* 1990;19:78–85.
16. Broman M, Kallskog O. The effects of hypothermia on renal function and hemodynamics in the rat. *Acta Physiol Scand* 1995;153:179–84.
17. Cooper DKC, Novitzky D, Wicomb WN. The pathophysiological effects of brain death on potential donor organs, with particular reference to the heart. *Ann R Coll Surg Engl* 1989;71:261–6.
18. Harms J, Isemer FE, Kolenda H. Hormonal alteration and pituitary function during the course of brain-stem death in potential organ donors. *Transplantation* 1993;56:363–7.
19. Novitzky D, Cooper DKC, Reichart B. Hemodynamic and metabolic response to hormonal therapy in brain-dead potential organ donors. *Transplantation* 1987;43:852–4.
20. Deman A, Peeters P, Sennesael J. Hydroxyethyl starch does not impair immediate renal function in kidney transplant recipients: retrospective multicentre analysis. *Nephrol Dial Transplant* 1999;14:1517–20.
21. Schneulle P, Lorenz D, Mueller A, Trede M, van der Woude FJ. Donor catecholamine use reduces acute allograft rejection and improves graft survival after cadaveric renal transplantation. *Kidney Int* 1999;56:738–46.
22. Iwai A, Sakano T, Sugimoto H, Yoshioka T, Sugimoto T. Effects of vasopressin and catecholamines on the maintenance of brain-dead patients. *Transplantation* 1989;48:613–17.
23. Katz K, Lawler J, Wax J, O'Conner R, Nadkarni V. Vasopressin pressor effects in critically ill children during evaluation for brain death and organ recovery. *Resuscitation* 2000;47:33–40.
24. Guesde R, Barrou B, Leblanc I, et al. Administration of desmopressin in brain-dead donors and renal function in kidney recipients. *Lancet* 1998; 52:1178–81.
25. Timek T, Vahl CF, Bonz AB, Schaffer L, Rosenberg M, Hagl S. Triiodothyronine reverses depressed contractile performance after excessive catecholamine stimulation. *Ann Thorac Surg* 1998;66:1618–25.
26. Novitzky D, Wicomb WN, Cooper DKC, Tjaalyard MA. Improved cardiac function following hormonal therapy in brain dead pigs: relevance to organ donations. *Cryobiology* 1987;24:1–4.
27. Taniguchi S, Kitamura S, Kawachi K, Doi Y, Aoyama N. Effects of hormonal supplements on the maintenance of cardiac function in potential donor patients after cerebral death. *Eur J Cardiothorac Surg* 1992;6:96–101.

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A desire to take medicine is perhaps the great feature, which distinguishes man from other animals.

William Osler (1849–1919), Canadian physician considered the "father" of modern medicine, and the first author of ***Harrison's Principles of Internal Medicine***