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Care of the Multiple Organ Donor

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The precise care of the multiple organ donor can reverse the derangements resulting from previous disease and brain death, stabilise the donor and help to obtain more and better functioning organs.

Introduction

Several diseases (cerebral haemorrhage or infarction, meningitis) or conditions (head trauma) can lead to severe intracranial hypertension and global ischaemia and thus to brain death (BD). Once this has been certified, absolute / relative contraindications to organ donation must be excluded and /or considered. Having done this, if according to the local laws there is no obstacle for the donation, the process can start. It's time for the Transplant Coordinator to start work that will end not only with the extraction of the organs, but after the transplant to the recipients and the recovery of their function.

Once BD has been established, the potential donor must be actively monitored and treated, not just considered as a corpse that awaits the extraction process and left to spontaneous evolution. After hours or days of fight against the progressive deterioration primarily of the brain and other organs, care of the donor must focus on the support, protection and treatment of the deranged organs considered for transplant. This has been termed '"targeted donor treatment"'. Knowledge of the physiopathological changes that accompany BD is crucial in order to delay or fight effectively against them (Power and Van Heerden 1995). Some brain-dead potential donors will go into an irreversible cardiac arrest shortly after the acute process of BD, irrespective of the treatments started.

The cardiovascular and respiratory systems show the most severe changes, but endocrine or metabolic changes can also be detected. Their adequate management will be key to correcting and preserving organ function and viability (Valero 2002). The more time elapsed since BD the more intense the

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degree of instability of the donor (Mascia et al. 2009), so the duration of the process from BD until organ extraction is important in order to get more and better organs, (as shown by Venkateswaran et al. (2008) and Cantin et al. (2003), for lungs and hearts).

Several years ago, inadequate donor management resulted in the loss of a high number of potential donors, due to cardiovascular collapse before organ extraction. Donor management programmes can reduce this loss (Salim et al. 2006). Great efforts have been made in this field, resulting in standardised protocols and detailed algorithms that should be used universally (Valero 2002; Salim et al. 2006; Shemie et al. 2006; Rosendale et al. 2002; Jenkins et al. 1999; Lopez-Navidad et al. 1997; Wood 2006). In addition, the progressive specialisation of the doctors charged with the donor's care has improved the results in terms of organs extracted and their functionality (Wheeldon et al. 1995).

Several models of organisation, such as the Spanish Model (Matesanz 2008, Manyalich 2011) and Transplant Coordinators' training (see Transplant Procurement Management Courses [www.tpm.org]), have been used successfully for more than 25 years and can be considered cornerstones of this practice. Initiatives such as the European Transplant Coordinators Organisation's Certificate of European Transplant Coordination (CETC)/ETCO [www.etco.org]) are basic to accredit the knowledge, training and experience of transplant coordinators, providing certification for an internationally recognisable level of expertise.

The different attitudes and demands of the surgical groups involved in the process of organ extraction and transplantation can influence the work of doctors charged with the care of these patients. One group can perhaps request the avoidance of inotropes; while another can seem not to be concerned at all by them, or there can be opposite opinions regarding the fluid balance in the donor. But one thing must be always kept in mind: the primary goal of donor management is to improve organ function, overcoming the physiopathological derangements caused by brain death, and to obtain as many viable and well-functioning organs as possible. This a global view, not a single-organ focused view.

Cardiovascular Problems Monitoring

Apart from a continuous ECG and SpO2, invasive monitoring of the donor is mandatory. An indwelling arterial catheter is necessary to monitor closely arterial pressure, and to obtain repeated samples to determine blood gases and acid-/base status. Although central venous pressure (CVP) values are usually close to pulmonary capillary wedge pressure (PCWP), in cases of left ventricular dysfunction CVP may remain low despite high PCWP values (Powner and Crommett 2003). In cases of haemodynamic instability and cardiac dysfunction (ejection fraction < 45%), a pulmonary artery catheter will help to measure left ventricular filling pressure and cardiac output, to guide the administration of vasoactive drugs or to adjust the fluid balance (Wood et al. 2004.) When haemodynamic management is difficult (no response to usual measures, previous heart disease, etc.), other invasive cardiovascular monitoring systems, such as PICCO or Vigileo devices, and transthoracic or transoesophageal echocardiography can be useful (Gu et al. 2009).

Recently, monitoring of mixed venous oxygen saturation (aiming at SvO2 values between 60-80%) has been proposed in potential organ donor patients. It could detect early changes in the patient's condition, allowing earlier interventions. (Shemie et al. 2006) The monitoring of base excess and lactate levels has been shown to be efficacious to guide fluid administration and resuscitation (Dominguez-Roldan et al. 2005).

Haemodynamic Disturbances

Two phases can be differentiated during the process of brain death: the first characterised by a massive sympathetic discharge and the second by a severe reduction of sympathetic tone. The first one can be qualified as a 'storm', with an acute elevation of blood pressure (often to extreme values) and other acute and severe cardiovascular disturbances. This can be followed shortly after by a severe episode of hypotension (loss of vascular tone) and reduction of cardiac output due to a disturbance in the inotropic and chronotropic status of the heart (Avlonitis et al. 2005).

In the first phase (lasting from minutes to hours), the findings are arterial hypertension, bradycardia that later progresses to supraventricular tachycardia and/or ventricular extrasystoles, changes in the ECG (ST-segment elevation) and hyperthermia. This period can be really difficult to manage. Some studies advocate the short-term use of beta-blockers such as esmolol, which would mitigate this hypertensive and arrhythmogenic response during cerebral herniation. In another study, esmolol, administered before BD, helped to preserve myocardial function (McLean et al. 2007). In donors in this phase, the treatment of hypertension with esmolol and urapidil seems to increase the number of viable heart grafts (Audibert et al. 2006).

After this, there is a dysfunction (or destruction) of the vasomotor centre, and the release of catecholamines is reduced. Vasodilatation and reduction of the peripheral vascular resistance ensue (Wood et al. 2004). Previous restriction of fluids, plus a multifactorial polyuria (ADH deficiency, hyperglycaemia, use of mannitol, hypothermia), lead to progressive hypovolaemia and worsen the hypotension.

The derangement in cardiac function is multifactorial (hormonal deficiency involving free thyroxin, cortisol, arginine -vasopressin and insulin; increase in the anaerobic metabolism). The result is an alteration of inotropism and chronotropism, with a subsequent drop in cardiac output. Some authors (Salim et al. 2006, Shivalkar et al. 1993) have described some degree of cardiac ischaemia in nearly 30% of donors.

The goals of optimal haemodynamic management of the donor must be the maintenance of an adequate circulating volume, a normal cardiac output and a good perfusion pressure to achieve optimal oxygen supply to the tissues. An adequate perfusion pressure in the donor is crucial for the viability and function of the transplanted organs. Diverse experiences show that a systolic arterial pressure over 100 mmHg must be the objective. Although controversial as an effective measurement of the cardiac filling pressure there is an agreement to recommend a target value

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of CVP of between 10 and 15 cm H2O in the donor.

With adequate management, cardiac function can recover after several hours, as demonstrated by several works (Casartelli et al. 2012; Christmas et al. 2012).

Cardiac Arrhythmias and Conduction Disorders

These appear in 20-30% of donors. Sinus tachycardia is the most common, (20-50%), followed by sinus bradycardia (15%) and auricular fibrillation (10%) (Powner and Allison 2006).

Bradycardia appears often, usually as part of the Cushing phenomenon (hypertension and bradycardia). After BD, the nucleus ambiguous of the brain stem is destroyed and vagal tone is lost; therefore atropine will not be capable of reversing the bradycardia. Drugs with a direct chronotropic effect must be used instead. Isoproterenol (1-3 µg/min) is the most effective. Dopamine, dobutamine and epinephrine also have a positive chronotropic effect.

Other types of ventricular and auricular arrhythmias as well as conduction abnormalities are also seen. The usual causes are electrolyte imbalance, hypothermia and myocardial ischaemia, but also iatrogenic (infusions of inotropic drugs, etc.), or can be of a central origin. The aetiological treatment should be applied first and, if proven insufficient, antiarrhythmic drugs should be used, amiodarone being the first choice (Powner and Allison 2006). In cases of refractory ventricular arrhythmias, hypothermia should be considered the triggering factor, and fought against. Prolongation of the QT interval may trigger ventricular extrasystoles and "torsade de pointes"- type ventricular tachycardia. If so, all medications that may prolong the QT interval must be stopped, the electrolyte imbalances corrected, particularly hypokalaemia, and magnesium given intravenously at a dose of 2 g IV/10 min. Occasionally it can be necessary to implant a temporary pacemaker to prevent the relapse of the arrhythmia (Nolan et al. 2005). In this situation management of the donor can be extremely difficult, and can progress to an irreversible cardiac arrest, with the loss of the donor. In this case some teams are now able to preserve the organs using the perfusion techniques developed for "non-heart-beating donors", that have been described elsewhere (Valero 2002).

Replacement of Losses of Fluids and Electrolytes

The donor suffers important losses of free water and of electrolytes. Imbalances such as hypernatraemia, hypocalcaemia, hypomagnesaemia, hypokalaemia and hypophosphataemia are important for the development of cardiovascular problems, such as arrhythmias, myocardial dysfunction and sudden cardiac arrest (Wood et al. 2004).

Regarding hypovolaemia, the possible causes (frequent: ADH deficiency, osmotic diuresis, hyperglycaemia; rare: hyperthermia) and the water deficit must be adequately corrected. Hyponatraemia and hyperglycaemia can derive from an excessive administration of glucose-containing fluids. If sodium-rich solutions are used, mainly in patients with an increased osmolarity, hypernatraemia can develop, and its treatment is difficult. Hypernatraemia is a negative prognostic factor for the function of liver grafts (Cywinski et al. 2008).

Fluid replacement can be done with isotonic crystalloid (normal saline or Ringer's) and colloid solutions. The rate of infusion should be of 5 ml/kg every 5-10 minutes until a systolic BP over 100 mmHg or a CVP of 12 cm H2O is reached. Complications of volume replacement can be pulmonary oedema, cardiac overload or hepatic congestion. A state of normovolaemia must be attained before starting vasopressor drugs. Apart from the recent findings about colloid administration to critically ill patients (Annane et al. 2013), and taking into account that we are talking about a short-term use, third generation colloids do not seem to produce acute tubular necrosis in the recipient. That problem had been reported when larger volumes of first and second-generation colloids were used, and the glomerular filtration was impaired (Cittanova 1996). The renal effect of hydroxyethylstarch (HES) solutions remains controversial. In a retrospective and comparative study (HES 130/0.4 and HES 200/0.6), the administration of HES 130/0.4 resulted in lesser incidence of delayed graft function and lower serum levels of creatinine (Blasco et al. 2008). When using a crystalloid / colloid combination, the ratio should not be higher than 65% / 35%. However, to this point there is no evidence supporting the use of hydroxyethil starch in brain-dead or other critically ill patients (Gattas 2012).

Adequate oxygenation must be ensured by maintaining the levels of haematocrit above 30%, and of haemoglobin between 90 and 100 g/L (Zaroff et al. 2002).

Use of Inotropes and Vasopressor Drugs

Persistent hypotension after adequate volume replacement should be treated with inotropic drugs. Dopamine has been the most extensively used drug. Several studies (Schnuelle et al. 1999; 2001; 2001; 2004) suggest that the use of catecholamines in donors would reduce the rates of acute rejection and increase graft survival. The pre-treatment of donors with low doses of dopamine reduces the need for dialysis after kidney transplant without clinically significant impact on graft or patient survival (Schnuelle et al. 2009). High doses (>10 µg/Kg/minkg/min) must be avoided, because, due to its action on alpha-adrenergic receptors, it can induce a progressive renal and systemic vasoconstriction, the depletion of endogenous norepinephrine and of ATP reserves in the organs, and affect their function after implantation, especially in the case of the heart. Some authors do not share this view.

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Dobutamine would also be beneficial in patients with altered cardiac contractility, such as patients with low ejection fraction (EF) after BD or with a myocardial contusion.

If fluids, dopamine and dobutamine do not maintain blood pressure, then noradrenalin at a dose of between 3 and 20 µg/kg/min may be used. Noradrenalin at low doses is included in some protocols as the vasoactive drug of first choice, since in many ICUs it has replaced dopamine for that indication. A recent meta-analysis (De Backer 2012) in septic shock patients favours the use of noradrenalin, because dopamine was associated with greater mortality and higher incidence of arrhythmias. The use of drugs with a predominantly vasoconstrictor effect (ephedrine, methoxamine) should be avoided when possible. Where it is available, vasopressin has become the drug of first choice for the treatment of organ donors requiring vasoactive support. Several authors have described its successful use and the catecholamine-sparing effect (Kutsogiannis et al. 2006; Pennefather et al. 1995). Vasopressin has demonstrated a stabilising effect on systemic BP after brain death, and an effect in diabetes insipidus, which appears in 80% of brain dead donors (Venkateswaran et al. 2009).

When the appropriate BP cannot be attained, the previous treatments may be replaced by an infusion of adrenaline at low dose (0.1 µg/kg/min). Renal function must be carefully maintained, with a strict control of diuresis. Maintenance of an adequate perfusion pressure with the use of vasopressors and mannitol or furosemide has been used to protect the kidneys.

Respiratory Problems

Up to 15% of all donors show simultaneously an acute respiratory distress syndrome (ARDS) or an acute lung injury (ALI) (Mascia et al. 2006). After BD, especially in young individuals, a neurogenic pulmonary oedema may appear, due to the abrupt increase of circulating catecholamines. Several physiopathological mechanisms can be implied. The catecholamine storm produces an alteration of capillary permeability, together with haemodynamic changes that produce an increase in hydrostatic pressure and damages to the alveolar-capillary membrane. Also, the activation of inflammatory mediators by the cerebral and organic ischaemia and the endothelial activation will have profound effects on the pulmonary function (Avlonitis et al. 2003).

Ideally, arterial pO2 should be kept above 100 mmHg, with the lowest FiO2 possible and the lowest level of Positive End Expiratory Pressure (PEEP). The low CO2 production, due to the absence of cerebral blood flow, and to the loss of sympathetic activity and muscular tone, requires the use of minute volumes lower than those currently used with the aim of maintaining normocapnia. In lung donors it is extremely important to follow standardised protocols to optimise and maintain optimal lung function (Powner et al. 2000). The management of these patients should include: the use of low FiO2 to avoid pulmonary toxicity (less than 60%), the general use of PEEP (8-10 cm H2O) to reduce atelectasis, the avoidance of an excessive fluid overload with close monitoring of the values of central venous, pulmonary and pulmonary capillary wedge pressures, the adequate use of inotropic agents (and/or vasopressin), and preventive measures against respiratory infections. As in any critically ill patient, the close monitoring of respiratory function, the use of alveolar recruitment manoeuvres, the early and precise diagnosis of respiratory infections using flexible bronchoscopy (Riou et al. 1994), plus bronchoalveolar lavage or the protected-specimen brush technique, as well as the use of protective ventilation (6 to 8 mL/kKg of ideal body weight, and PEEP of 8 to 10 cm H2O), improve lung function in the donor and the number of potential organs for transplant (Mascia et al. 2010). A closed circuit should be used for tracheal suction. The apnoea test should be performed with the ventilator in continuous positive airway pressure (CPAP) mode, and recruitment manoeuvres are recommended after any disconnection from the ventilator. An aggressive protocol aimed at improving the obtention of lungs for transplant is not deleterious for other organs (Minambres et al. 2013).

The systemic inflammatory response and lung damage due to an inadequate mechanical ventilation setting (volutrauma and barotrauma) may exacerbate the organ damage due to inflammatory mediators (Mascia et al. 2006). Methylprednisolone at doses of 15 mg/kg has been demonstrated to improve the gas exchange and is an independent predictor of successful lung transplant (Follette et al. 1998).

Control of Temperature

This is another crucial point in the management of the organ donor. After BD, the hypothalamic control of temperature is lost, and the donor becomes poikilothermic. The loss of body heat leads to deterioration of the haemodynamic state by vasoconstriction and cardiac instability. Hypothermia also induces arrhythmias (general delay of conduction, inversion of T wave, QT lengthening, appearance of Osborn J wave [between 32-33ºC], atrial fibrillation, and ventricular fibrillation with temperatures lower than 30ºC), disorders of renal function due to the reduction of glomerular filtration and the incapacity to maintain tubular concentration gradients (cold diuresis), coagulation disorders and a left shift of the oxygen-haemoglobin dissociation curve with a reduction of free oxygen delivery to the tissues.

Treatment consists of heated intravenous solutions, the humidification and heating of respiratory gases, as well as the use of insulating or warming electric blankets to maintain the body temperature above 35ºC.

Endocrine Disorders

Diabetes Insipidus

Diabetes insipidus is common in BD, (occurring in 38% to 87% of cases (up to 98% in some series), and is due to a deficiency of anti-diuretic hormone (ADH). There is a loss of hypothalamic-pituitary control over ADH secretion and release, [in response to osmotic stimuli (sodium concentration) on the hypothalamic osmoreceptors and to other non osmotic stimuli from receptors of cardiac and pulmonary volume that are integrated in the hypothalamus]. A few hours after BD, plasma levels of vasopressin are not detectable (<0.1-0.5 pg/ml). This results in an uncontrolled increase in the production of hypotonic urine (diuresis >4 ml/kg/h; density <1005; plasma osmolarity >300 mmol/kg and urinary

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osmolarity <300 mmol/kg) and subsequent hypernatraemia, hypomagnesaemia, hypokalaemia, hypocalcaemia and hypophosphataemia. These losses should be treated with fluids and the adequate ionic supplements. When urine production exceeds 200-250 ml/h (3-4 ml/kg/h) ADH analogues should be administered.

At low doses (1-2 U/h; 2-10 mU/kg/min), vasopressin acts on the V2 receptors of renal cell membranes, increasing water reabsorption and reducing diuresis, while at higher doses it acts on the V1 receptors of blood vessels, producing arterial hypertension and vasoconstriction in the pulmonary, mesenteric, hepatic and coronary territories, and reducing renal flow without increasing its effect on diuresis. Its duration of action is close to 2-3 hours and should preferably be administered as continuous infusion. The recommended dose is 5-10 IU [units] of subcutaneous or intramuscular vasopressin sc or im every 2-4 hours or an infusion of 10 IU in 500 ml of saline at a rate of 50 ml/h.

Desmopressin (dDAVP, 1-deamino-8- D-arginine vasopressin), is a synthetic analogue of natural hormone (arginine vasopressin), and has a selective action on V2 receptors with a powerful anti-diuretic effect (anti-diuretic / pressor ratio = 2.000 to 3.000:1), so is the drug of choice. The latency time is 15 to 30 minutes and is more powerful and long acting (5-12 hours). It can be administered as an intravenous bolus of 0.03- 0.15 µg/kg/8-12 hours or 1-5 µg/8-12 hours. Subcutaneous or intramuscular administration should not be used due to the erratic drug absorption depending on the haemodynamic status and temperature. The use of desmopressin was not associated with better kidney graft outcomes in a recent meta-analysis (Rech 2013). Nevertheless, it is safe and useful to limit the harmful effects of profuse polyuria, decreasing the need to infuse large volumes and preventing haemodynamic collapse (Dictus 2009).

Other Endocrine Disorders

The consequences of BD on the anterior pituitary are not fully elucidated. Triiodothyronine levels are decreased, and do not respond to the exogenous administration of thyrotropin-releasing hormone (TRH). After BD, aerobic metabolism is gradually replaced by anaerobic metabolism, leading to progressive metabolic acidosis, increased lactate levels, and haemodynamic instability. The administration of T3 promotes a rapid increase of Ca++, ATP, glucose, and pyruvate levels, together with a reduction of the production of CO2 and the normalisation of lactate levels. Those findings would suggest the return to aerobic metabolism, the replenishment of cell energy reserves and an improvement in the myocardial function and the haemodynamic status of the donor (Garcia-Fages et al. 1993; Novitzky et al. 1988; 1990; 1991). Other authors suggest that the findings could correspond to a '"sick euthyroid syndrome"' and, in some cases, argue against the use of hormonal therapy in patients with severe brain damage. The previously described results have not been reproduced and T3 is not widely used. A recent meta-analysis did not find any benefit of triiodothyronine replacement on donor heart function (Macdonald 2012).

However, the use of hormone '"cocktails"' in donor management is gaining acceptance acceptance in some countries (Rosendale et al. 2003; Shemie et al. 2006). One paper described the use of triiodothyronine, arginine vasopressin, methylprednisolone and insulin as part of a general protocol of donor management, but with poor results (Rosendale 2002). Other authors recommend the use of hormone replacement therapy only in unstable donors requiring dopamine doses >10 µg/kg/min or with an ejection fraction lower than 45% (Wood 2004). Treatment with hydrocortisone or even fludrocortisones could result in better outcomes in terms of haemodynamic stability and reversal of relative adrenal insufficiency, but has not been widely used nor been the object of controlled trials (Rech 2013).

Hyperglycaemia

Common causes of hyperglycaemia are the high levels of adrenal hormones, the administration of glucose-containing solutions, treatment with glucocorticoids and catecholamines, hypothermia and changes in pancreatic microcirculation. This may lead to imbalances of fluid and electrolytes, such as metabolic acidosis, osmotic diuresis, dehydration and hypovolaemia. Therefore, these parameters should be strictly controlled, administering a continuous intravenous infusion of insulin if necessary. Donor hyperglycaemia seems to be associated with lower graft survival in pancreatic transplants, but cannot be considered a contraindication for organ donation, because pancreatic function is usually not affected. The dose of rapid-acting insulin should range between 0.5 and 7 IU/hour of rapid-acting insulin (Blasé-Ibanez et al. 2009).

Coagulation Disorders

Up to 55% of organ donors may show coagulation disorders, which may even constitute a state of disseminated intravascular coagulation (DIC) (Salim et al. 2006). The brain tissue releases fibrinolytic agents (thromboplastin, brain gangliosides) from ischaemic-necrotic foci, and these can probably be the initial cause of coagulopathy and its maintaining factor (Powner et al. 2000). Coagulopathy must be aggressively treated with plasma, factor concentrates or platelets in order to maintain coagulation parameters within normal limits. Donor coagulopathy is multifactorial, and previous treatments, such as warfarin, aspirin or non-steroidal anti-inflammatory drugs and hypothermia may contribute, and must be corrected.

Infectious Complications

Lung infection can be the result of the initial event, or appear as a complication of prolonged mechanical ventilation. Furthermore, there can be different injuries that may cause localised infections, and the treatment and monitoring devices may promote the entry of microorganisms to the body, and the development of sepsis. When necessary, antibiotic prophylaxis should be started, and in case of suspected infections, adequate treatment prescribed, supported by adequate cultures. The high incidence of pulmonary infections is one of the most important factors that preclude lung donation. Adequate antibiotic treatment (ideally according to the results of Gram staining and culture of tracheo-bronchial secretions, and protected brush samples (PBS) or bronchoalveolar lavage (BAL) specimens) is crucial to avoid the transmission of the infection to the recipient, and may facilitate the final success of the donation (after having demonstrated adequate treatment before the extraction process starts).

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Future Improvements

Future research must include fighting against inflammatory and coagulation pathways (avoiding its activation, modulating the response and inhibiting the end-organ damage). The possibility of prolonged care of the donor in order to increase the number of organs obtained after a period of careful management (establishing a balance between the desired improvement in the function of some and avoiding the progressive deterioration of others, including the possibility of loss of the donor), will be a field widely explored. In such cases, some aspects, perhaps neglected nowadays, such as adequate provision of nutrients (micro and macro) will also gain relevance. The indications for organ transplants have increased with time (undoubtedly due to the success of the actual programmes), but the availability of organs is still very low, even in the countries with the most successful programmes of organ donation such as Spain (that has determined the objective of 40 donors per million inhabitants in the near future) (Matesanz et al. 2009).

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