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ORGAN PROTECTIVE MANAGEMENT OF THE BRAIN-DEAD DONOR

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Abstract: The adequate management of brain dead donors on an Intensive Care Unit (ICU) is one of the major key points for a successful transplantation of harvested organs. In addition to an invasive monitoring like in any other ICU patient these patients needs a meticulous attention to their hemodynamic. The early administration of desmopressin to treat diabetes insipidus, a differentiated use of fluid resuscitation and a distinct catecholamine support are special features of an appropriate basic treatment. The administration of corticoids has to be considered if a sufficient circulation can not be regained.

Key words: Brain death, intensive care of organ donors, vasopressin, hemodynamic

INTRODUCTION

The maintenance of an appropriate intensive care treatment, after a proofed brain death, has a significant impact on graft function after transplantation. By an optimal management of the potential donor both, the number and quality of harvested organs can be improved. It could be shown that these organs have a better primary function after transplantation resulting in a faster recovery of the recipients [3, 8].

Fortunately traumatic brain injuries due to accidents are continuously declining. Thus, the number of healthy organ donors, without any comorbidities is decreasing. In spite of that the total number of harvested organ has remained nearly the same, due to the acceptance of organs of older donors [17, 52].

At the same time the number of harvested organs per donor has also increased. A careful monitoring and aggressive intensive care treatment is necessary due to the acceptance of older donors with also probable more comorbidities. A couple of possible complications during the stay on an intensive care unit (ICU) are listed in Table 1 (modified to [1]). The goal of the ICU therapy is to provide the possibility of organ donation. ICU treatment directed towards organ protection has to recognize the pathophysiologic sequels of the brain death.

The main target of this treatment is the maintenance of an optimal organ perfusion and oxygenation.

PATHOPHYSIOLOGIC DISORDER AFTER BRAIN DEAD

The initial phase after brain death is characterized by a central neurohumoral disorder. Proinflammatory mediators are released very early. The activation of PMN granulocytes is accompanied by a release of proteases and an oxygen burst with a local cell injury [34].

Additionally a couple of cardiopulmonary changes are observed: The lungs are at risk for alveolar haemorrhage and capillary leakage with consecutive lung edema [38]. In animal trials an extended rise of endogenous catecholamines could be demonstrated [4]. The serum concentration of epinephrine and norepi-

Table 1. Complication in brain dead (modified to (1))

Hypotension	72 %
Diabetes insipidus centralis	79 %
Electrolyte disorder	75 %
Arrhythmia	65 %
Hypothermia	50 %
Pulmonary complication	39%
Coagulation disorder	5 %

Table 2. Target values of the donor. (modified due to [52])

1. MAP: 70 – 90 mmHg
2. CVP 10 – 12 mmHg
3. urine output 1- 2 ml/kg/h
4. paO_2 > 80 mmHg or SaO_2 > 95 %
5. regular Electrolyte – and acid/base balance
6. Hämatocrit 20 – 30 %
7. Blood sugar 100 - 150 mg/dl

Abbreviation:
MAP: mean arterial pressure
CVP: central venous pressure
paO_2: oxygen partial pressure
SaO_2: arterial oxygen saturation

nephrine increased nearly to 20'Th fold. The increased oxygen consumption is mainly caused by the increased myocardial contractility accompanied by a reduced coronary blood flow resulting in local myocardial necrosis [18, 24]. In an experimental setting these damages of the heart could be prevented by a pharmacologic α and β blockade [49].

The second phase, shortly after the initial one, shows the characteristics of a systemic inflammatory response syndrome (SIRS) with an imbalance of proinflammatory mediators (IL 1, IL 6, TNFα) and anti-inflammatory mediators (IL 10). Additionally, there is a complete loss of the central sympatho-adrenerg control. There is a peripheral vasoplegie and a declining of cardiac output (CO) and mean arterial pressure (MAP) with a consecutive reduced organ perfusion [36].

The pathophysiologic changes in the initial phase of brain death, which last about 60 minutes, have no therapeutic consequences for the donor. In contrast in phase two the effects of the SIRS determine the treatment of a brain dead donor.

Hormone Deficiency

Brain death leads to a decline of the serum concentration of hormones produced or stored in the pituitary gland, like oxytocine, vasopressin (ADH), thyreoidea stimulating hormone (TSH), adrenocoticotropic hormone (ACTH). As a consequence of this decrease the concentration of those hormones, which are produced in the target organs, e.g.cortisol, aldosterone and thyroxine reduced, too [28, 29].

ADH Deficiency

One of the main key topics for the ICU treatment in brain dead donors is the loss of the hypothalamic-pituitary hormone release. As a result of ADH deficiency a central diabetes insipidus occurs [40]. Due to ADH shortage there is a lack of water resorption in the collecting tubes of the kidneys. The patients have an excessive urine output. The urine has a low densitiy (< 1005 g/l) and the donors suffer from a hypertonic dehydration with a high serum sodium [42]. A prolonged high serum sodium concentration (> 155 mmol/l) damages the hepatocytes with an increased rate of primary non function after transplantation.

If the urine output exceeds 5 ml/kg/h (about 500 ml/h) the use of Desmopressin (Minirin™) is indicated. Most times a pulse dose between 0.5 – 2 μg intravenous (i.v.) effectively reduces the urine output.

If this management fails to restore the polyuria a continuous application of vasopressin (40 – 70 μU/kg/h) is necessary [22]. At a dose rate up to 70 μU/kg/h vasopressin only provides anti diuretic effects. At dose rates higher than 70 μU/kg/h an additional vasoconstrictive effect of vasopressin is observed [22]. A persistent hypernatremia has to be corrected by infusions of glucose 5%.

Thyroid Hormone Deficiency

The potential organ donor suffers from Euthyroid Sick Syndrome (ESS), like many other ICU patients. The characteristics of ESS shows a low Triiodthyronine (T_3) level, normal or low thyroxine (T_4), increased reverse T_3 level and a variable TSH level.

Some authors point out that a low T_3 level is responsible for the impaired myocardial cell metabolism and finally for the impaired myocardial contractility [16].

In some studies [4, 8] the use of i.v. T_3 is recommended. The authors suggest administration of 2- 4 μg i.v. till an effect is observed, then to start a continuous infusion with 2 μg/h till the end of organ harvesting [35, 37]. In some other studies [28, 39] the use of T_3 could improve the cardiac function. In face of the simultaneous use of vasopressin, cortisol and insulin this effect can not clearly be attributed to T_3 application only.

In 2 other studies [20, 21] the only use of T_3 could improve the mean arterial pressure. In opposite to this study another clinical trial [45] showed that the use of T_3 deteriorated the hemodynamic situation and led to acidosis.

In a prospective randomized trial (PRT) Goarin et al. [16] analyzed the impact of T_3 (0.2 μg/kg/h) on the hemodynamics. An improved cardiac function could not be confirmed with a trans-esophageal echocardiography. The conclusion of this study was that ESS is not the main cause for the impaired myocardial contractility. Besides this lacking effect on hemodynamic of T_3 there are evidences that the use of T_3 leads to intractable hypertension [27].

From this point of view the only application of thyroid hormones cannot be recommended.

Cortisol Deficiency

After breakdown of the hypothalamic-pituitary-adrenergic axis cortisol deficiency occurs in a time dependent fashion.

A brain death associated with SIRS, with a cardiovascular failure can be prevented by early use of corticoids. The side of action is listed below:

1. Suppression of the inflammatory response [6].
2. Improvement of the Horovitz index (paO_2/FiO_2) due to reduction of cytokine induced cell damage of the lung [12].

In septic patients the use of hydrocortisone reduces significantly the need of vasopressor support [5], and decreases the incidence of organ failure [6]. Briegel recommended as dose for hydrocortisone, first a pulsed dose of 100 mg, followed by a continuous infusion of 240 mg/die.

In a prospective randomized trial the use of high dose steroids (e.g. 100 mg Methylprednisolone) could significantly improve the Horovitz index and could increase the number of transplanted lungs (31% vs 8%) [13]. This fact is supported by Meduri et al [31], who could show a benefit of methylprednisolone on the outcome of patients with ARDS.

For an improved hemodynamic and an enhancement in organ quality a complete hormone substitution is recommended [46, 47].

Rosendale recommended the replacement of:

1. Methylprednisolone: 15 mg/kg
2. Triiodthyronine: 4 μg as pulsed dose followed by continuous infusion of 3 μg/h
3. Vasopressin: 1 U as bolus, then continuous infusion 0.5 – 4 U/h
4. Insulin: adjusted to blood glucose 100 – 150 mg/dl

Actually there is an evidence based recommendation only for cortisol and vasopressin, whereas for insulin and triiodthyronine further evaluation is warranted.

Hemodynamic

The maintenance of stable hemodynamic seems to be one of the major challenges in potential donors. The target MAP should be maintained, like any other ICU patient, above 70 mmHg [30].

The monitoring for a potential donor has to be the same like for any other ICU patient. This includes measurement of temperature, urinary output, the use of an arterial line, central venous line and large bore peripheral venous access. If this is not feasible, a 12 Fr Shaldon or 8.5 Fr Introducer should be placed in a central vein for a rapid volume replacement. Donors with advanced age or impaired myocardial contractility need a pulmonary arterial catheter (PAK) or a Pulse Contour Cardiac Output System (PiCCO-System) [56].

In addition brain dead donors are at risk for a sustained and intractable hypotension. The reasons for that are listed below:

1. Relative hypovolemia due to impaired sympathetic nervous system and vasodilation like in septic patients [25].
2. Volume deficit due to
   a. Diuretic therapy for brain edema therapy [43]
   b. Untreated diabetes insipidus and osmotic diuresis because of hyperglycemia [44]
3. Activating of mediator systems [56]
4. Cortisol deficiency [7, 43, 44, 53, 56].

Drug of first choice is volume. Fluid resuscitation can be done with crystalloids or with colloids. Crystalloids remain only to 25% intravascular in comparison with colloids which remain nearly to 100% intravascular. As a result of this a 4'Th fold volume of crystalloids in comparison to colloids has to be infused to reach the same volume effect [51].

For the maintaining of optimal oxygen providing, beside the cardiac output, the red blood count is essential. Which hematocrit would be the best for organ donors has not been investigated till now. But in recent years a restrictive transfusion regime has been established in ICU patients. Hebert et al. [19] could show that ICU patients with a restrictive transfusion protocol (transfusion trigger for Hb < 7 g/dl) in comparison with a liberal protocol (transfusion trigger Hb < 10 g/dl) had a significant lower mortality. Since a potential donor has to be regarded similar like an ICU patient this restrictive protocol could be assigned to brain dead donors, too.

The volume expansion has to be adjusted to CVP. Values of 10 -12 mmHg have to be reached. The use of a Swan-Ganz Catheter with a target pulmonary capillary wedge pressure (PCWP) of 15 mmHg allows best control of fluid management.

If an adequate volume replacement fails to restore the MAP to 70 mmHg a vasoconstrictor is indicated. In some recent studies norepinephrine could be proofed to overcome the vasodilatation caused by the non-functioning sympathetic nervous system [44, 56].

Acid-base, Fluids, and Electrolytes

Disorders in acid-base and electrolytes are common in brain dead patients [36, 56].

With an early and aggressive therapy of diabetes insipidus (administration of vasopressin, if urine output exceeds 7 ml/kg/h and early fluid resuscitation) a hypernatremia has to be avoided. Sustained (> 24 h) serum sodium concentration above 155 mmol/l is one of the major causes of primary non function (PNF) of transplanted livers [10]. A hypernatremia can be reversed with glucose 5 % infusion. A rapid declining of sodium concentration may produce an organ edema. For this reason a drop of sodium concentration must not exceed 5 mmol/h.

Hypokaliemia due to diabetes insipidus can produce malignant dysrhythmia, especially in older donors or in donors with coronary heart disease.

However it still has to be proven if an euglycemia (90 – 110 mg/dl) has the same benefit for quality of transplanted organs like for ICU patients, where a recent study could reduce the mortality, the morbidity, the infection rate as well as the critical illness neuropathy [54].

Ventilation

Only a small number of donors is recognized as lung donors (about 20%) [26, 55]. Some recent reports showed a silent aspiration soon after an acute brain injury [9, 11].

Clinical practice shows that this event is associated with a lower rate of acceptance. However, from medical point of view this activity is not always correct [9, 11].

The lung function (Horovitz index) with respect to ventilation mode, Chest X-ray or better CT scan of the chest in combination a with bronchoscopy is much more crucial for a possible transplantation.

In recent years lung protective ventilation with low tidal volume and permissive hypercapnia has been established in patients with ARDS. In a prospective randomized study Amato et al. [2] showed a significant reduction of mortality with the use of protective ventilation mode and permissive hypercapnia. A follow up ARDS Network study [33] examined the impact of low tidal volume (6 ml/kg) in comparison to high tidal volume (12 ml/kg). In conclusion ARDS patients have to be ventilated with small tidal volumes, high PEEP and use of permissive hypercapnia.

Unfortunately for possible lung donors there is a lack of such data. But we have to maintain the paO_2 > 100 mmHg or SaO_2 > 95%. If a ventilation mode with PEEP 5 mbar, does not provide this target values, PEEP has to be increase first (10 -15 mbar). Increased inspired oxygen has to be avoid, because of possible atelectasis.

In a couple of uncontrolled trials the improvement of prone position on ventilation/perfusion ratio and improvement of oxygenation could be proved [41, 50].

In a prospective clinical trial [15], which included 304 patients, an improvement of oxygenation was shown, but the 10 day mortality was the same. In organ donors comparable data are deficient.

In conclusion prone position is only indicated in severe damaged lungs. But these organs will not be transplanted. There is no evidence for prone position to improve the quality for possible transplanted lungs.

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Temperature Deregulation

The brain dead patient will get poikilothermal. The daily temperature oscillation is abolished. Most times there is a risk for hypothermia, which has some deleterious side effects:

Cardiovascular and Hemodynamic Effects

The risk of arrhythmias during mild or moderate hypothermia is very low. The incidence rises when the temperature drops below 30 °C. The initial arrhythmia is usually atrial fibrillation.

Initially, the induction of mild hypothermia increases myocardial oxygen demand relative to support; the mechanism is probably a hypothermia-induced increase in plasma levels of adrenaline and noradrenaline leading to an increase in cardiac output and oxygen demand [14].

Coagulation

Hypothermia induces bleeding diathetesis, with an increased bleeding time due to its effect on platelet count [32], platelet function [32] and the kinetics of clotting enzymes and plasminogen activator inhibitors [32].

Colonisation

Evidence from clinical studies and in vitro studies show that hypothermia can impair immune function. Hypothermia inhibits the release of various pro-inflammatory cytokines [23] and suppresses chemotactic migration of leukocytes and phagocytosis [48]. Furthermore hypothermia-induced insulin resistance and hyperglycemia may further increase the risk of colonisation [54].

This is a plausible mechanism for an immunosuppressive effect of hypothermia.

In conclusion one of main topics in brain dead donors is to avoid heat loss and to keep the body temperature at 37 °C. This can be reached with active warming systems (e.g. Bair-hugger™) and the use of warming systems for infusions.

Summary

Currently, extending the boundaries of marginal donor acceptability offers the best chance of dealing with donor shortage. However, this requires an optimal ICU management of the brain dead donor.

The challenge will be an early aggressive hemodynamic management and hormonal resuscitation.

Central venous pressure (CVP) or PCWP- guided (up to CVP 10 – 12 mmHg or PCWP 15 mmHg) volume replacement and if needed in combination with vasopressors like noradrenaline is recommended. The target MAP has to be above 70 mmHg.

Early administration of vasopressin (if urine output exceeds 7 ml/kg/h) to avoid hypovolemia should be strictly done.

If volume replacement and vasopressors fail to restore the MAP above 70 mmHg, hydrocortisone infusion (pulsed dose 100 mg, than 10 mg/h) should be started.

If the intensivist is able to provide these issues, he will have a major impact on graft quality and thus on successful transplantation.

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