REVIEW ARTICLE

Organ-Protective Intensive Care in Organ Donors

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SUMMARY

Background: The ascertainment of brain death (the irreversible, total loss of brain function) gives the physician the opportunity to limit or stop further treatment. Alternatively, if the brain-dead individual is an organ donor, the mode of treatment can be changed from patient-centered to donation-centered. Consensus-derived recommendations for the organ-protective treatment of brain-dead organ donors are not yet available in Germany.

Methods: This review is based on pertinent publications retrieved by a selective search in PubMed, and on the authors' clinical experience.

Results: Brain death causes major pathophysiological changes, including an increase in catecholamine levels and a sudden drop in the concentration of multiple hormones, among them antidiuretic hormone, cortisol, insulin, and triiodothyronine. These changes affect the function of all organ systems, as well as the hemodynamic state and the regulation of body temperature. The use of standardized donor management protocols might well increase the rate of transplanted organs per donor and improve the quality of the transplanted organs. In addition, the administration of methylprednisolone, desmopressin, and vasopressin could be a useful supplement to treatment in some cases. Randomized controlled trials have not yet demonstrated either improved organ function or prolonged survival of the transplant recipients.

Conclusion: The evidence base for organ-protective intensive care is weak; most of the available evidence is on the level of expert opinion. There is good reason to believe, however, that the continuation of intensive care, in the sense of early donor management, can make organ transplantation more successful both by increasing the number of transplantable organs and by improving organ quality.

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The German Medical Association has adopted the rules for ascertaining death according to § 3 section 1 p 1 No. 2 TPG (German Transplant Act) including the procedural rules for ascertaining the final, irreversible loss of the overall function of the cerebrum, cerebellum, and brain stem according to § 3 section 2 p 1 No. 2 TPG last year in the act's fourth update (1). The German Ethics Council has confirmed that ascertaining the irreversible, total loss of cerebral functioning (brain death) is one of the prerequisites for organ harvesting for the purposes of organ transplantation (2). This makes it possible to minimize intensive medical treatment or, in case of organ donation, to adapt intensive care of the dead patient with a view to the optimal functioning of the organs that are due for donation. For the latter, no consented recommendations exist in Germany to date. Such so called organ-protective intensive care is of crucial importance in the organ donation process, however. Brain death leads to serious pathophysiological changes and is followed by the loss of multiple organ functions. The inflammatory syndrome leads to the release of catecholamines and the sudden drop in concentrations of cortisol, insulin, and triiodothyronine (T3), as well as thyroxine (T4) (3–6). Hypothalamic and pituitary failure contributes to hemodynamic and metabolic instability. The lost secretion of antidiuretic hormone (ADH) is of particular significance in this setting (7, 8). Strict organ-protective intensive care in the organ donor is therefore the first step towards the successful treatment of the future organ recipient. Functional damage and loss in the organs designated for transplantation need to be avoided. The aim is to ensure optimal organ functioning at the time of harvesting. The number of transplanted organs per organ donor may be increased and the quality of transplant function improved by means of organ-protective intensive care (9–13). Even though data on this topic are scarce, this article aims to provide suggestions on how to proceed in terms of pharmacology. We make recommendations on how to provide organ-protective intensive care in organ donors. The article is based on selective literature searches, the authors' own experience, and interdisciplinary exchanges of experiences (*Table 1, eTable*).

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TABLE 1

Randomized controlled trials investigating donor therapy

Author, year (source)	Method	Number	Intervention	Control	Results	Organ function after Tx	Patient survival
Venkateswaran et al. 2009 (6, e11)	Prospective, randomized, double blind	N = 80	Triiodothyronine, methylprednisolone	Placebo	Hemodynamic parameters: no effect	HTx: no effect	Survival reported only for the entire group
Schnuelle et al. 2009 (26)	Prospective, randomized, multicenter	N = 264	Dopamine	Standard care	KTx patient dialysis post Tx: 24.7% versus 35.4%	KTx: transplant survival after 12, 24, 36 months: no effect	Survival after 12, 24, 36 months: no effect
Benck et al. 2011 (30)	Prospective, randomized, multicenter (subgroup post-hoc analysis)	N = 93	Dopamine	Standard care	HTx patient hemofiltration post Tx: 21.7% versus 40.4%	Not reported	Survival after 12, 24, 36 months: significant effect
Al-Khafaji et al. 2015 (24)	Prospective, randomized, multicenter	N = 556	Volume therapy according to protocol	Standard care	Transplanted organs per donor: no effect	Not reported	Survival after 12 months: no effect
Mascia et al. 2010 (e24)	Prospective, randomized, multicenter	N = 118	Protective lung ventilation	Standard care	LTx: 54% versus 27%	Not reported	Survival after 6 months: no effect

Tx, transplantation; LTx, lung transplantation; KTx, kidney transplantation; HTx, heart transplantation

Pathophysiological changes in irreversible, total loss of brain function

Clinical studies have shown that in irreversible loss of brain function or during its development, the central sympathoadrenergic regulation of the circulation and pituitary temperature regulation are disrupted; the hypothalamic–pituitary adrenocortical regulation is interrupted (14). The rising intracranial pressure leads to a massive release of pro-inflammatory and anti-inflammatory cytokines and catecholamines (15).

Serum concentrations of interleukin 1 and 6 (IL-1, IL-6), tumor necrosis factor α (TNF- α), C-reactive protein (CRP), and procalcitonin (PCT) are strongly raised (6, 16). Plasma concentrations of noradrenalin and adrenalin may increase enormously due to the elevated intracranial pressure but then drop as a result of irreversible loss of brain function (17).

This loss of central regulatory mechanisms leads to massive pathophysiological changes in hemodynamics, hormone balance, body temperature, and lung function (18–21) (Table 2).

Cardiovascular changes

The loss of sympathoadrenergic vascular regulation will result in hypotension and relative hypovolemia if untreated (18–20, 22, e1). Organ-protective therapy therefore aims to restore sufficiently high mean arterial pressure and normovolemia, with the aim of maintaining organ perfusion.

Differentiated volume substitution with close monitoring of hemodynamic parameters is the first step in circulation-stabilizing therapy (9, 18–20, 23). In order to correct the intravascular volume depletion, full elec-

TABLE 2

Frequency of pathophysiological changes in irreversible loss of brain function

	Cause	Frequency
Hypothermia	Hypothalamic dysfunction, vasoplegia	100%
Hypotension	Vasoplegia, hypovolemia, myocardial dysfunction	80–97%
Diabetes insipidus	Hypothalamic/pituitary dysfunction	65–90%
Arrhythmias	Catecholamine release, myocardial injury	25–32%
Pulmonary edema	Injury to vascular endothelium	15–20%
Cardiac arrest	Prolonged hypotension, arrhythmia	5–10%

trolyte solutions are recommended, but insufficient data exist in terms of drawing any recommendations from this (24). A recent article described how the administration of hydroxyethyl starch (HAES) as an additional volume expander resulted in an increase in late organ dysfunction in recipients of kidney transplants (25).

If volume therapy using crystalloids is not sufficient for ensuring the perfusion of individual organs, inotropes and/or vasopressor agents should be administered (23).

Very few, mostly retrospective, studies exist on the selection of catecholamines in organ-protective intensive care (26–31). In Germany, norepinephrine is most often used. With a view to the target parameters, it

BOX 1

Treatment of diabetes insipidus

- Desmopressin as bolus injection 1–4 µg i. v.
- Alternatively, desmopressin continuously 0.5–2 µg i. v.
- Alternatively, vasopressin continuously 0.05–0.5 U/h i. v.
- Administration of fluids low in sodium;
Target: sodium level ≤ 150 mmol/L
- Close monitoring of blood glucose;
Target: blood glucose level 6–10 mmol/L
- In blood glucose level ≥ 10 mmol/L continuous administration of insulin i. v.

BOX 2

Intensified management of respiratory function

- Volume controlled, pressure regulated ventilation
- Tidal volume 6–8 mL per kg calculated body weight
- Plateau pressure <30 cm H₂O (alternatively, if not available in the ventilator: peak pressure <35 cm H₂O)
- PEEP 8–10 cm H₂O, if lung function is impaired, up to 15 cm H₂O
- Minimal FiO₂ for a saturation of at least 92–95%
- Regular recruitment measures
- Regular bronchial hygiene, bronchoscopies if required
- Patient positioning protocol to prevent extended periods of lying in a supine position (less than 30° upper body elevation)
- Disinfection of the hands preceding measures on the respiratory tract
- Oral care and oral decontamination
- Avoidance of oral aspiration, for example by using cuff pressure measuring, subglottic secretion drainage

From (e14); PEEP, positive end-expiratory pressure

should be used at low dosages. In the Anglo-American arena, vasopressin is often used, rather than norepinephrine. The recommended dose is 0.5–4 U/h (27–29, e2). In a retrospective study, the rates of transplanted organs per donor and of transplanted lungs were increased (29).

If the cardiac output is lowered, dobutamine can be given additionally. A prospective, randomized, double blind study found indications that dopamine at low

dosages improves renal function after kidney or heart transplantation, but not transplant survival or mortality after kidney transplantation (26, 30). A subsequent subgroup analysis of patients with heart transplants did, however, show lower mortality after heart transplantation (30). This post hoc analysis does, however, not provide a basis for clear recommendations.

Hypotension and hypodynamic circulatory states should be treated by using differentiated volume and circulation management (18, 31, e1, e2). In case of doubt, extended hemodynamic monitoring may be helpful. Exact benchmarks can, however, not be given on a clinical-scientific basis. However, it may be assumed that excessive doses of catecholamines are not promising, because, among others, they can negatively affect capillary perfusion and oxygen consumption.

The release of proinflammatory enzymes shortly after the irreversible loss of brain function is associated with left-ventricular cardiac dysfunction (32). This also affects young organ donors with healthy hearts. Serial echocardiography, combined with intensified volume and catecholamine treatment, can increase the rate of transplantable hearts (33).

The critical hematocrit value for organ-protective intensive care has not been studied to a satisfactory degree (20). The indication for administering platelet concentrates to improve oxygen transport capacity has to be weighed up individually. For critically ill patients, the rule applies that a restrictive transfusion regimen is more likely to lead to success (34, 35). The side effects of transfusions also have to be considered in terms of the potential recipient. The transfusion of platelet concentrates should be guided by the cross-sectional guidelines for the therapy with blood components and plasma derivatives (36). This also applies for the substitution of fresh frozen plasma, clotting factors, and thrombocyte concentrates.

Endocrine changes

In 65–90% of brain dead patients, the neurohypophysis will be damaged owing to a lack of antidiuretic hormone (19, 20). Subsequently, polyuria will develop, as will hypovolemia and hypernatremia (hypertonic dehydration), followed by hypokalemia in some patients.

Diabetes insipidus (*Box 1*) is treated by fractionated administration of desmopressin 0.5–4 µg intravenously (i.v.) or by continuous administration of 0.5–2 µg i.v. and administration of crystalloid solutions. Vasopressin (0.05–0.5 U/h) can be given as an alternative to desmopressin (18, 22). In hypernatremia, 5% glucose solution should be preferred. Although hypertonic dehydration is the most common cause of hypernatremia in this setting, other causes will need to be ruled out. When administering glucose solution, the blood glucose concentration has to be closely monitored because of the risk of hyperglycemia with subsequent osmotic diuresis. The administration of desmopressin in combination with dopamine in organ donors improves organ function in recipients of kidney transplants (37).

In a prospective randomized study, the upregulation of proinflammatory cytokines in the liver as a result of irreversible loss of brain function was reduced significantly by applying methylprednisolone; the same was observed for the rate of acute rejections of the liver transplant (38). A dosage of 250 mg methylprednisolone given as a bolus injection, followed by 100 mg/h continuously, is an often recommended scheme (18, 20, 39, 40).

Furthermore, serum concentrations of triiodothyronine (T3) often fall in this setting. A lowering of serum concentrations of thyroxine (T4), thyroid-stimulating hormone (TSH), cortisol, and insulin is less commonly observed (e3, e4). For example, the synthesis of insulin is initially downregulated but normalizes spontaneously over time (e5). Blood glucose measurements are therefore tolerated at a generous level of <10 mmol/L (e6).

The guidelines of the United Network for Organ Sharing (UNOS) recommend the application of triiodothyronine, methylprednisolone, and vasopressin for potential heart or lung donors (e7). Several larger retrospective studies showed an increased rate of transplanted organs per donor and improvements in the organ function of the transplanted heart compared with a historical control group (e8–e10). The few prospective studies did not show this effect (e11–e14). The substitution of triiodothyronine and/or thyroxine is therefore not generally recommended (e15).

Temperature dysregulation

After irreversible loss of brain function, loss of central temperature regulation follows as a rule (e1). Furthermore, vasoplegia results in a loss of body heat. The result is hypothermia, which, if pronounced, can additionally trigger disrupted intravascular clotting and organ failure (e16). Myocardial contractility decreases and the heart becomes increasingly prone to arrhythmias (e17, e18). The therapeutic aim is therefore to maintain a body temperature of >35°C. Initial measures are avoiding passive heat loss by covering the body with foil insulation blankets, using convection hot air devices, and by warming up the solutions that are to be infused. The discussion about which body temperature is best for which organ transplantation has recently been revived by Niemann et al, who reported that mild hypothermia in the organ donor (34–35 °C) lead to improved rates of functioning in patients after kidney transplant surgery compared with normothermia (36.5–37.5 °C (e19). However, the literature is full of contradictory data, and to date no consensus is possible on hypothermia as a therapeutic goal (e20, e21).

Changes in lung function

The increase in intracranial pressure subsequent to irreversible brain function loss can lead to neurogenically induced lung injury as a result of the release of proinflammatory cytokines. Additionally, the consequences of mechanical ventilation, aspiration, atelectasis and infiltrations, infections, trauma, and previous

BOX 3

Basic monitoring

- ECG
- Invasive arterial pressure measurements
- Central venous saturation (CVP measurement)
- Hourly balancing of intake and output
- Sodium, potassium, hematocrit, blood glucose, arterial blood gases (2- to 4-hourly intervals)
- Pulse oxymetry
- Core temperature measurement

CVP, central venous pressure

BOX 4

Therapeutic benchmarks

- Mean arterial pressure (MAP) >70 mm Hg
- Central venous or mixed venous oxygen saturation (SvO₂) >70%
- Peripheral arterial oxygen saturation (SaO₂) >92%
- Arterial blood gases in the normal range (exception: permissive hypercapnia)
- Central body temperature >35 °C
- Urine volume 1–2 mL/kg body weight/h (depending on possible pre-existing impaired renal function)
- Na: 135–145 mmol/L
- K: 3.5–5 mmol/L
- Blood glucose <10 mmol/L
- Lactate <3 mmol/L

resuscitation can all have negative effects (e22). Lungs can be successfully harvested and transplanted from only 15–30% of organ donors (e22–e24). The introduction of protocols with intensified pulmonary therapy have led to an increased rate between 25.5% and 54% of successfully transplanted lungs (10, e24).

In spite of an extensive intravascular volume deficit, peripheral or pulmonary edema may develop as a result of severe capillary leakage. Especially where an explantation of the lungs is planned, restrictive volume therapy should be considered while accepting the fact that the intravascular volume deficit will continue. Increased positive end-expiratory pressure (PEEP) can counteract pulmonary edema.

BOX 5

Organ-protective intensive care

- Differentiated volume and catecholamine therapy
- Lung-protective ventilation
- Maintaining homeostasis (electrolyte, acid–base balance)
- Preventing loss of heat
- Administration of methylprednisolone
- Consider extended hemodynamic monitoring
- Consider administration of desmopressin, vasopressin
- Consider administration of dopamine

The treatment is based on the recommendations for lung-protective ventilation of intensive-care patients with lung injury (e23–e25). Healthy lungs should also be protectively ventilated by using PEEP. A PEEP of 15 cm H₂O and recruitment measures can improve the function of injured lungs (e26) (*Box 2*). As with the other target parameters it needs to be pointed out that the evidence in the context of outcomes of transplanted organ recipients is scarce.

Monitoring

The basic monitoring of potential organ donors includes ECG, pulse oximetry, invasive arterial blood pressure measurements, temperature measurements, and diuresis monitoring (20) (*Box 3*). In patients with a great need of volume or catecholamines, extended hemodynamic monitoring may be useful—for example, by using a pulmonary artery catheter, pulse index continuous cardiac output (PiCCO) monitoring, or transesophageal echocardiography (18–20).

Therapeutic benchmarks

The parameters listed in *Box 4* should be aimed for and monitored during organ-protective intensive therapy. The target parameters are therefore identical to those of other critically ill patients in intensive care.

Using donor management protocols may help increase the rate of transplanted organs per donor and the number of transplanted hearts and lungs. As far as the survival of the organ recipients is concerned, the four prospective randomized controlled trials (RCTs) that have been published so far, which included a total of 1018 patients, did not show any effect of organ protective intensive care (6, 24, 26, e11, e24). Only a post-hoc analysis of a subpopulation of 93 recipients of heart transplants showed a significant reduction in 3-year mortality as a result of dopamine administration to the organ donor (30). However, as this is a subanalysis of the study by Schnuelle et al (26), a definite evaluation is not possible. The randomized controlled trials are

shown in *Table 1*; the *eTable* lists further important studies. The validity of the individual interventions is not clear because multicenter prospective randomized studies are lacking. The protocols mostly recommend extended hemodynamic monitoring, early differentiated volume and vasopressor/catecholamine therapy, and lung protective ventilation (9, 27, e9–e11) (*Box 5*). The evidence level of most of those studies is based on expert opinion.

Conclusion

The evidence for organ-protective treatment in organ donors is mostly scarce. Furthermore, the data are contradictory. The focus is on the stringent continuation of intensive treatment in the sense of early donor management and on defining therapeutic goals. The recommendations in this article are intended to provide practical help in this setting. Improvements to this therapy and the timing of its initiation are decisive factors for the quality of the respective donor organ and therefore for the success of a transplantation procedure. Internationally, attempts are being made to compile recommendations for intensive care in patients after irreversible loss of brain function (e2, e27). The recommendations described in this article differ from those in the Anglo-American literature. In Germany, the focus is on differentiated volume and norepinephrine therapy, whereas in other countries, the hormone-based triad consisting of vasopressin, thyroxine/triiodothyronine, and steroids is usually given. Because of the very few scientific studies in this setting, more research is desirable (e28, e29).

According to the authors' clinical experience we recommend the therapeutic measures explained in this article when dealing with patients after irreversible loss of brain function.

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Conflict of interest statement

The authors declare that no conflict of interest exists.

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KEY MESSAGES

- Using standardized donor management protocols helps to improve the rate of transplanted organs per donor and the organ quality of the transplanted organs.
- Additional administration of methylprednisolone, desmopressin, or vasopressin may provide a useful adjunct to treatment in individual cases.
- The target parameters of organ-protective intensive care are based on the target parameters for other critically ill patients in intensive care.
- The evidence for organ-protective intensive care is weak and is based primarily on retrospective studies and studies with historical control groups.
- Prospective studies with sufficiently large control groups are desirable, but difficult to realize because of small case numbers.

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eTABLE

Selection of additional relevant studies on donor therapy

Author, year (source)	Method	Number	Intervention	Control	Results	Organ function after Tx	Patient survival
Rosendale et al. 2003 (e10)	Retrospective	N = 4543	Triiodothyronine, methylprednisolone, vasopressin	None	See "Organ function after Tx" and "patient survival"	HTx – early transplant dysfunction: 11.6% versus 5.6%	1-month survival: 96.2% versus 92.1%
Rosendale et al. 2003 (e8)	Retrospective	N = 10 292	Triiodothyronine, methylprednisolone, vasopressin	None	Transplanted organs per donor: 3.8 versus 3.1	Not reported	Not reported
Salim et al. 2007 (e9)	Retrospective, historical control group	N = 123	Thyroxine	None	Transplanted organs per donor: 3.9 versus 3.2	Not reported	Not reported
Benck et al. 2011 (37)	Retrospective	N = 264	Desmopressin	None	Transplant survival after 24 months: 85.4% versus 73.6%	NTx – late transplant dysfunction and acute rejection: no effect	Not reported
Callahan et al. 2014 (29)	Retrospective	N = 7686	Vasopressin	None	Transplanted organs per donor: 3.75 versus 3.33 LTx: 26.3% versus 20.5%	No effect	Not reported
Plurad et al. 2012 (27)	Prospective	N = 47	Donor management protocol	Standard care	Transplanted organs per donor: 4.73 versus 3.08 HTx: 68.2% versus 24.0% LTx: 40.9% versus 8.0%	Not reported	Not reported
Singbartl et al. 2011 (10)	Retrospective, historical control group	N = 78	Donor management protocol	Standard care	Transplanted organs per donor: 2.6 versus 1.9 LTx: 24% versus 11%	Not reported	Not reported
Mimbres et al. 2013 (e25)	Cohort study, historical control group	N = 62	Protective lung ventilation	Standard care	LTx: 53.2% versus 20.1%	NTx – transplant survival after 12 months: no effect	LTx – 30-day survival: no effect
Angel et al. 2006 (e23)	Cohort study, historical control group	N = 711	Protective lung ventilation	Standard care	LTx: 25.5% versus 11.5%	Not reported	LTx – 30-day and 1-year survival: no effect

Tx, transplantation; LTx, lung transplantation; KTx, kidney transplantation; HTx, heart transplantation; HAES, hydroxyethyl starch