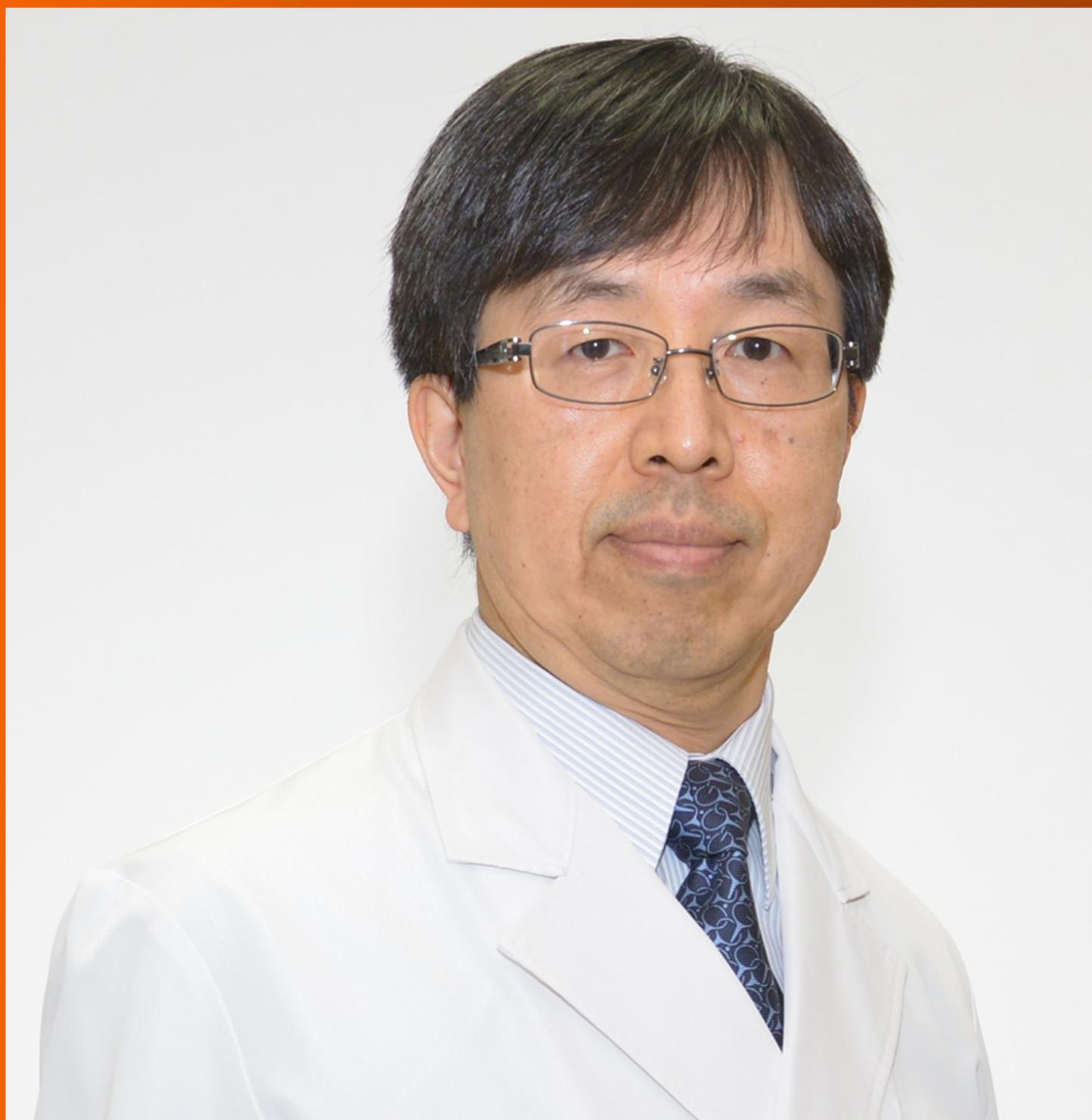


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Hemodynamic management in brain dead donors

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Abstract

Donor management is the key in the complex donation process, since up to 20% of organs of brain death donors (DBD) are lost due to hemodynamic instability. This challenge is made more difficult due to the lack of strong recommendations on therapies for hemodynamic management in DBDs and more importantly to the epidemiologic changes in these donors who are becoming older and with more comorbidities (marginal donors). In the present manuscript we aimed at summarizing the available evidence on therapeutic strategies for hemodynamic management (focusing on vasoactive drugs) and monitoring (therapeutic goals). Evidence on management in elderly DBDs is also summarized. Donor management continues critical care but with different and specific therapeutic goals since the number of donor goals met is related to the number of organs retrieved and transplanted. Careful monitoring of selected parameters (possibly including serial echocardiography) is the clinical tool able to guarantee the achievement and maintaining of therapeutic goals. Despite worldwide differences, norepinephrine is the vasoactive of choice in most countries but, whenever higher doses (> 0.2 mcg/kg/min) are needed, a second vasoactive drug (vasopressin) is advisable. Hormonal therapy (desmopressin, corticosteroid and thyroid hormone) are suggested in all DBDs independently of hemodynamic instability. In the single patient, therapeutic regimen (imprimis vasoactive drugs) should be chosen also according to the potential organs retrievable (*i.e.* heart *vs* liver and kidneys).

Key Words: Brain-dead donors; Hemodynamic; Management; Vasoactive drugs; Hormonal therapy; Echocardiography

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Core Tip: Donor management continues critical care but with different and specific therapeutic goals since the number of donor goals met is related to the number of

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INTRODUCTION

The number of patients on waiting list for transplant is increasing with a still high mortality rate and greater efforts should be made to maximize the organ pool and optimize organ quality from donors.

Donor management is key in the complex donation process, since up to 20% of organs of brain death donors (DBD) are lost due to hemodynamic instability[1-3]. This challenge is made more difficult due to the lack of strong recommendations on therapies for hemodynamic management in DBDs and more importantly to the epidemiologic changes in these donors who are becoming older and with more comorbidities (marginal donors)[4].

In the present manuscript we aimed at summarizing the available evidence on therapeutic strategies for hemodynamic management (focusing on vasoactive drugs) and monitoring (therapeutic goals). Evidence on management in elderly DBDs is also summarized.

A "PubMed" search was made using the words "Brain death donors and hemodynamics and adults". Only articles in English language were included referring to adults, while case reports and investigations on children were not comprised.

RATIONALE

A consistent number of donors are unfortunately lost because not properly treated[5], underscoring the pivotal role of active critical care to mitigate the imbalance between demand and supply of organs for transplantation. Though complex, intensive care management of potential donors, by the achievement of therapeutic goals, was associated with a 2-fold increase in transplanted organs[6]. This concept is further proved by the analysis of outcomes of two renal recipients from the same donor and of failure of multiorgan transplantation from the same donor[7,8].

THERAPEUTIC GOALS

In essence, donor management continues critical care but with different and specific therapeutic goals.

A checklist of nine therapeutic donor goals (DG) was proposed by eight organ procurement organization in United Network for Organ Sharing region[9]. The number of met DGs was reported to progressively increase from the time to diagnosis of brain death to organ recovery (from 15% to 38%). DG met at the time of consent were related to the number of transplanted organs, since if more four DGs were met at the time of consent, an odd ratio of 2.03 was reported for at least four organs transplanted. Moreover, if more than 7 DGs were met after consent a reduced need of dialysis in the first week after transplant was observed[10].

A key question was whether the time of donor treatment could influence the number and quality of transplanted organs. According the results of prospective studies, a longer period of donor treatment was associated with a higher number of organs transplanted in the lack of differences in the number of DGs achieved. This phenomenon was more evident for heart and lung transplantation probably thanks to

an efficacious treatment of potential reversible cardiac diseases such as stress cardiomyopathy[11-14]. In the United States longer periods of management are common and a “relax and repair approach” was proposed in opposition to a “rush and retrieve” one (that is, in presence of donor stability a risk of deterioration can be avoided since little can be achieved).

Due to the frequently encountered hemodynamic instability, historically DG were developed in order to maintain physiologic homeostasis. An early series of goals, the so-called series of 100: Systolic pressure > 100 mmHg, urine output > 100 mL/h, partial pressure of O₂ (PaO₂) > 100 mg and hemoglobin concentration > 100 mg/dL [15].

In the subsequent years, guidelines for donor treatments and other goals were introduced, even if there is great worldwide variations in management strategies[16, 17].

DG is shown in Table 1. Despite disparities in guidelines[18], these goals are based on clinical practice and their clinical significance comes from serial measurements during donor management and subsequent adaptation of therapies. Each parameter should be clinically and critically interpreted in the single patient. For instance, high values of central venous pressure can be observed in patients with chronic cor pulmonare and moderate tricuspid regurgitation, independently of the volemic status; in this clinical condition, dynamic changes of central venous pressure should be considered.

HEMODYNAMIC MANAGEMENT

Hemodynamic management is considered really a challenge due to the quite high frequency of donor instability. The severity of circulatory changes have been related to the speed of brain death. More severe hemodynamic alterations were described when brain death develops in a shorter time[19].

Two are the main physiopathologic steps in hemodynamic derangements: (1) The sympathetic storm (following the increase in intracranial cerebral pressure and progressive brainstem ischemia) causes compensatory arterial hypertension and raised systemic vascular resistance, associated with central redistribution of blood volume. It follows an increased after load and eventually visceral ischemia; and (2) Peripheral vasodilation due to the abrupt loss of sympathetic tone. Endocrine changes may worsen this phenomenon mainly by volume depletion.

In these patients, as brain death develops, treatment for hemodynamic imbalance shifts from preventing injuries from increased sympathetic tone (ischemic injury) to counterbalancing systemic injuries due to magnified vasodilation (ineluctably leading to reperfusion injury).

Despite no major studies specifically addressed which monitoring tools should be applied in DBDs, the following monitoring sets could be suggested according to clinical practice: (1) Invasive arterial pressure (mean arterial pressure \geq 65 mmHg); (2) Urine output (\geq 1 mL/kg/h); (3) Central venous pressure (8-10 cm H₂O); (4) Lactate values; (5) Mixed venous oxygen saturation; and (6) Echocardiography (mainly to assess left and right ventricular functions and to exclude previous or newly developed cardiac alterations).

Echocardiography has emerged as a clinical useful tool in intensive care unit (ICU) every day clinical practice. In patients with severe neurologic injury, serial echocardiographic assessments give the opportunity to provide useful information to tailor hemodynamic regimen in the single patient and, moreover, to identify potential reversible clinical conditions (*i.e.* stress cardiomyopathy) whose early treatment could lead to an increased number of trapiantable hearts and, even in the older donor, to an hemodynamic stabilization.

The reversibility in left ventricle (LV) dysfunction in patients with severe brain injury has been described as “neurogenic stunned myocardium”[20], mainly on the basis of data obtained in experimental models[21-23] and on a few investigations performed in humans[24,25]. Several papers documented that aggressive treatment in BD donors was associated with improvement in myocardial function and with an increased number of transplanted hearts, previously considered not suitable for transplantation[26-28]. In 49 patients with severe brain injury (potential heart donors), our group observed that echocardiography performed after ICU admission led to the identification of LV abnormalities potentially reversible after tempestive aggressive treatment. Indeed, in our series, two patients were considered eligible for heart donation, resulting in 20% increase in donor retrieval rate[14].

Table 1 Donor management goals

Goals	Monitoring
MAP \geq 65 mmHg	Invasive arterial pressure
CVP \geq 10	Central venous catheter
Hemoglobin \geq 10 g/dL	Blood gas analysis
Diuresis \geq 1 mL/kg/h	
Na 135-155 meq/L	

MAP: Mean arterial pressure; CVP: Central venous pressure.

In a large analysis[12] (United Network of Organ Sharing database, 2007-2015) of 472 donor hearts with left ventricular ejection fraction $<$ 40%, on initial transthoracic echocardiography which recovered during donor treatment, it was reported successful transplantation of these hearts with no increase in adverse outcomes (cardiac allograft outcome, primary graft failure) when compared to hearts which did not experienced LV dysfunction. Similarly, in Sweden (dataset 2006-2016) 45 hearts (of 338 donor hearts) with LV dysfunction were transplanted, and after transplantation LV ejection fraction normalized in all recipients. Short-term outcomes or the composite end point of death or retransplantation over time were comparable between recipients of donor hearts with *vs* without LV dysfunction[29].

All these findings underscore the utility of serial echocardiographic examinations in severe neurologic acute injury for the identification of potential reversible cardiac conditions, eligible for early aggressive treatments. Thanks to this clinical and methodologic approach, some hearts considered not suitable for transplantation could be successfully transplanted.

VASOACTIVE DRUGS

Dopamine

A retrospective-case control study, performed in Germany in 1999, reported that dopamine use in DBDs resulted in improved graft survival after kidney transplantation[30-34]. These results were confirmed in a large cohort study of 2704 DBD kidney grafts (Eurotransplant Registry)[31] and in 254 recipients of kidney transplantation [33]. The beneficial effects of dopamine on kidney grafts were related not only to the hemodynamic effects of dopamine but mainly to its ability to scavenge reactive oxygen species (by preventing the depletion of glutathione)[34]. In a randomized controlled trial including 264 DBDs, the use of low dose dopamine (4 mcg/kg/min) was associated with a reduced requirement for dialysis in recipients of the dopamine group [35]. However, the percentage of patients also on norepinephrine was quite high both in the dopamine and in the control groups (78.4% and 85.6%, respectively).

According to the follow-up trial, an improved survival was observed only if dopamine treatment was longer than 7 h till cross clamp. In the same trial, an improved outcome of heart grafts was observed in dopamine treated patients[36].

Regarding the effects of dopamine use on the outcomes of other organs, data are more conflicting. Dopamine pretreatment has no effect on liver transplantation probably because it is rapidly degraded in hepatocytes[34]. Concerning the heart, high dose of dopamine donor treatment ($>$ 10mcg/kg/min) showed no association with mortality in 568 heart transplants[37]. In the study by von Ziegler *et al*[38] donor pretreatment with norepinephrine was compared with dopamine pre-treatment in heart transplants and no differences were observed in survival between the two subgroups. However, in a subset population of long term (5-year) follow-up, norepinephrine was associated with better survival.

In recent years, dopamine was eliminated from routine use in ICU due to large individual variation in dopamine clearance (with unpredictable adrenergic stimulation [34,39,40]). Regarding DBD management and based on growing evidence, dopamine use cannot be advised due to the lack of evidence of beneficial effects in the multiorgan donor and the scarce vasoconstrictor effect of dopamine at low doses. Indeed, its use has been progressively replaced by norepinephrine in most countries worldwide[18].

Vasopressin

Vasopressin can be used to treat both diabetes insipidus and hypotension thanks to its action on V2 renal receptors and on V1 receptors on smooth muscle cells. Due to its short half life, it should be administered by infusion with an usual dosage range of 0.5 to 2.4 units *per* hour. Higher doses may cause deleterious vasoconstrictor effects in several districts (renal, splachnic, pulmonary and coronary districts[41]). In a large cohort of 10431 DBDs, donor vasopressor use was an independent predictor of a high number (≥ 4 organs) of procured organs. However, this study focuses on donor hemodynamic parameters and not on allograft outcomes[42]. To date, no data are consistent with the potential advantage of vasopressin over other vasoactive agents, even if vasopressin is the drug of choice for hypotension in DBDs in some countries such as Canada, Ireland and India[18].

Norepinephrine

Norepinephrine is the vasoactive drug of choice in several countries including Europe [4,18] with an increasing use in the last years, despite not univocal literature data. A beneficial effect of norepinephrine use was reported in 270 kidney recipients, since decreased rates of graft rejection and loss followed increased number of norepinephrine infusion days[43].

In regard to heart transplantation, conflicting results are reported on norepinephrine dosage and graft outcomes[44,45]. According to a survey, in potential heart donors, most heart transplant centers in United States are reluctant to accept donors under moderate dose of catecholamine[46]. High dose norepinephrine was correlated with right ventricular impairment and adverse 1-year outcome in a prospective investigation[47]. Conversely no differences in short term mortality was observed in a German Registry between different norepinephrine doses[48].

Based on this conflicting evidence, in potential heart donors we suggest to add vasopressin (continuous infusion) when a dose of norepinephrine > 0.2 mcg/kg/min is needed.

Hormonal therapy

The rationale for hormonal supportive therapy in BD donors comes from the physiopathology of brain death. Insulin and glucose management can be considered part of the intensive care management.

In human brain death, posterior pituitary dysfunction is commonly encountered (as documented by the frequency of diabetes insipidus), while anterior pituitary function may be only partially affected, probably thanks to the preserved pituitary blood flow. Thus, the hormones usually affected are antidiuretic hormone (ADH), thyroid hormones and cortisol[41].

Deficient levels of vasopressin (also known as ADH) were reported in up to the 80% of brain dead donors[49] and diabetes insipidus was described in the 77% of donors in Australia[50]. Low free T3 are frequently encountered in human donors, while variable concentrations of TSH and T4 are reported. The changes in thyroid hormones in brain death seem to resemble the euthyroid sick syndrome, commonly seen in critically ill patients[22,51,52].

Growing evidence does support the use of hormonal replacement therapy in DB donors, independently of hemodynamic instability[52-55]. In 1995, in an United Kingdom center, most donors were initiated on hormone replacement therapy by infusion, which led to the conversion of many of donors initially considered to be unacceptable, based on hemodynamic parameters, to acceptable donors[56]. In a cohort of 47 DBDs (2006 to 2011), hormonal replacement therapy initiated in the lack of hemodynamic instability was independently associated with highly-yield (≥ 4 organs) procurement[29]. A shorter duration of norepinephrine administration was also observed in this subgroup.

Treatment of diabetes insipidus is essential for donor stability. If untreated, diabetes insipidus causes hypovolemia, and marked hypernatremia which may be detrimental to organ outcome, especially for liver and kidney graft outcomes[57,58]. Diabetes insipidus should be suspected in presence of polyuria of ≥ 3 mL/kg/h and/or rising serum sodium levels) and the synthetic vasopressin analogue 1-deamino-8-D-arginine vasopressin (DDVAP) should be used. It selectively acts on V2 renal receptors and it does not have vasoconstrictor activity. DDVAP can be given as an intravenous bolus of between 2 and 6 mcg since it has a much longer half-life than vasopressin. At higher doses (0.3 mcg/kg) DDVAP exerts procoagulant effects (Table 2).

Administration of thyroid hormone has been highly suggested in guidelines and reviews[54,59-62]. According to animal and humans studies[63,64], replacement of

Table 2 Vasoactive drugs and hormonal therapy in brain death donors–proposed regimen

	Dosage	Comments
Vasoactive		
Norepinephrine (mcg/kg/min)	≤ 0.2 mcg/kg/min, if higher dosage needed add vasopressin	In potential heart donors, the lowest dosage is preferable
Vasopressin (U/h)	Up to 2.5 U/h	
Hormonal replacement therapy		
Hydrocorticosteroid	100 mg bolus, 200 mg/24 h infusion	
T3	4 mcg intravenous bolus, followed by infusion of 3 mcg <i>per</i> hour	T3 could be preferred since it is immediately available to tissues
Desmopressin (DDVAP)	4 mcg intravenous bolus eventually repeat every 6 to 8 h as needed	

DDVAP: 1-deamino-8-D-arginine vasopressin.

thyroid hormone is able to restore and reactivate mitochondrial energy metabolism. At the cardiac level, it induces an increase alpha heavy chain formation and a decrease in beta heavy chain formation, and an improvement in calcium handling, up regulation of beta adrenergic receptors, leading to a positive inotropic effect[65].

In an interesting review[66], it was reported that all retrospective analyses documented that thyroid hormone administration was beneficial. Recent evidence[64, 67] does support the notion that thyroid administration in brain death is associated with an increased number of organ transplanted and improved survival of heart recipients. A 5-year recipient survival improvement was documented in heart recipients when thyroid hormone had been administered[68].

T3 may be initiated with a 4 mg intravenous bolus followed by infusion of 3 mg *per* hour alternatively, T4 may be given initially with a 20 mg intravenous bolus followed by infusion of 10 mg *per* hour.

The rationale for the administration of cortisols, the third component of hormonal replacement therapy, relies on replacing steroid in pituitary-adrenal dysfunction, on supplementing steroid because of a “functional” or “relative” adrenal insufficiency, and on the immunomodulatory and anti-inflammatory beneficial effects of steroids.

Evidence supports this notion. Weaning of norepinephrine was more frequent in the 80 BD donors who received steroids than the 128 ones who did not, although no benefit was observed in primary functional recovery of transplanted grafts[69]. Recipients of donor livers who had received steroids showed less ischemia-reperfusion injury and acute rejection[70]. Low-dose of steroids is preferred since high dose did not show differences in number of retrieved and transplanted organs[52,71-73].

Different regimens of steroids were described with no documented benefit of one over the other[18]. Based on our experience, we suggest the use of hydrocortisone 100 mg bolus followed by 200 mg/d (continuous infusion).

AGE AND BRAIN DEAD DONORS

The characteristics of the pool of BD donors have deeply changed over the past years especially in developed Western countries. While DBDs were once largely young and declared dead due to traumatic brain injury, they are now older, with more comorbidities and declared dead due to cerebrovascular injury[74,75]. This phenomenon was confirmed in Italy (Tuscany Region) in a cohort of 1286 potential heart donor (aged ≤ 60) over a 15-year period in whom we observed an age increase and a change in brain dead causes (mainly a reduction in the incidence of traumatic brain injury)[4].

After BD development, the only variation observed with advancing age is lower values of diastolic blood pressure, which is most likely related to arterial changes due to aging[76]. Diastolic blood pressure is known to increase up to the age of about 50 years due to the rise in arteriolar resistance, but, later in life, the large artery stiffening contributes a wider pulse pressure including a decreased diastolic blood pressure. In the BD donor, this phenomenon may affect perfusion pressure, highlighting potential difficulties in hemodynamic management in older donors, and it may be worsened by the age-related reduction in β -receptor function[77]. In 92 consecutive DBDs[78],

advancing age was associated with a more pronounced vasodilatation (lower values of diastolic blood pressure) probably due to age-related reduction in arterial stiffness and beta-receptor function (conditioning a reduced response to endogenous and/or exogenous norepinephrine stimulation).

Older DBDs usually donate liver and/or kidney. Though the monitoring set and hemodynamic goals do not differ from younger DBDs, clinical peculiarities in management may apply to older DBDs. Due to the coexistence of atherosclerotic age-related disease (involving also small vessels), the lowest dosage of vasoactive drugs should be used, able to achieve and grant the best perfusion of abdominal organs, as mainly indicated by urine output and dynamic lactate values. Though fluid restriction is not required, close monitoring of sodium is needed in potential liver donors. In older DBDs, the possibility of *ex vivo* perfusion should be considered, mainly in presence of comorbidities (in primis diabetes and hypertension) and not optimal indices of organ perfusion (*i.e.* Transaminases values).

TIMING FOR AN OPTIMAL MANAGEMENT

The main target of “an early management” is the achievement of good systemic perfusion since ICU admission in a patient with severe neurologic injury, despite his/her potential non favorable outcome. According to our experience, three steps can be identified for an efficacious treatment. The first one starts with ICU admission of a patient with severe neurologic injury and it is strictly part of critical care, consisting of hemodynamic, metabolic and infectious monitoring. In this phase, an echocardiographic assessment allows the detection of previous (eventually unknown) heart disease as well as new-onset cardiac conditions, such as stress cardiomyopathy, which deserve targeted therapies. Dosages of vasoactive drugs should be tailored in order to avoid excessive organs’ vasoconstriction, possibly by means of close monitoring of hemodynamic targets (in primis central venous pressure and lactate values). The second step is represented by treatments during brain death development and it mainly consists in the management of hemodynamic and metabolic derangements. Finally the third step, that is properly “DBD management”, since brain death diagnosis to the operating theatre.

KEY MESSAGES

Intensive care management should begin on ICU admission of a patient with severe acute neurologic injury at risk of developing brain death. With the aim to reach optimal systemic organ perfusion and identify all reversible clinical conditions (*i.e.* stress cardiomyopathy) eligible for efficacious treatment.

In the single patient, therapeutic regimen (in primis vasoactive drugs) should be chosen also according to the potential organs retrievable (*i.e.* heart *vs* liver and kidneys).

Donor age may affect management due to peculiarities of brain death in older donors.

The utility of serial echocardiographic examinations in severe neurologic acute injury for the identification of potential reversible cardiac conditions, eligible for early aggressive treatments. Thanks to this clinical and methodological approach, some hearts considered not suitable for transplantation could be successfully transplanted.

Hormal replacement therapy should be initiated in DBDs independently of hemodynamic instability.

CONCLUSION

Donor management continues critical care but with different and specific therapeutic goals since the number of DG met is related to the number of organs retrieved and transplanted. Careful monitoring of selected parameters (possibly including serial echocardiography) is the clinical tool able to guarantee the achievement and maintaining of therapeutic goals. In the single patient, therapeutic regimen (in primis vasoactive drugs) should be chosen also according to the potential organs retrievable (*i.e.* heart *vs* liver and kidneys).

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