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EXPERTS' OPINIONS

Management to optimize organ procurement in brain dead donors

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ABSTRACT

The demand for donor organs continues to exceed the number of organs available for transplantation. Many reasons may account for this discrepancy, such as the lack of consent, the absence of an experienced coordinator team able to solve logistical problems, the use of strict donor criteria, and suboptimal, unstandardized critical care management of potential organ donors. This has resulted in efforts to improve the medical care delivered to potential organ donors, so as to reduce organ shortages, improve organ procurement, and promote graft survival. The physiological changes that follow brain death entail a high incidence of complications jeopardizing potentially transplantable organs. Adverse events include cardiovascular changes, endocrine and metabolic disturbances, and disruption of internal homeostasis. Brain death also upregulates the release of pro-inflammatory molecules. Recent findings support the hypothesis that a preclinical lung injury characterized by an enhanced inflammatory response is present in potential donors and may predispose recipients to an adverse clinical prognosis following lung transplantation. In clinical practice, hypotension, diabetes insipidus, relative hypothermia, and natremia are more common than disseminated intravascular coagulation, cardiac arrhythmias, pulmonary oedema, acute lung injury, and metabolic acidosis. Strategies for the management of organ donors exist and consist of the normalization of donor physiology. Management has been complicated by the recent use of "marginal" donors and donors of advanced age or with "extended" criteria. Current guidelines suggest that the priority of critical care management for potential organ donors should be shifted from a "cerebral protective" strategy to a multimodal strategy aimed to preserve peripheral organ function.

Key words: Brain death - Tissue donors - Tissue and organ procurement.

The worldwide demand for donor organs continues to exceed the number of organs available for transplantation.[1] The disparity between the demand for solid organs and the current supply is a growing problem in the United States and Europe. Only 15-20% of individuals who satisfy criteria for becoming organ donors actually donate.[2] Many reasons may account for this discrepancy, such as the lack of consent,[2] the absence of an experienced coordinator team able to solve logistical problems,[3] the use of strict donor criteria,[4] and suboptimal, unstandardized critical care management of potential organ donors.[2-4] This has resulted in efforts to improve the medical care delivered to potential organ donors so as to reduce the organ shortage, improve the conversion rate, increase organ procurement, and promote graft survival.[1]

The majority of organ donors (>90%) are patients who die in Intensive Care Units (ICUs) after the irreversible cessation of all brain functions (brain death). During their period of clinical observation (irreversibility of brain death criteria), 5% to 10% of potential donors suffer car-

diac arrest and their organs can no longer be harvested, mainly due to insufficient or inaccurate physiological and therapeutic support (defined as "biological reanimation" of the brain dead subject, "donor maintenance," or "donor intensive treatment").

Preventing or attenuating organ dysfunction in pulsatile heart beating potential donors requires in-depth knowledge of the pathophysiological consequences of brain death. This accounts for the growing interest in donor management, a topic widely considered the most neglected area in transplant medicine. After the declaration of brain death, treatment of the potential organ donors should aim to curtail progressive somatic deterioration, and sustain or improve specific transplantable organ function. Conserving optimal donor physiology and stability preserves organ quality, viability, and eventually organ function in the recipient. For this purpose, organ perfusion must be optimized, endocrine homeostasis stabilized, and the weaker organs safeguarded.

Management of the potential organ donor: clinical practice

The widespread physiological changes that follow brain death entail a high incidence of complications jeopardizing potentially transplantable vital organs. Adverse events include cardiovascular changes, endocrine and metabolic disturbances, and disruption of internal homeostases such as blood coagulation and hydro-electrolytic balance. Brain death also upregulates the release of pro-inflammatory molecules.

The occurrence and severity of these dysfunctions depend on the etiology and time course of brain death, and will increase with time after the onset of brain death. In clinical practice, hypotension (>80% of donors), diabetes insipidus (65%), relative hypothermia, and plasma electrolyte imbalance (namely natremia) are more common than disseminated intravascular coagulation, cardiac arrhythmias, pulmonary edema, and metabolic acidosis.[5, 6]

Strategies for the management of organ donors exist and consist of the normalization of donor physiology. Management has been further complicated by the recent use of "marginal" donors and donors of advanced age or with "extended" criteria.[7-9]

Much of the management strategy is not specific to the organ donor and should reflect optimum ICU care that should be continued beyond the observation of brain death, *i.e.*, continued invasive monitoring, adherence to infection control procedures, aggressive treatment of arrhythmias and electrolyte imbalance, hygiene needs, regular patient repositioning, and the presence of nursing staff. A multitude of standardized management protocols and clinical practice guidelines (a few evidence-based medicine [EBM] based) have been published to simplify the treatment of these complicated patients.[10-18] At present, each country, or even each inter-regional or regional transplant coordination center or ICU, has its own donor management protocol.

Recommendations for treatment and points of debate: cardiovascular system

Maintaining hemodynamic sufficiency and stability in brain dead patients until organ procurement is paramount to organ viability.

The progression of intracranial hypertension brain stem infarction causes death of the vasomotor centers (loss of blood pressure autoregulation) and a loss of sympathetic tone with a massive reduction of systemic vascular resistance and profound vasodilation. Subsequently, severe relative hypovolemia (venular blood pooling) and hypotension occur, sometimes leading to multifactorial cardiac dysfunction. Not all of these physiologic changes are serious in every potential organ donor, but during the observation period, hemodynamic instability is common. Furthermore, the degree of instability appears to be directly related to the time of post mortem development and consequential degree of autonomic dysfunction.[16, 17, 19, 20]

The goals of management for the donor's hemodynamic status are to achieve normovolemia by volume expansion, maintenance of blood pressure, and optimization of cardiac output so as to reach perfusion pressure and blood flow gradients that promote organ function with the least support of vasoactive drugs. These compounds often represent a vasoconstrictive load potentially inducing organ ischemia.

Among the support strategies for adequate organ perfusion of cadaveric pulsatile organ donors, the current guidelines, protocols, and diagnostic or interventional algorithms agree on standard monitoring of the clinical signs of perfusion and the hemodynamic targets of the treatment. These vital signs include the following: mean arterial blood pressure 70 mmHg, urine output 0.5-3 mL/kg/h, central venous pressure 8-12 mmHg, heart rate 60-120 b/min, Hb >10 g/dL). In addition, donors need to be considered for volume expansion therapy (crystalloids and/or colloids), the use of vasopressor drugs at the lowest possible dosage (dopamine, noradrenaline), and inotropic support (dobutamine) if cardiac failure occurs.

Although not always evident, brain death is associated with a massive increase in catecholamine levels (the sympathetic/autonomic storm) sometimes resulting in increased heart rate, blood pressure, cardiac output, and systemic vascular resistance. The consequences of autonomic storm are an imbalance between myocardial oxygen demand and supply, which triggers metabolic functional alterations and sometimes anatomical heart damage (myocytolysis and micronecrosis).[21, 22] Electrocardiographic signs of myocardial ischemia, conduction abnormalities, and arrhythmias are also common during this period.

Not surprisingly, histological examination of cardiac tissue exposed to autonomic storm show changes typical of widespread ischemic damage and necrosis, and profound end-organ vasoconstriction has also been demonstrated in animal models.[23] However, this period of intense catecholamine release is short-lived (typically minutes) and self-limited, and may require no treatment.[23] Nevertheless, many experimental studies and recent clinical observations suggest that treating autonomic storm (short-acting β-blocker drugs or nitroprusside) is a viable strategy to attenuate myocardial dysfunction and increase the number and success rate of heart procurements and cardiac transplantations.[24-26]

Regardless of whether the systemic arterial pressure is low or high, the donor is usually hypovolemic. Brain death-induced physiologic changes lead to an increase in capillary permeability and create a functional intravascular hypovolemia. In addition, absolute or relative hypovolemia is commonly present in these patients because of increased fluid loss (*i.e.*, mannitol, other diuretic therapy, or diabetes insipidus). This hypovolemic state is difficult to assess without monitoring central venous or pulmonary artery occlusion pressures. Central venous pressure (CVP) monitoring is mandatory. Although, the insertion of a pulmonary artery catheter (PAC) should be considered if the ejection fraction is <40%, and if hemodynamic instability persists despite adequate fluid resuscitation and/or escalation of intropic/vasopressor therapy.[11, 16, 18] The hemodynamic targets with PAC monitoring are PCWP 6-10 mmHg, CI >2.4 L/min.m,^{2} and SVR 800-1 200 dynes/s/cm.^{5}

Echocardiography is useful to exclude major structural abnormalities affecting the suitability of the heart for transplantation, and to measure the left ventricular ejection fraction. However, transthoracic 2D-echocardiography may be inaccurate and better images are often obtained with transesophageal echocardiography.[27] Transient regional wall motion abnormalities are common and systolic inward motion and thickening may improve with hemodynamic optimization. Dobutamine stress echocardiographic studies will disclose dobutamine-responsive wall motion abnormalities that may reveal potentially reversible myocardial dysfunction in a "neurogenically stunned myocardium". These approaches have improved the management of the hemodynamic status of potential donors and increased the rates of transplanted hearts and other organs.[28, 29]

Cardiovascular support should be based on rational physiology and the use of vasopressors to maintain donor stability has been shown to improve organ viability, thereby increasing the recipient's survival rate. There are widely divergent opinions regarding the best inotrope or vasopressor agents for intensive donor management. The choice of vasoactive and inotropic support varies among centers and may be guided by data arising from monitoring, but the following caveats may be observed:

– the vasodilator effects of dobutamine may lead to undesirable hypotension and tachycardia;

– β-agonist therapy should be used with caution in potential donors given concerns over myocardial adenosine triphosphate depletion and down regulation of β-receptors;

– high dose β-agonists may result in detrimental vasoconstriction in donor organs;

– pure vasopressors, like arginine vasopressin, are less likely to cause metabolic acidosis or pulmonary hypertension and may be a more appropriate than noradrenaline for the vasoplegic shock phase.[16, 18]

Central venous oxygen saturation ($ScvO_2$) is a relatively reliable indicator of adequate organ perfusion and is measured intermittently by blood sampling or continuously *via* oxymetric central venous catheters. Both variables are used extensively in the treatment of critically ill patients with severe sepsis, shock, and trauma. Likewise, it would be advisable to maintain organ donor $ScvO_2$ >70% or SvO_2 >65%.[11, 16, 18] Maintaining this oxygenation status means keeping oxygen extraction within physiological ranges as an indicator of adequate organ perfusion.[30, 31] Although central venous oxymetry is not well studied in subjects declared neurologically dead, higher values of $ScvO_2$ than SvO_2 are recommended. This increase ratio is due to the suppression of cerebral oxygen consumption.[32] Thus, the combination of intensive monitoring and aggressive management of the organ donor is not too far from early goal directed therapy (EGDT), the well known successful approach to severe sepsis and septic shock. A pilot trial of EGDT for donor management proved encouraging since the aggressive volemic expansion goal to rapidly achieve $ScvO_2$ >85% resulted in shorter hypotension time, lower vasoactive total doses, and better organ retrieval (Caldes Index).[33]

Recommendations for treatment and debate points: endocrine system

The effects of brain death on the hypothalamic-hypophyseal axis are profound. The most frequent and almost immediate manifestation is diabetes insipidus due to loss of antidiuretic hormone incretion secondary to supraventricular and paraventricular hypothalamic nuclei ischemia. The kidneys are unable to concentrate urine and excrete large amounts (4 mL/kg/h) of dilute urine (specific gravity: <1 005 and urine osmolality: <200 mosm/L). Polyuria may lead to hypernatraemia (>145 mEq/mL, which is common and sometimes severe and progessively worsening), associated with rising serum osmolality and hypovolemia. Undetectable levels of ADH have been noted in 75% of brain dead donors and are associated with hemodynamic instability and compromised transplantable organ function.[34] The course for interventions is primarily based on the volume status, serum sodium, and osmolality, and is secondarily based on an acceptable urine output. Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) is the drug of choice for substitutive therapy (administered intravenously in repeated doses or at a low infusion rate adjusted to achieve the optimal effects).

Anterior pituitary function (blood supply *via* hypophyseal extradural arteries) is usually preserved, but variable deficiency of hormones regulated by the anterior pituitary including (T3), thyroxine (T4), adrenocorticotropic hormone, thyroid stimulating hormone, and growth hormone have been described. This striking and acute hormonal depletion, very common in experimental animal models, but uncertain and questionable in clinical practice, has been implicated in the hemodynamic derangement seen after brain death.[5] Several detrimental metabolic effects follow acute adrenopituitary insufficiency. These include shifts in the myocardial energy supply from aerobic to anaerobic, as shown in animal brain death models, and depletion of myocardial high energy phosphates that is accompanied by an increase in lactate production.[35] Sometimes, a rapid decline in plasma levels of free tri-iodothyronine (T3) is seen after brain stem death as a result of impaired thyroid stimulating hormone (TSH) secretion and peripheral conversion of tetraiodothyronine (T4), but attempts to study thyroid disturbances in organ donors have produced conflicting data.[36] Moreover, there has been inconsistent improvement or conflicting results in the assessed physiological parameters after replacement of these hormones in both animals and humans.[19]

Despite these findings, recent guidelines advocate the addition of a standardized hormonal resuscitation package (a three drug "hormone resuscitation" or "combined hormonal therapy") to the standard management protocol consisting of methylprednisolone (15 mg/kg in a single intravenous bolus) or low dose hydrocortisone (50 mg e.v. q6h), a triiodothyronine (4 μg bolus intra-

venously followed by infusion of 3 μg/h), and arginine vasopressin (1 U bolus infusion at 0.5 to 4 U/h). The combined hormonal therapy is strongly recommended in donors assessed with a low ejected fraction (<40%) or hemodynamic instability in full vasoactive support.[10, 11, 17, 18] Currently available evidence in a large retrospective UNOS cohort study suggests a substantial benefit from triple hormone therapy with minimal risk. Specifically, a multivariate logistic regression analysis showed diminished requirements for vasoactive therapy and a significant increase in kidney, liver, and heart utilization in donors receiving "hormonal resuscitation".[26] Significant improvements in one-year graft kidney survival and heart patients were also demonstrated.[37] Although no prospective randomized trial has been performed, consideration should be given to triple hormone therapy use in all donors.

Recommendations for treatment and debate points: respiratory system

Lung transplantation is often the only available treatment option for patients with end-stage lung disease. Due to important advances in surgical techniques and pharmacologic management, lung transplantation offers many patients an improved quality of life and increase likelihood of survival.[38] However, despite these advances, few patients benefit from transplantation because of the scarcity of lung donors. In 2005, among patients on the United Network for Organ Sharing waiting list for lung transplantation, only 35% received transplants, and 10% died while awaiting a graft. Approximately, half of the listed patients waited more than 2 years before receiving a transplant.[39] This trend worsens each year since the number of new additions to the waiting list annually is nearly double that of the number of patients who receive transplants.[38]

The main clinical reasons contributing to the lack of donor lungs are the use of suboptimal, under standardized critical care management and strict donor criteria of potential organ donors.

Critical care management for potential organ donors

More than 30% of the lungs theoretically suitable for donation are not actually harvested because following brain death, they often develop severe hypoxemia and an abnormal chest X-ray reveals them to be unsuitable.[40] The association between the brain death process and subsequent pulmonary dysfunction is well recognized. Severe brain injury resulting in brainstem death is characterized by the release of proinflammatory mediators in the systemic circulation.[41] Recent findings support the hypothesis that a preclinical lung injury characterized by an enhanced inflammatory response is present in potential donors and may predispose recipients to an adverse clinical prognosis following lung transplant.[42]

Severely brain injured patients develop ALI/ARDS in 15-20% of cases. In addition, lung function can be impaired through different mechanisms including neurogenic pulmonary edema, aspiration, hemo-pneumothorax, atelectasis, and later on pneumonia.[43] The presence of pulmonary dysfunction in acute brain injury is well known and has previously been attributed to a hydrostatic phenomenon induced by a massive increase in sympathetic activity.[44] However, an acute systemic inflammatory response also appears to play an integral role in the development of such injury by initiating infiltration of activated neutrophils into the lung.[45] Moreover, we have previously suggested that severe brain injury resulting in brainstem death is characterized by the release of proinflammatory mediators into the systemic circulation.[41] This inflammatory response may determine the preclinical lung injury present in potential donor lungs, which together with the ischemia-reperfusion injury may affect primary graft failure.[42] Indeed Follette *et al.* reported that the administration of high dose steroids after brain death improved oxygenation and increased lung donor utilization by limiting the cytokine-mediated cellular injury.[46]

Primary graft failure is a form of ALI that results from the sequence of events involved in lung transplantation including brain death of donor, pulmonary ischemia, preservation of donor tissue, transplant procedures, and reperfusion of donor tissue in the recipient.[47] The primary graft failure also represents a risk factor for bronchiolitis obliterans syndrome,[41] which results in prolonged mechanical ventilation, an increased ICU length of stay, and carries a mortality rate up to 60%.

Guidelines suggest that the priority for critical care management of potential organ donors should be shifted from a "cerebral protective" strategy to a strategy able to preserve peripheral organ function. Recently, recommendations of the "Lung Work group"[48] suggested the following ventilatory strategy: maintain adequate oxygenation (paO_2 >100 mmHg) with low FiO_2 and PEEP of 5 cm H_2O and use tidal volumes equal to 10-12 mL/kg to maintain $PaCO_2$ equal to 30-35 mmHg (pH=7.35-7.45) with a peak airway pressure <30 mmHg. Bronchoscopy, frequent suctioning, and aspiration precautions are also recommended. Fluid management guided by PAC monitoring is desirable to ensure end-organ perfusion targeting a CVP of 6-8 mmHg and wedge pressure of 8-12 mmHg. Guidelines for brain injured patients propose a similar ventilatory strategy in order to protect the brain. The guidelines are based on the use of high tidal volumes to obtain moderate hyperventilation for acute treatment of intracranial hypertension, and to optimize oxygenation with low levels of PEEP to preserve cerebral venous drainage.[49] This ventilatory strategy based on the use of high tidal volume and low levels of PEEP may further exacerbate the pulmonary and systemic inflammatory response in patients with acute lung injury ALI/ARDS, with injurious effects on peripheral organs.[50-52]

Therefore, even though patients with ALI/ARDS are excluded from lung donation, their ventilatory management may be an important aspect of preserving their peripheral organ function. Although the use of low PEEP and high tidal volume does not initiate an inflammatory response in normal lungs during general anesthesia,[53] a further enhancement of the inflammatory response has been observed in lungs of patients recovering from cardiac surgery where the primary inflammatory stimulus was represented by the cardiopulmonary bypass.[54, 55] Similarly, the function of the "primarily inflamed" lungs of potential organ donors may be further impaired by the injurious effects of mechanical ventilation, leaving lungs unsuitable for transplantation.

Nevertheless, recommendations for the ventilatory strategy aimed at optimizing potential organ donors are similar to those for severe brain injured patients, and are potentially injurious for the lung graft even in the absence of ARDS.

Mascia *et al.* recently showed that 45% potential organ donors had a PaO_2/FiO_2 ratio <300, making them ineligible for lung donation although they had normal chest X-rays and low plateau pressures. After the diagnosis of brain death, ventilatory management was not modified from a "cerebral protective" to a "lung protective" strategy and no procedures for recruiting the lung and preventing mechanical stretch were routinely performed. Conversely, cardiovascular management was modified to optimize peripheral organ perfusion.[56] In this patient population, the use of low tidal volume and high PEEP with the implementation of tracheal suction by a closed circuit, and apnea testing by continuous positive airway pressure has the theoretical presupposition of preventing hyperinflation and derecruitment of the lung.

However, critical care management is currently focused on preservation of non-pulmonary organ systems by the maintenance of hemodynamic stability and intravascular volume. This is accomplished with the titration of ventilatory parameters primarily relegated to the preservation of acid-base balance *via* control of $PaCO_2$.

However, still unresolved is the extent to which the PaO_2/FiO_2 ratio might be improved over initial values by systematic, dynamic ventilatory strategies to combat reversible problems, such as atelectasis.[57]

Currently, there appears to be significant variability among medical centers, regional organ procurement organizations, and countries regarding specific ventilatory protocols and procedures to optimize donor lung availability for transplantation.

Criteria for lung donors

Current standard criteria for lung donors have existed for more than two decades. In general, standard lung transplant donor criteria are the following:[58]

– age <55 years;

– clear chest X-ray;

– PaO_2/FiO_2 >300 on FiO_2 of 1, Peep 5 cm H_2O;

– absence of chest trauma;

– no evidence of aspiration, sepsis, or purulent secretion at broncoscopy;

– sputum or bronchoalveolar lavage Gram stain

free of bacteria, fungus, and significant numbers of white cells;

– smoking history of <20 packs/year.

The scarcity of lung donors has led to a re-examination of traditional criteria to determine the acceptability of donor lungs and, by extension, specific intensive care-based strategies to alleviate the scarcity of donor lungs by increasing the pool of donors. The recognition that standard lung donor criteria were arbitrarily selected rather than evidence-based, has led multiple investigators to verify if extended selection criteria can be safely tolerated. This concept of an aggressive "extended" donor approach to otherwise marginal lungs is perhaps best typified by the common ICU scenario of the potential organ donor in whom moderate abnormalities of oxygenation are initially encountered.

Angel *et al.* implemented the San Antonio Lung Transplant (SALT) donor management protocol, including educational and donor management interventions, as well as changes in the classification and selection criteria. Extended donor criteria included one or more of the following characteristic: age >55 years, cumulative smoking history of >20 packs/year, history of pulmonary disease, severe chest trauma, >4 days on mechanical ventilation, and positive result from Gram staining of tracheal or bronchoalveolar lavage fluid. Using the SALT criteria, the authors were able to increase the percentage of lung procured per eligible donors from 11.5% to 22.5%, resulting in a dramatic increase in the number of transplant procedures while recipient outcomes were not adversely affected.[59]

Improvements in lung procurement with donor management strategies have also been reported by Gabbay *et al.*[58] These authors reported that the use of extended donor organs and aggressive donor management increased procurement rates from 33% to 51%. They reported an Australian cohort of 20 donors out of 140 lung transplants (14.3%), which had of an initial PaO_2/FiO_2 ratio of <300 with FiO_2=1, and 5 cmH_20 of PEEP. However, aggressive ICU management, including the adjustment of ventilatory settings and positive end-expiratory pressure levels, combined with repeated blood gas analyses to assess the effect of such intervention, enables an improvement in PaO_2/FiO_2 ratios (>300) making these lungs suitable for donation. Importantly, postoperative gas exchange and ICU, stay as well as overall recipients survival over 3 years were not different in this cohort compared with recipients with an initial PaO_2/FiO_2 ratio >300.

Similar findings were reported by the California Organ Bank, where the use of a donor-management protocol has increased procurement rates by as much as 35% over the last few years.[59] However, the increase in organ donation was not associated with a change in the survival rates of recipients.

These reports of clinical lung transplantation [38, 40] confirm the paucity of evidence that the function of the donor lung after transplantation is related to the donor's initial PaO_2/FiO_2 ratio. These results suggest that lung donors considered marginal on the basis of initial oxygenation may still be effectively utilized without compromising allograft function or recipient survival post-transplantation. The validation of specific protocols in this population to improve oxygenation by alveolar recruitment, as well as their systematic implementation across institutions and regional organ procurement networks will be required to meaningfully increase the availability of donor lungs.[38]

The future

Our understanding of the pathophysiology of brain death and its effects on donor and recipient organ function has significantly progressed over the last two decades. Ultimately, attenuation of donor organ damage and improvement of post-transplant organ function will best be achieved by specifically targeting the unique systemic changes that occur after brain death. It seems likely that the key to such treatment will lie with protective management strategies. These therapies may be advanced by new insights into different aspects of emerging post mortem sciences including pharmacogenomic responsiveness, inflammation prevention, and biological modulation.

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