Medical management to optimize donor organ potential: review of the literature

[Traitement médical pour optimaliser le potentiel de don d'organe : une revue documentaire]

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Purpose: Over the past two decades, the demand for donor organs continues to outpace the number of organs available for transplantation. Parallel with this has been a change in the demographics of organ donors with an increase in older donors and donors with marginal organs as a proportion of the total organ donor pool. Consequently, efforts have been made to improve the medical care delivered to potential organ donors to improve the conversion rate and graft survival of available organs. The purpose of this literature review is to provide updated recommendations for the contemporary management of organ donors after the neurological determination of death in order to maximize the probability of recipient graft survival.

Sources: A comprehensive review of the literature obtained through searches of MEDLINE/PubMed, and personal reference files.

Principal findings: Contemporary management of the organ donor after neurological determination of death includes therapies to prevent the detrimental effects of the autonomic storm, the use of invasive hemodynamic monitoring and aggressive respiratory therapy including therapeutic bronchoscopy in marginal heart and lung donors, and the use of hormonal therapy including vasopressin, corticosteroids, triiodothyronine or thyroxine, and insulin for the pituitary failure and inflammation seen in brain dead organ donors. The importance of normalizing donor physiology to optimize all available organs is stressed.

Conclusion: Aggressive hemodynamic and respiratory management of solid organ donors, coupled with the use of hormonal therapy improves the rate of conversion and graft survival in solid organ recipients.

***Objectif** : Depuis plus de deux décennies, il y a une disproportion croissante entre les demandes de transplantation et la pénurie d'organes disponibles. En même temps, les données démographiques des donneurs ont changé, car une partie de leur nombre total compte plus de gens âgés dont les organes sont marginaux. Par conséquent, on tente d'améliorer les soins médicaux prodigués aux donneurs potentiels pour augmenter le taux de conversion et la survie du greffon des organes disponibles. Notre revue visait la mise à jour de recommandations de traitement aux donneurs d'organes, chez qui la mort neurologique a été établie, pour maximiser la probabilité de survie du greffon chez le receveur.*

***Sources** : Une revue documentaire étendue obtenue par des recherches dans MEDLINE/PubMed et des fichiers de référence personnels.*

***Constatations principales** : Le traitement actuel du donneur d'organe, après la détermination de la mort neurologique, comprend la prévention d'effets nuisibles du choc subi par le système nerveux autonome, l'usage d'un monitorage hémodynamique effractif et une thérapie respiratoire énergique dont la bronchoscopie thérapeutique chez des donneurs marginaux de cœur et de poumons et l'usage d'hormonothérapie dont la vasopressine, les corticostéroïdes, la triiodothyronine ou thyroxine et l'insuline pour la défaillance hypophysaire et l'inflammation observée lors de la mort encéphalique des donneurs. L'accent est mis sur la normalisation physiologique du donneur afin de mieux protéger tout organe disponible.*

***Conclusion** : Le traitement hémodynamique et respiratoire énergique des donneurs d'organes pleins, couplé à l'usage d'hormonothérapie, améliore le taux de conversion et la survie du greffon chez les receveurs.*

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THE gap between the number of patients awaiting transplantation and those undergoing transplantation widens yearly, and failure to maintain adequate support of cadaveric donors accounts for at least 25% of lost organs.[1,2] Wide variations in the rates of organ procurement and allograft survival between the ten United States Organ Procurement Organizations has motivated clinicians to promote guidelines for the management of cadaveric donors.[3] Indeed, consensus on the optimal care of the cadaveric donor may increase the number of organs retrieved for transplantation.[4–6] The purpose of this review is to synthesize the available literature on, and provide recommendations for the medical management of organ donors for the purposes of improving conversion rates and graft survival of recipient organs.

Literature search strategy

A comprehensive search of MEDLINE/PubMed was undertaken, utilizing each and combinations of the MeSH headings, "brain death", "transplantation and heart/lung/liver/kidney/pancreas/pituitary", "organ donor", "hormonal therapy", "pituitary", "thyroid", "adrenal", "corticosteroids", "vasopressin", and "DDAVP". All relevant literature was abstracted and further references were obtained from the abstracted literature, and personal files of members of the executive committee of a recent forum entitled "Medical Management to Optimize Donor Organ Potential: A Canadian Forum".

Temporal considerations

The time between the neurological determination of death (NDD) and the beginning of the cold ischemia time during explantation influence renal allograft survival. Renal allografts retrieved from donors with a duration from NDD over 470 min demonstrated significantly better primary graft function than those procured from donors prior to 470 min after NDD.[7] In a study of orthotopic liver transplants, longer donor time after NDD was not found to be associated with primary allograft dysfunction.[8] Data from lung procurement has been conflicting with associations between longer time to donor network referral and a reduced probability of lung procurement demonstrated in a California study in contrast with an Australian study, which successfully delayed lung procurement to provide time for bronchial toilet in marginal lung donors.[9,10]

For all solid organs, longer cold ischemia times correlate with worsened allograft survival. Significant negative interactions between ischemia time over six hours and increasing donor age over 45 yr on recipient survival have been demonstrated for lung allografts.[11,12] The major factors contributing to the failure of cardiac allografts include donor age, coronary artery disease, left ventricular hypertrophy, donor-recipient size mismatch, donor hepatitis B status, and cold ischemia time.[5] In the Collaborative Transplant Study of kidney transplants, a cold ischemia time over 12 hr resulted in progressively worsening recipient graft survival.[13] A cold ischemia time of over 18 hr, along with reduced size livers, donor age over 49 yr, and moderate to severe fatty changes in the donor liver biopsy have also been found to be independent predictors of primary liver allograft dysfunction.[8]

The cardiovascular response to brain death

Brain death results from cerebral herniation following raised intracranial pressure. As intracranial pressure rises, brainstem ischemia progresses in a rostral-caudal fashion and mean arterial pressure rises in an effort to maintain cerebral perfusion pressure. Midbrain ischemia results in parasympathetic activation and sinus bradycardia. Subsequent pontine ischemia results in sympathetic stimulation with superimposed hypertension (Cushing's reflex).[14,15] Further ischemia of the vagal cardiomotor nucleus in the medulla oblongata occurs, resulting in unopposed sympathetic stimulation and loss of baroreceptor reflexes termed "autonomic storm".[15,16] The vasoconstrictive effect of the autonomic storm compromises end organ blood flow and its severity correlates with the rate of rise in intracranial pressure.[17,18] Following the autonomic storm, a normotensive or hypotensive phase ensues, resulting from reduced sympathetic flow and impairing vascular tone and cardiac output.[19] As a consequence of both the loss of sympathetic nervous system control and concomitant diabetes insipidus (DI), only a minority of cadaveric donors are able to maintain hemodynamic stability.[20–23]

Cardiovascular monitoring and support

Traditionally, dopamine has been used as the inotrope of choice in the cadaveric donor, however recent studies have not supported the beneficial effect of dopamine on renal or hepatosplanchnic circulation, and dopamine may suppress the function of anterior pituitary hormones.[24,25] Consequently, there has been a move towards the use of medications such as vasopressin for the vasodilatory shock seen in cadaveric donors. Organ donors who require catecholamine support have been shown to be deficient in vasopressin.[26] Several authors have described the successful support and catecholamine sparing effect of *iv* vaso-

pressin with or without 1-desamino-8-D-arginine vasopressin for up to 14 days after brain death.[27–30] The catecholamine sparing effects of vasopressin have also been shown in several case series of patients in septic shock.[31–33] Consequently, vasopressin has been recommended as initial therapy for hemodynamic support and the treatment of DI in the cadaveric donor by the American College of Cardiology.[34]

Expert consensus recommends that every cadaveric donor should undergo central venous pressure (CVP) monitoring.[4,35] In studies of hemodynamically unstable cadaveric donors, there is observational evidence to suggest that the use of a pulmonary artery catheter, vasopressin, glucocorticoids, and triiodothyronine (T3) is successful in converting "unsuitable" donor organs into transplantable organs.[35] The American College of Cardiology has recommended maintaining a systolic blood pressure 90–140 mmHg, a CVP of 8–12 mmHg, or pulmonary capillary wedge pressure of 12–14 mmHg using a pulmonary artery catheter.[34] Other authors recommend a CVP of less than 8 for potential lung donors.[16] Vasopressors, as opposed to inotropic medications should be used in the setting of low systemic vascular resistance and normal or elevated cardiac output.[36] In both canine models and humans, right ventricular function appears to be worse than left ventricular function after NDD, and is postulated to be related to both increased pulmonary capillary permeability and from pulmonary overflow injury caused by a reduction in pulmonary vascular resistance.[28,37,38] Care should be taken with respect to aggressive fluid loading as even targeting of CVP to 8–10 mmHg has been demonstrated to increase the alveolar-arterial oxygen gradient as compared to a target of 4–6 mmHg.[4,5,39,40]

Echocardiographic parameters have predictive value of the success of cardiac allograft function.[41] However, echocardiographic myocardial dysfunction differs by etiology of cerebral injury and does not correlate well with pathological findings of contraction band necrosis.[42] Moreover, improvement in myocardial function has been demonstrated when serial echocardiography has been performed and dobutamine responsive donors may predict successful recovery of myocardial function.[43,44] Coronary angiography is often performed on donors if they are over 40 yr, require high inotropic support, or have other risk factors for coronary artery disease and recent indications for angiography in the cadaveric donor have been published.[5,45,46] If angiography is performed, numerous studies support the use of acetylcysteine and bicarbonate to prevent the development of contrast nephropathy.[47–53] Changes in catecholamine levels seen in massive subarachnoid hemorrhage and resulting in an increase in peripheral resistance may result in a sudden increase in myocardial work and oxygen consumption leading to myocardial infarction and subsequent elevation of cardiac troponin I and T.[54] Cadaveric donor levels of troponin I or T have been correlated with pathological findings of subendocardial myocytolysis, higher catecholamine requirements, and increased rates of recipient allograft rejection.[55–58]

Endocrine considerations

Dysfunction of the posterior pituitary is common with resultant low to undetectable levels of vasopressin manifest clinically as DI, and occurring in up to 90% of adult and pediatric organ donors.[16,23,59–61] In contrast, variable deficiency of hormones regulated by the anterior pituitary including T3, thyroxine (T4), adrenocorticotropic hormone, thyroid stimulating hormone, and human growth hormone have been described. Moreover, there has been inconsistent improvement in physiological parameters after replacement of these hormones in both animals and humans.[24,59,60,62–65]

Vasopressin produces its physiological effects through three different receptors: V1, V2, and V3.[66] The V1 receptors are located within blood vessels and mediate the vasopressor effect. The antidiuretic effect of vasopressin is mediated via V2 receptors found on renal collecting duct epithelia. Stimulation of adrenocorticotropic hormone secretion is mediated by vasopressin via the V3 receptor located in the anterior pituitary. Diabetes insipidus from vasopressin deficiency has been associated with hemodynamic instability in cadaveric donors.[22,23] The vasopressin analogue 1-desamino-8-D-arginine vasopressin is highly selective for the V2 receptor subtype with no significant vasopressor activity in man.[66] Its duration of action ranges from six to 20 hr and may be given at doses of 2 – 6 μg *iv* every six to eight hours, as compared to the 15-min half-life of vasopressin.[14] Because of the combined vasopressor and antidiuretic effect of vasopressin, its use has been described in case series of adults and children with DI, and a wide range of doses between 0.5–15 $U \cdot hr^{-1}$ have been recommended.[4,5,14,28,34,40,67–70] The use of vasopressin at doses greater than 0.04 $U \cdot min^{-1}$ may cause coronary, renal, and splanchnic vasoconstriction, potentially jeopardizing cardiac, renal, and hepatic function.[31] However, the safety and efficacy of using a combination of vasopressin and 1-desamino-8-D-arginine vasopressin in organ donors also remains an option, and has been described in one randomized trial.[28]

Results from early descriptions of thyroid hormone therapy following brain death were conflicting and

could not support the routine use of thyroid hormone after the NDD.[30,59,61,63-65,71] Results from observational studies and randomized trials using T3 in patients undergoing coronary artery bypass grafting have been equally inconsistent.[72–79] The strongest evidence supporting the use of *iv* T3 or T4 in organ donors comes from a recent analysis of the United Network for Organ Sharing database.[6] Hearts procured from donors receiving triple hormonal therapy including T3 or T4 therapy demonstrated a significantly improved one-month survival rate (96.2%) as compared to those donors not receiving triple hormonal therapy. Both corticosteroid and T3/T4 therapy independently resulted in a 46% reduced odds of recipient death within 30 days, and a 48% reduced odds of early cardiac graft dysfunction.

Hyperglycemia is common after NDD and is thought to be secondary to insulin resistance.[80] No randomized trials exist to evaluate glycemic control in organ donors, however a large randomized trial and an observational study of glycemic control and insulin therapy in critically ill patients demonstrated the survival benefits of tight glycemic control between 6.1 and 8.0 mmol·L^{-1} respectively.[81,82]

Severe traumatic brain injury results in a "stress" associated rise in serum cortisol and may produce relative adrenal insufficiency.[59] In critically ill patients in septic shock, the use of corticosteroids has improved survival in those patients with relative adrenal insufficiency.[83,84] However, it is uncertain whether the beneficial effect of corticosteroids in cadaveric donors is a result of hormonal replacement or a modulatory effect of the inflammatory process described after the NDD.[21,85–88]

A recent consensus has recommended that donors with a left ventricular ejection fraction of less than 45% after standard management be treated with a combination of methylprednisolone, T3, and vasopressin.[4,5] This recommendation is supported by an observational study involving 10,292 consecutive brain dead organ donors within the United Network for Organ Sharing database which showed a significant improvement in organ procurement and an increased odds of a donor becoming an organ donor if treated with triple hormonal therapy.[40]

Pulmonary considerations

Successful lung procurement is challenging because of the association of brain death with neurogenic pulmonary edema, pneumonia, and systemic inflammation.[26,89–92] Unfortunately, in less than 20% of cadaveric donors are lungs retrieved.[93] Pathological studies of lungs deemed unsuitable for donation have indicated that bronchopneumonia, diffuse alveolar damage, and diffuse lung consolidation are the most common reasons for being deemed unsuitable.[94] Bronchial colonization or infection with bacteria or yeast is seen in up to 80% of organ donors, correlates with lung recipient survival, and varies by mechanism of brain death.[95–97] Moreover, transplantation mismatch of a cytomegalovirus positive donor lung into a cytomegalovirus negative recipient greatly increases the risk of recipient cytomegalovirus infection.[98] Given these findings it is recommended that every lung organ donor undergo bronchoscopy for therapeutic bronchial toilet, and to isolate potential pathogens in order to guide antibiotic therapy in both the donor and the recipient.[4,40] However, the benefits of empiric antibiotic administration prior to the diagnosis of pneumonia has only been demonstrated in a canine model.[99] Corticosteroids have an important role in the management of lung donors. One retrospective study of 118 lung donors administered methylprednisolone at a mean dose of 14.5 mg·kg^{-1} compared to 38 donors not receiving methylprednisolone demonstrated a significant improvement in donor oxygenation in the steroid-treated group.[100] A more recent analysis comparing donor factors predicting the procurement of lungs with or without hearts *vs* the procurement of hearts alone demonstrated an independent beneficial effect of using methylprednisolone in the organ donor.[9] These findings have been adopted in the recommendation of the use of methylprednisolone as part of a hormonal resuscitation strategy.[5,6] Due to prolonged ventilation in the supine position, microatelectasis is a common finding in the lungs of cadaveric donors. In animals, donor lungs develop microatelectasis and a reduction in pulmonary compliance and functional residual capacity despite positive end expiratory pressure (PEEP) and a relatively short ventilation period. This effect is worsened by preservation solution and ischemia reperfusion injury.[101,102] Shearing forces that produce stress on alveoli, epithelial and endothelial damage, and augmentation of the cytokine response are mechanisms for the alveolar injury seen during mechanical ventilation.[103] Given the similarity of the lung injury seen in organ donors with the acute respiratory distress syndrome, lung protective strategies used in the treatment of acute respiratory distress syndrome may prevent further lung injury in marginal lung donors.[104,105] However, these strategies have not been formally studied in organ donor populations.[106] Lung recruitment maneuvers utilizing high PEEP or pressure-controlled ventilation for short durations have been proposed as an adjunct to the lung protective strategies used in acute respiratory distress syn-

drome. However, higher levels of PEEP must be used immediately after recruitment maneuvers in order to produce a sustained effect.[105,107,108] A strategy of aggressive pulmonary care of the organ donor including bronchoscopic bronchial toilet, physiotherapy, and increasing PEEP was able to convert 34% of "unsuitable" lung donors to suitable donors with no difference in lung allograft survival when compared to recipients of lungs from "suitable" donors.[10]

Renal considerations

Brain death is associated with histologic evidence of both immunological and non-immunological damage to the kidney and the development of delayed allograft function. Delayed allograft function is associated with decreased renal recipient survival, increased rejection rates, and increased renal allograft nephropathy.[86,109–113] The incidence of acute tubular necrosis and allograft failure increase when high doses of dopamine are used (> 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to support the donor and if donor systolic blood pressure is consistently lower than 80–90 mmHg, as autoregulation of renal blood flow and glomerular filtration declines below this threshold.[14,114,115] Consequently, timely hemodynamic management of the organ donor is important. Although at an increased risk for recipient renal allograft dysfunction, marginal kidneys from donors over 60 yr of age, with cerebrovascular accidents as an etiology of death, with hypertension or diabetes mellitus, or with a serum creatinine greater than 133 $\mu mol \cdot L^{-1}$ should still be considered as candidates for organ donation.[116–121] This is an important consideration, as data from the United Network for Organ Sharing registry have demonstrated a reduction in the annual death rate from 6.3% in those recipients waiting for a renal transplant as compared to 4.7% for those receiving a marginal kidney and 3.3% for those receiving an ideal kidney.[120]

Hepatic considerations

Initial poor function of liver allografts result from factors such as the inflammatory process of brain death and preservation-reperfusion injury to the liver.[8,122–124] Cold preservation causes the sinusoidal lining cells of the liver to become edematous and detach, leaving the hepatocyte microvilli exposed to the sinusoidal lumen and resulting in cell death.[124] The importance of monitoring donor sodium levels and correcting hypernatremia has been emphasized in several observational studies. Both ABO incompatibility and donor plasma sodium > 155 $mmol \cdot L^{-1}$ have been independently associated with an increased rate of recipient death and retransplantation.[125] In a series of 168 liver transplants, a high donor serum sodium concentration, longer cold ischemia time, large platelet transfusion during surgery and prolonged recipient prothrombin time were independently associated with more severe hepatic dysfunction after transplantation.[126] High donor serum sodium concentrations may promote the accumulation of idiogenic osmoles within liver allograft cells. The subsequent transplantation of these livers into recipients with relatively normal sodium levels may promote intracellular water accumulation, cell lysis and death. Correcting donor serum sodium to levels below 155 $mmol \cdot L^{-1}$ has been shown to decrease the incidence of liver allograft loss.[127]

Infectious considerations

Several cases of solid organ infection in the donor being transmitted to the recipient with resultant sepsis and poor initial allograft function have been reported.[128–131] However, by using prophylactic antibiotics in recipients immediately after transplantation, two studies totaling 124 organ recipients have demonstrated no transmission of bacterial infection from bacteremic donors to organ recipients.[132,133] In an analysis of all organ donors cared for by the New England Organ bank between 1990 and 1996, only 95 (5.1%) of 1,775 organ donors were identified as being bacteremic.[133] No evidence of bacterial transmission could be identified in 212 recipients and there was no difference in allograft or recipient survival for recipients of organs from bacteremic as compared to non-bacteremic donors.

Transfusion thresholds

There are no studies investigating the use of red blood cell transfusions in brain dead donors. Recent consensus has recommended maintaining a hemoglobin level of ≥ 10.0 $g \cdot dL^{-1}$ or a hematocrit > 30% in organ donors.[5,14] In contrast, current critical care practice advocates a more restrictive transfusion strategy with a hemoglobin threshold of 7.0 $g \cdot dL^{-1}$.[134,135] Likewise, no guidelines exist in the literature regarding appropriate thresholds for either plasma or platelet transfusions in donors although large platelet transfusion requirements during liver transplant surgery was an independent predictor of severe hepatic dysfunction after transplantation in one cohort study.[126] However, higher platelet requirements in this study may have been confounded by a more technically complicated procedure.

Conclusions

Our understanding of the pathophysiology of brain death and its effects on donor and recipient organ

function has progressed over the last two decades. Several cohort studies have provided valuable information to clinicians regarding donor characteristics predisposing to adverse recipient outcomes and the potential benefits of respiratory, hormonal and hemodynamic therapies. These studies have also been helpful in outlining the risk of allograft failure from marginal donor organs. As the demand for organs increase, future emphasis should be placed on evaluating potential therapies within the context of clinical trials.

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