DONOR MANAGEMENT AND ORGAN VIABILITY

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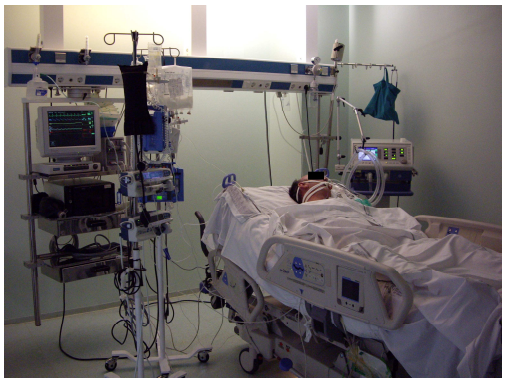
Subject 1 – Donor Management

Topic 1 – Introduction

Once a clinical diagnosis of brain death (BD) has been established, the treatment of the potential donor should be redirected and should centre on the support and protection of the organs to be transplanted (organ-targeted donor treatment). This means that the progressive dysfunction of organ function that occurs after BD must be recognised in order to delay it or treat it.[1] BD will irreversibly lead to cardiac arrest. During this process there are major pathophysiological changes in the cardiovascular and respiratory systems as well as changes in hormonal and metabolic balance. Donor management should correct these disturbances with the aim of preserving organ viability for as long as possible.[2]

Despite the disparity between the number of persons awaiting an organ transplant and the number of organs available, donor management continues to be one of the most neglected areas in transplant medicine.[3] Up to 25% of potential donors are lost due to cardiovascular collapse before the organs can be obtained. Establishing intensive and focused donor management could reduce the number of cadaveric donors lost due to cardiovascular collapse.[4]

Picture 1:



Topic 2 – Cardiovascular Management

Section 1 – Pathophysiology

BD is characterised by two haemodynamic phases. Initially, there is a massive sympathetic discharge (sympathetic or autonomic “storm”) which results in a hypertensive crisis together with severe cardiovascular disturbances. A second phase follows, induced by a profound reduction in the sympathetic discharge. The inotropic and chronotropic status of the heart deteriorates, resulting in a reduction in cardiac output. [5]

Arterial hypotension is one of the most constant pathophysiological disorders. It is caused by several factors and requires a structured approach in order to make a differential diagnosis.

Vasodilatation

BD causes dysfunction of the vasomotor centre and a reduction in catecholamine release, which results in vasodilatation due to the reduction of peripheral vascular resistance (Table 1).[6]

Causes of haemodynamic disturbances in the potential organ donor. Modified from Wood et al.

HYPOVOLAEMIA	CARDIAC DYSFUNCTION	VASODILATATION
Absolute hypovolaemia	Pre-existing disease	Spinal shock
Initial injury	Initial injury	Catecholamine depletion
Inadequate resuscitation	Myocardial contusion	Loss of vasomotor control and autoregulation
Fluid leaking into interstitial space	Pericardial tamponade	Relative adrenal insufficiency as a result of trauma or critical illness
Decrease in intravascular oncotic pressure after crystalloid resuscitation	Myocardial ischaemia or infarction	Endocrinopathy of brain death
Treatment for intracranial pressure	Process of brain death	Acquired sepsis
Fluid restriction	Catecholamine damage	
Urea	Ischaemia-reperfusion injury	
Diuretics	Metabolic depression	
Mannitol	Acidosis	
Hyperglycaemia-induced osmotic diuresis	Hypothermia	
Diabetes insipidus	Hypophosphataemia	
Hypothermic "cold" diuresis	Hypocalcaemia	
Effective hypovolaemia	Hypoxia	
Loss of vasomotor tone and pooling in venous capacitance bed	Endocrinopathy of brain death	
Hypothermia treated with rewarming	Volume overload resulting in congestive heart failure	
	Arrhythmias	
	Catecholamines	
	Ischaemia	
	Hypokalaemia	
	Hypomagnesaemia	

Hypovolaemia

Hypovolaemia, either secondary to previous fluid restriction (for brain edema control) or secondary to polyuria due to antidiuretic hormone (ADH) deficiency or due to hyperglycaemia, leads to hypotension in the potential donor. Changes in volume status frequently require the use of invasive techniques in order to be monitored.

Cardiac dysfunction

Likewise, deterioration of cardiac function also exists in BD, which is probably due to a number of different factors: hormonal deficiency (a reduction in levels of free thyroxine, cortisol, arginine

vasopressin and insulin), increased anaerobic metabolism (metabolic damage due to hypoxia in all tissues and reduction of ATP energy reserves). Cardiac inotropism and chronotropism are altered and consequently cardiac output drops. It has been suggested that spinal shock at C1 which occurs after tonsillar herniation may contribute to the reduction of peripheral vascular resistance.[1]

Section 2 – Objectives

The goal in haemodynamic management is to maintain adequate circulating volume, suitable cardiac output and good perfusion pressure to ensure optimal oxygen supply to tissues. It has been demonstrated that the most crucial factor for the viability and functioning of the transplanted organ is appropriate perfusion pressure in the donor. The incidence of post-transplant acute tubular necrosis is substantially higher when donor systolic blood pressure (BP) is between 80-90 mmHg. Likewise, given the extreme sensitivity of the liver to ischaemia, a systolic BP <80 mmHg gives rise to a high incidence of post-transplant failure. For this reason it is essential to maintain a minimum systolic BP >100 mmHg which enables adequate perfusion of all organs. Correction of hypotension should be one of the principal aims in the management of organs for transplantation.

Plasma volume expansion, with monitoring of the vascular refilling rate (central venous pressure [CVP] between 10-15 cm H_2O), is the first measure to be considered. Although CVP is usually similar to pulmonary capillary wedge pressure (PCWP), occasionally CVP and PCWP do not coincide and CVP may remain low despite high PCWP due to left ventricular dysfunction.[7] In situations of haemodynamic instability (left ventricular dysfunction by echocardiography with an ejection fraction <45%), the donor should be monitored using a pulmonary artery catheter to define left ventricular filling pressure and cardiac output, guide administration of vasoactive drugs and adjust the fluid balance between the various organs, thereby optimising cardiac resuscitation.[6]

Recently, importance has been given to the monitoring of mixed venous oxygen saturation (SvO_2) in potential organ donor patients in order to adequately monitor peripheral perfusion of organs (SvO_2 between 60-80%). Continuous monitoring of this parameter alerts us to changes in the patient's condition sooner than with other indicators, thus allowing earlier intervention.[8]

Base excess and lactate monitoring have also been shown to be efficacious in providing guidelines on fluid administration and resuscitation.[9]

Section 3 – Fluid and electrolyte balance

It is not easy to maintain the fluid and electrolyte balance in these patients. There are losses of free water and electrolytes. The appearance of fluid and electrolyte imbalances such as hypernatraemia, hypocalcaemia, hypomagnesaemia, hypokalaemia, hypophosphataemia favour the onset of cardiovascular complications such as arrhythmias, myocardial dysfunction and sudden cardiac arrest.[10]

Losses due to polyuria, which is quite frequent, (secondary to ADH deficiency or osmotic diuresis due to hyperglycaemia) and losses secondary to hyperthermia, which is quite rare, should be corrected appropriately. Excessive glucose-containing fluids may cause hyponatraemia and hyperglycaemia with the resulting increase of intracellular dehydration and polyuria. Moreover, fluid replacement with sodium-rich solutions in patients with increased osmolarity due to hypohydration may cause hypernatraemia within a few days, which is difficult to correct. On the other hand, hypernatraemia is a negative prognostic factor for liver graft function. Lactated Ringer's solution with a lower sodium concentration may be the crystalloid of choice. The response to urinary losses should preferably be based on the calculated electrolyte losses in urine. Fluid replacement should be conducted with isotonic crystalloid solutions (physiological saline, Ringer's solution) and colloid solutions at a rate of 5 ml/kg every 5-10 minutes until systolic BP over 100 mmHg or CVP of 12 cm H_2O is reached. Rehydration should be carefully conducted to avoid pulmonary oedema, cardiac overload or hepatic congestion. Normovolaemia should be restored before starting any vasopressor drug therapy.

There is no evidence to determine if colloids or crystalloids are more beneficial. Blood components, crystalloids and albumin are frequently used with a view to maintaining adequate plasma and blood volume with moderate haemodilution, improved tissue oxygenation and microcirculation and to reduce the risk of microembolisms. The use of hydroxyethyl starch should be avoided, with the aim of preventing renal tubular lesions and post-operative renal graft dysfunction.[11]

Blood losses should be replaced, keeping haematocrit above 30% and haemoglobin above

100 g/l in order to maintain adequate oxygenation.[12]

Picture 2:Fluids

Section 4 – Vasoactive drugs

Once the correct fluid balance is achieved, persistent hypotension should be treated with inotropic drugs. Traditionally, dopamine has been the inotropic drug of choice in cadaveric donors. However, recent studies have not supported a beneficial effect of dopamine on renal, liver and splanchnic circulation; moreover, dopamine may suppress the hormonal functions of the anterior pituitary gland.[13]

Prolonged administration of high doses of dopamine may cause depletion of endogenous noradrenaline (degradation of receptors) and ATP reserves in the organs and affect their functioning after implantation, particularly in the heart. In contrast, some authors maintain that dopamine, at a maximum dose of 12 µg/kg/min, does not cause damage to heart tissue that would significantly compromise the transplanted heart, nor do they refer to increases in post-operative mortality. If doses of dopamine over 12 µg/kg/min are required, then it should be combined with dobutamine to reduce dopamine administration to levels which are not deleterious to organ perfusion. Dobutamine would also be of benefit in patients with cardiac contractile dysfunction, such as patients with myocardial contusion.

Drugs with a predominantly vasoconstrictor effect (ephedrine, methoxamine) should be avoided if possible.

Vasopressin

In some centres vasopressin has become the first choice for organ donors requiring vasoactive support, as many authors have described the successful support and the catecholamine-sparing effect of intravenous vasopressin.[13;14] Vasopressin has been shown to have a stabilising effect on systemic BP after brain death, allowing the use of adrenaline or noradrenaline to be reduced or discontinued in some cases. In addition, vasopressin helps to maintain energy metabolism and is effective in diabetes insipidus, which occurs in 80% of brain dead donors.[15]

Complex cases

In patients where haemodynamic management is difficult (not responding to usual measures, chronic heart disease, etc) monitoring of pulmonary pressure and ventricular filling using a Swan-Ganz catheter is advised. This will better enable us to finely adjust the treatment to donor requirements. In donors with severe spinal shock, the use of α-adrenergic and vasoconstrictor drugs may be necessary to maintain organ perfusion. If blood pressure is not maintained with fluids, dobutamine and dopamine, then noradrenaline at a dose of between 0.2 and 1.6 µg/kg/min may be administered. Some protocols include noradrenaline as the first choice vasoactive drug. Some studies have described an association between the empirical use of noradrenaline and deterioration of right ventricular contractility.[16] When the appropriate BP is not attained, this treatment may be replaced by a low dose adrenaline infusion (0.1 µg/kg/min).

Catecholamine effects

It should be borne in mind that prolonged use of inotropic drugs may compromise the quality of the organ to be transplanted. However, recent papers[17-20] suggest that catecholamine use in donors may reduce acute rejection and improve graft survival. Furthermore, they may exercise a neuromodulating effect as in the case of dopamine which, according to a study by Schnuelle[20], may reduce endothelial expression of adhesion molecules and exercise a protective effect on renal cells against oxidative stress in cold ischaemia and subsequently in the reperfusion associated with an improved initial renal function.

Sympathetic storm

During the initial phase (first three hours) of the onset of BD, before the appearance of vasoplegia, a clinical picture emerges that is characterised by arterial hypertension, bradycardia that later progresses to tachycardia, cardiac arrhythmias (supraventricular tachycardia, ventricular extrasystoles), electrocardiographic changes (ST-segment elevation) and hyperthermia, secondary to an abrupt catecholamine discharge. This period is difficult to manage. Some experimental studies suggest the short term use of beta blockers such as esmolol, which would mitigate this hypertensive and arrhythmogenic response during cerebral herniation. In practice they are rarely necessary.

Renal function

Renal function must be carefully maintained with strict control of diuresis. Maintaining proper perfusion pressures with the use of vasopressors and the administration of mannitol infusion or furosemide have been used to provide renal protection.

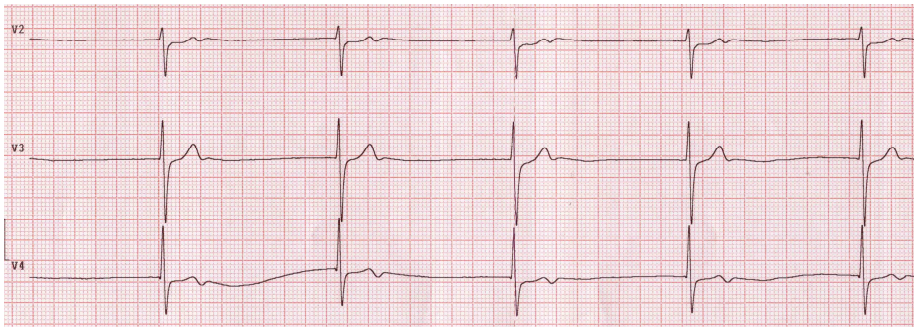
Section 5 – Cardiac rhythm abnormalities

About 20-30% of donors present arrhythmic episodes. Sinus tachycardia is the most common appearing in 20-50% of donors, followed by sinus bradycardia in 15%, auricular fibrillation in 10% and other less frequent arrhythmias.[21]

Bradycardia

Bradycardia frequently appears in the evolution of BD, commonly as part of the Cushing phenomenon (hypertension and bradycardia). In a patient in brain death, the nucleus ambiguus of the brain stem is destroyed and vagal tone is lost, so atropine will not be capable of reversing bradycardia in this situation. The use of medications with a chronotropic effect directly on the heart is therefore recommended. Isoprenaline at a dose of 1-3 µg/min is the most effective. Other drugs with a positive chronotropic action are those commonly used as inotropic agents such as dopamine, dobutamine and epinephrine.

Picture 3: Bradycardia

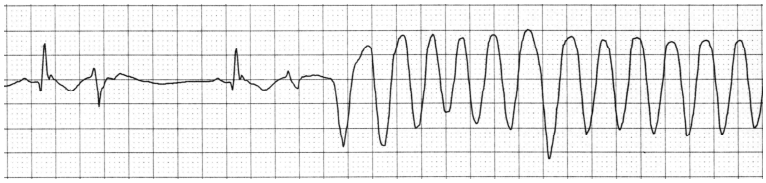


Tachyarrhythmias

Ventricular and auricular arrhythmias as well as conduction abnormalities frequently occur in organ donors. These are generally secondary to electrolyte imbalance, hypothermia, myocardial ischaemia, iatrogenic disorders (inotropic drug infusions etc) or those of central origin. Aetiological treatment for the cardiac rhythm disorder should be first applied and if this proves insufficient, antiarrhythmic drugs should then be used, with amiodarone being the first choice.[21] In the case of refractory ventricular arrhythmias, hypothermia should be considered as the triggering factor. Lengthening of the QT interval may trigger ventricular extrasystoles and torsade de pointes-type

ventricular tachycardia. In this case, it would be necessary to discontinue all medications that may cause lengthening of the QT interval, correct the electrolyte imbalances, particularly hypokalaemia, and administer intravenous magnesium at a dose of 2 g IV/10 min. On occasion it may be necessary to fit a pacemaker to prevent relapse once the rhythm has been corrected.[22]

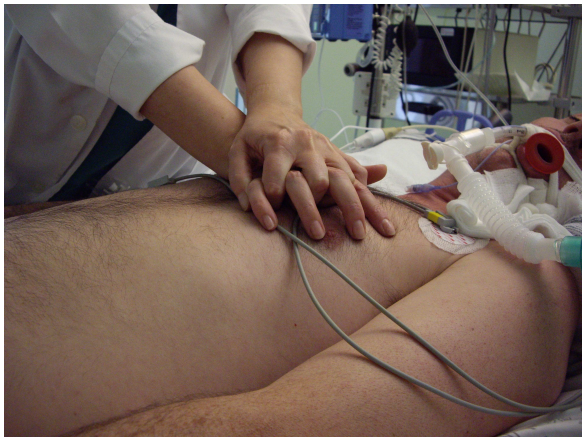
Picture 4: Onset of Ventricular Tachycardia



Cardiac arrest

At times, donor management in this situation can be very difficult, presenting within a few hours a cardiac arrest which is difficult to overcome and which would imply loss of the donor. In these cases, at present, organ function may be preserved using “non-heart-beating donor” perfusion techniques. This technique is performed either by renal perfusion with a preservation solution by gravity via the femoral artery, using the appropriate catheters to block renal circulation (in situ perfusion) or by perfusion of the donor’s organs using extracorporeal circulation similar to that used in cardiac surgery (normothermic recirculation).[2]

Picture 5: CPR



Topic 3 – Temperature and Endocrine Disorders

Section 1 – Temperature control

Monitoring body temperature should be another of the fundamental points in organ donor management. After BD, hypothalamic control of temperature is lost leading to donor poikilothermy. This produces a progressive loss of body heat and the consequent deterioration of the haemodynamic state by vasoconstriction and cardiac instability. Hypothermia also leads to arrhythmias [general conduction delay, T wave inversion, QT lengthening, appearance of J wave (between 32-33 ºC), auricular fibrillation; and with temperatures less than 30ºC, ventricular fibrillation], renal function disorders due to the reduction of glomerular filtration, incapacity to maintain tubular concentration gradients (cold diuresis), coagulation disorders and left shift of the oxygen-haemoglobin dissociation curve with a reduction of free oxygen delivery in tissues.

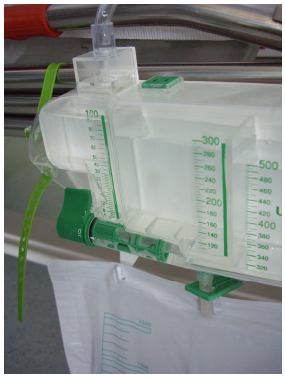
The use of heated intravenous solutions, humidification and heating of respiratory gases as well as insulating or electric blankets are necessary to maintain the body temperature above 35^{o}C.

Picture 6: Thermal blanket

Section 2 – Diabetes Insipidus

Diabetes insipidus is common in BD, occurring in 38% to 87% of cases, up to 98% in some series, and is caused by a deficiency of antidiuretic hormone (ADH). This is due to the loss of hypothalamic-pituitary control over ADH secretion and release in response to osmotic stimuli (sodium concentration) on the hypothalamic osmoreceptors and other non-osmotic stimuli from receptors of cardiac and pulmonary volume that are integrated in the hypothalamus. Three hours after the onset of BD, plasma levels of vasopressin cannot be detected (less than 0.1-0.5 pg/ml). This causes an uncontrolled increase in hypoconcentrated urine production (diuresis >4 ml/kg/h; density < 1005; plasma osmolarity > 300 mmol/kg and urinary osmolarity < 300 mmol/kg) and the appearance of hypernatraemia, hypomagnesaemia, hypokalaemia, hypocalcaemia and hypophosphataemia.

Picture 7: Hyposomolar polyuria



Treatment

These losses should be treated with the correct ion supplement (including calcium, magnesium and phosphate) and fluids. When urine production exceeds 200-250 ml/h (3-4 ml/kg/h) ADH analogues should be used. Vasopressin action is dose dependent. At low doses (1-2 U/h; 2-10 mU/kg/min), it acts on the V2 receptors on renal cell membranes increasing water reabsorption and reducing diuresis, while with higher doses it acts on the V1 receptors on blood vessels, causing arterial hypertension and vasoconstriction in the pulmonary, mesenteric, hepatic and coronary territory and reducing renal flow without increasing its effect on diuresis. Its duration of action is about 2-3 hours and should preferably be administered via continuous infusion. The doses recommended by various authors range between 5-10 U of vasopressin subcutaneously or intramuscularly every 2-4 hours or 50 ml/h infusion with 10 IU in 500 ml of saline.

ADH analogues

Modifications in the vasopressin structure may selectively increase the antidiuretic properties of the hormone. Desmopressin or DDAVP (1-deamino-8-D-arginine vasopressin), a synthetic analogue of natural antidiuretic hormone (arginine vasopressin), has a selective action on V2 receptors with an antidiuretic effect (antidiuretic/pressor ratio = 2000 to 3000:1) and is the drug of choice. The latency

time is 15 to 30 minutes and its action is more potent and prolonged (5-12 hours). It is often administered as an intravenous bolus of 0.03-0.15 µg/kg/8-12 hours or 1-5 µg/8-12 hours. It may be administered at doses five times higher via the intranasal route. Subcutaneous or intramuscular administration would not appear to be advisable due to erratic drug absorption in donors with peripheral perfusion (muscular and subcutaneous tissue) which may vary greatly depending on haemodynamic status and body temperature. 8-lysine vasopressin (LVP) acts predominantly on V1 receptors, with a significant pressor effect and low, if any, antidiuretic effect. (Table 2)

Table 2. Antidiuretic hormone analogues used in diabetes insipidus (AVP= arginine vasopressin; 8-LVP= 8-lysine vasopressin; dD-AVP= 1-deamino-8-D-arginine vasopressin; IN= intranasal administration; +++ = strong effect; + = moderate effect; +/- = weak effect).

TRADE NAME (COMPOUND)	ADMIN ROUTE	DOSE	ANTI- DIURETIC EFFECT	VASOPRESSOR EFFECT
Pitressin Tannate (AVP)	IM	5-10 U/6-8 h	at low doses	at high doses
Aqueous pitressin (AVP)	IV	2-10 mU/kg/min (1-2 U/h)	at low doses	at high doses
Vasopressin SANDOZ® (8-LVP)	IV	1-2 U/h	+	+++
Vasopressin SANDOZ® (8-LVP)	IM	8 U/4h	+	+++
Minurin (dD-AVP)	IV	0.03-0.15 µg/kg/8-12 h (1-5 µg/8-12h)	+++	+/-
Minurin (dD-AVP)	IN	5-25 µg/8-12 h	+++	+/-

Section 3 – Pituitary disorders

The disturbances caused by BD to the anterior pituitary are not clear. Levels of thyroid hormone (triiodothyronine) are decreased in donors and do not respond to exogenous administration of TRH. After BD, aerobic metabolism is gradually replaced by anaerobic metabolism which leads to a progressive tendency towards metabolic acidosis, due to increased lactate levels, and haemodynamic instability. Experimental animal studies in myocardium demonstrate that intracellular ATP is reduced after BD, with the consequent reduction in cardiac energy reserves (glycogen) and the accumulation of lactates, leading to a progressive deterioration of cardiac functioning and the development of haemodynamic instability. Triiodothyronine would appear to play a predominant role. There is evidence that administration of T3 stimulates, within a short time, a rapid increase of Ca++, ATP, glucose, and pyruvate, together with a reduction in CO_2 production and normalisation of lactate levels. This would suggest the return of aerobic metabolism, recovery of cell energy reserves and improved myocardial function and the haemodynamic status of the donor. The studies by Novitsky et al and García-Fages et al appear to point in this direction.[23-26]

Euthyroid sick syndrome

Other authors suggest that thyroid hormonal disturbances could be encompassed within what is called the “euthyroid sick syndrome” and, in some cases, they are against hormone replacement therapy in patients with severe brain traumatism. It has not been possible to universally reproduce Novitsky's results and T3 is not widely used.[24-26]

Hormone replacement therapy

However, the use of hormone "cocktails" for donor management is being taken up again in some Anglo-Saxon countries. Rosendale et al published a paper on the use of triiodothyronine, arginine vasopressin, methylprednisolone and insulin as part of a general donor management protocol, but with poor results. These treatments continue to be used today in various American and Australian centres.[27]

Wood suggests that it would be wise to reserve hormone replacement therapy for unstable donors requiring dopamine doses over 10 µg/kg/min or with a cardiac ejection fraction of less than 45%.[6]

Section 4 – Glycaemic abnormalities

Glycaemic control is often altered in BD patients because of hypersecretion of adrenal hormones, the glucose solutions, glucocorticoid and catecholamine treatment, hypothermia and changes in pancreatic microcirculation. This may lead to fluid and electrolyte imbalances such as metabolic acidosis, osmotic diuresis, dehydration and hypovolaemia. Therefore, these patients should be strictly controlled using insulin in continuous endovenous infusion. Donor hyperglycaemia appears to be associated with lower graft survival in pancreas transplants. However, hyperglycaemia taken in isolation cannot be considered as a contraindication for organ donation, as donor plasma glycaemic levels are not correlated with insulin, C-peptide or glycosylated haemoglobin levels and do not affect pancreatic functioning. For all these reasons, hyperglycaemia in the cadaveric donor should be detected early and treated with insulin, preferably by continuous intravenous infusion as absorption by other administration routes is variable and difficult to control. The dose to be administered would range between 0.5 and 7 IU/hour of rapid-acting insulin.

Furthermore, BD reduces pancreatic microcirculation via the reduction of functional capillary density, increasing leukocyte adherence and increasing histological damage.[28]

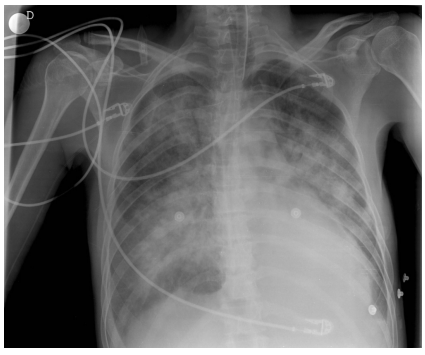
Topic 4 – Respiratory Management

Section 1 – General aspects

Maintaining correct tissue oxygenation requires close attention to donor ventilation support during management, particularly bearing in mind that up to 15% of all donors present acute respiratory distress syndrome (ARDS) or acute lung injury (ALI).[29] At the onset of BD, particularly in donors aged between 13 and 30 years, neurogenic pulmonary oedema may occur due to the abrupt increase of circulating catecholamines.

Ideally, pO_2 should be maintained above 100 mmHg, with the lowest FiO_2 possible and lowest levels of positive end expiratory pressure (PEEP). Low CO_2 production due to the absence of cerebral blood flow, sympathetic tone and muscular tone conditions the use of minute volumes lower than those currently used in conventional ventilation with the aim of maintaining normocapnia.[30] Formerly, it was postulated that the use of PEEP in donors with respiratory impairment may cause the haemodynamic status of the patient to deteriorate due to reduced venous return and cardiac output, which would imply a drop in renal vascular flow and progressive impairment of renal function.

Picture 8: Pulmonary edema

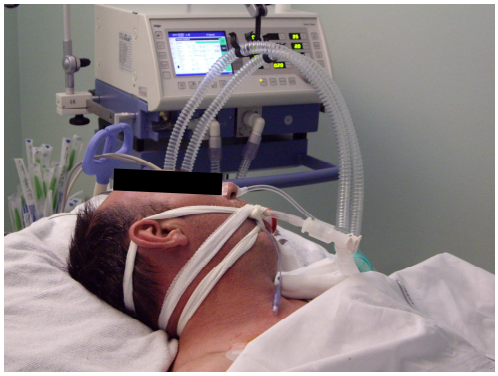


Section 2 – Lung transplant

It is of vital importance in lung transplants to follow standardised protocols that optimise and maintain optimum lung function.[27;31;32] Following these protocols, respiratory management of these patients should include: the use of low FiO_2 to avoid pulmonary toxicity, the use of PEEP (8-10 cm H2O) to reduce atelectasis, avoiding excessive fluid overload with close monitoring of central venous

pressure, pulmonary pressure and wedge pressure, controlling the correct administration of inotropic agents (and/or vasopressin), and taking all the preventive measures necessary to avoid respiratory superinfection.

Picture 9: Mechanical ventilation



Section 3 – Pulmonary care

As with any other patient admitted to the ICU, close monitoring of ventilatory function, alveolar recruitment, early and precise diagnosis of respiratory infection by flexible bronchoscopy, bronchoalveolar lavage and sample taking with the protected-specimen brush technique, as well as the use of the least harmful methods of ventilation for lung parenchyma (reduction of tidal volume and lower airway pressure, etc) improve lung viability and the number of potential grafts.[32]

Protective ventilation

BD initiates a severe systemic inflammatory response by the release of proinflammatory mediators into circulation, which is particularly severe in the lungs and especially in lungs with acute injury.[29] It is known that ventilation with high tidal volume and low pressure at the end of expiration may exacerbate the systemic and pulmonary inflammatory response. The recommended "protective ventilation" strategy includes low tidal volume, high PEEP, Continuous Positive Alveolar Pressure (CPAP) during the apnoea test and recruitment manoeuvres.[29;33]

Picture 10: Bronchoscopy

Corticosteroids

The use of corticosteroids has been suggested to reduce the inflammatory response that determines preclinical lung injury, thereby increasing the potential number of lung donations. The use of methylprednisolone at doses of 15 mg/kg has been shown to improve gaseous exchange and is an independent predictor of successful lung transplantation.[29;31]

Transport to the OR

Ventilation for around 20-30 minutes with FiO_2=1 is advisable prior to transfer of donor to operating theatre.

Topic 5 – Coagulation Abnormalities and Infections

Section 1 – Coagulopathy

As with patients with severe brain trauma, organ donors may occasionally present coagulation disorders which can even manifest as signs of disseminated intravascular coagulation. Release of fibrinolytic agents from ischaemic-necrotic brain tissue (thromboplastin, brain gangliosides) would probably be the initial cause of coagulopathy and why it is maintained. Plasma or platelet concentrate transfusions may be necessary when this occurs, to maintain coagulation parameters within normal limits.

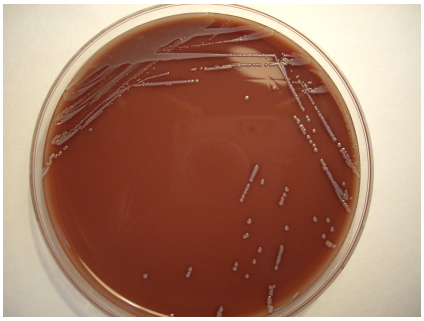
Donor coagulopathy is multifactorial, and prior medications such as warfarin, aspirin or non-steroidal anti-inflammatory drugs may, on occasion, be contributory factors.

Section 2 – Infectious complications

BD patients may present respiratory superinfections secondary to bronchoaspiration or prolonged mechanical ventilation. At the same time, they may present trauma in the thoracic cage, extremities or abdomen, which may also cause localised infection. Furthermore, the presence of bladder catheters, nasogastric tubes and arterial or venous catheters may promote the entry of microorganisms and sepsis into the donor. A risk factor analysis and appropriate antibiotic prophylaxis may minimise these cases.

One of the problems to most commonly impede lung transplants is the high incidence of infection in this organ. This is due to the contact of the lungs with the external environment which leads to a high rate of microbial contamination and infection. Prophylaxis is advisable with broad spectrum antibiotics (according to the results of Gram staining and culturing of tracheobronchial secretions) to avoid transmission of the infection to the recipient.

Picture 11: Cultures



Topic 6 – Other Aspects

Section 1 – Free radical release

Studies on organ preservation have demonstrated the involvement of oxygen-derived free radicals in microcirculation and parenchymal cell disturbances, associated with reperfusion of ischaemic tissues. Mannitol has been used with the aim of reducing the appearance of oxygen-derived free radicals. Corticosteroids, due to their membrane stabilising effects, have also been used for this same purpose. The use of allopurinol is based on its inhibitory effect on the conversion of hypoxanthine to xanthine, thus preventing the release of oxygen-derived free radicals during reperfusion. Allopurinol may be administered to the donor before organ retrieval or to the preservation solution used for each individual organ. Other drugs such as superoxide dismutase, catalase and other "anti-oxidant" substances and slow calcium channel blockers (diltiazem) have been used for this purpose.

The lung is very sensitive to the effect of oxygen-derived free radicals and the addition of these drugs to the perfusion or preservation fluid has been shown to reduce lung damage secondary to ischaemia or reperfusion. Prostaglandins and particularly prostacyclin (vasodilator, platelet aggregation inhibitor and cytoprotectant) have been used with a view to avoiding the formation of free radicals.

Section 2 – Nutritional aspects

Patients with brain trauma and brain death are in a hypercatabolic state, which is associated with a systemic inflammatory response and ischaemic reperfusion injury. Nutritional intervention may modulate the repercussions of these phenomena in the donor. The use of glucose solutions, the starting or maintenance of enteral nutrition and the continuation (though perhaps not starting) of parenteral nutrition may be recommendable. Micronutrient therapies have also been suggested, containing micronutrients, polyphenols, fish oil and glutamine, which may improve the functioning of the implanted organ.[8;34]

Section 3 – Immunological and inflammatory response

The appearance of a systemic inflammatory response after brain death is the cause, which until recently was unknown, of a large number of pathophysiological disorders (pulmonary, pancreatic, etc) which manifest in the potential organ donor.

There are various lines of research that examine the impact of up-regulation in the synthesis of proinflammatory cytokines such as the tumour necrosis factor-α, IL-2, IL-6 and IL-8 as well as the use of antibodies which inhibit their action in various donor organs. Likewise, the impact of cell adhesion molecules, such as selectins and ICAM, and the influence of macrophages and T-cells are also being studied.[5;35-37]

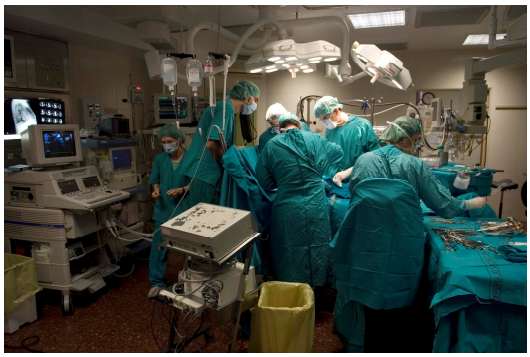
Advances in these lines of investigation have enabled a better understanding of these disorders, and will provide new therapeutic approaches in the near future.

Topic 7 – Intra-Operative Management

Section 1 – The role of the anaesthesiologist

The anaesthesiologist should continue the care of the donor to maintain correct perfusion and oxygenation of organs until they are retrieved. Multiorgan retrieval is increasingly more frequent with the procedure lasting around 3-4 hours, depending on the organs being retrieved. Therefore, donor management during this period should be carefully conducted to preserve organ function and should be similar to the management conducted during the previous days or hours. The anaesthesiologist should evaluate the patient's condition (haemodynamic, respiratory, biochemical, etc), establish the size and number of the perfusion catheters necessary for the procedure and, in the majority of occasions, transfer the patient from the intensive care unit to the operating theatre.

Picture 12: Multiongan retrieval



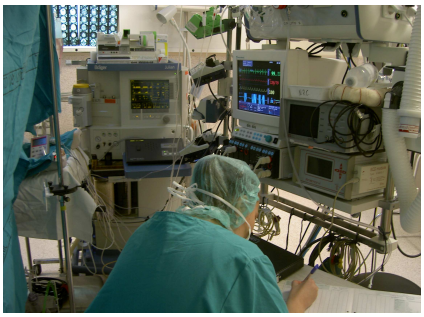
Section 2 – Monitoring

Monitoring should include: ECG, CVP, arterial blood pressure, urine output, central body temperature, capnography and pulse oximetry. At times it may be recommendable to monitor lung

pressure and PCWP. Acid-base balance, electrolyte, glycaemia and haemoglobin concentrations should be monitored simultaneously. Gelb et al suggest the "100 rule" (arterial pressure > 100 mmHg; urine output > 100 ml/h; PaO_2 > 100 mmHg; haemoglobin > 100 g/l) as the goals to be maintained during organ retrieval.[38]

The operating theatre should also be maintained at the appropriate temperature to prevent cooling of the donor and similar measures should be taken to those used in ICU to maintain body temperature, bearing in mind that the opening of the abdominal and thoracic cavities implies major heat losses.

Picture 13: Monitoring



Section 3 – Common problems

The problems commonly seen during donor management (hypotension, arrhythmias, diabetes insipidus, oliguria, coagulopathies, etc) may persist during the intra-operative procedure and these should be managed in a similar manner to donor maintenance. Reflex movements may occur in the donor due to the integrity of the lower motor neuron system, which is responsible for spinal reflexes. These movements may occur suddenly, stimulated by surgery, and should not raise suspicions on the validity of the BD diagnosis. The use of neuromuscular blockers is recommended to avoid the occurrence of these reflex movements.

Furthermore, sweating, tachycardia or hypertension may occur in the donor after the surgical incision and although their pathophysiology is not clear, it may be due to a spinal response caused by vasoconstriction or to the stimulation of the adrenal medulla by a spinal reflex. The use of analgesics to avoid the medullar response to surgical stimulation is acceptable. In this case, it would be wise to reduce the dose of inotropic agents or the use of vasodilators. Halogenated gases may be useful.

The response to blood and fluid losses due to exposure of viscera should be similar to that of any surgery, so it is necessary to ensure a reserve of blood products prior to the surgery, especially if it is a multiorgan operation.

Section 4 – Special measures

During retrieval, administration of mannitol (1-1.5 g/kg) and methylprednisone (30 mg/kg) reduces the harmful affects of reperfusion of the organs. Alpha-blockers (phenoxybenzamine, phentolamine or chlorpromazine), verapamil or prostaglandins have been used to reduce renal spasm after traction of vascular hila during retrieval and are also used in some protocols during liver and lung retrieval to favour the correct perfusion of preservation liquids and good organ flushing. Use of α-blockers is reserved for cases where haemodynamic support is suspended while awaiting cardiac arrest (cardiac arrest donors; Maastricht category III), counteracting the massive catecholamine release and allowing better organ perfusion. However, the use of these drugs in BD organ donors does not appear to be very effective. Administration of lidocaine 2 mg/kg followed by continuous infusion in the period prior to retrieval has been associated with a reduction of the risk of acute tubular necrosis in transplanted kidneys. Likewise, heparin (3-5 mg/kg) should be administered immediately before clamping to avoid intravascular thrombosis. Removal of the catheters inserted in the territory of both cavas must not be forgotten at this point.

Topic 8 – Final remarks

Finally, it should be highlighted that the most effective tool available to reduce organ loss, improve organ recovery and improve functioning of implanted organs is the application of universal standardised protocols and algorithms,[2-4,8,27,39-41] and also the professionalisation of the specialists

who are most involved in the potential donor management process, namely anaesthesiologists and transplant coordinators.[3,40]

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Subject 2 – Organ Viability Criteria

Topic 1 - Introduction

Organ viability is a term used to obtain as much information as possible about current organ function as it relates to the general condition of the donor, the medical history, the cause of death and the medical evolution following critical admission and management of the potential donor. These criteria are directly related to possible organ outcome.

Although theoretically this seems to be an objective measurement and a standardised system for evaluating and accepting an organ for transplant, in practical situations a standardised approach depends upon several factors. An organ donor procedure is mostly performed in a short time span with limited information, related to the momentum of the acute admission.

From the transplant community and the various transplant acceptation criteria, there is no real standard. This is because of different policies that may influence the acceptance of the specific organ as such:

- The type of patient and the medical condition of a patient for whom the organ is offered
- The allocation policy of the system in which the donor organs are offered
- The experience of the transplant team itself with standardised or extended organs

In order to be able to objectively evaluate the clinical viability criteria of a specific organ for transplant, we need to evaluate general and organ-specific viability criteria. The general criteria influence all organ functions and may compromise the clinical outcome of every organ. There are some clinical viability criteria that may compromise one organ but are totally irrelevant for other organs. What is important is that this policy is the standard starting point in every clinical evaluation of the donor and the viability criteria that need to be followed in order to accept or decline an organ offer. Criteria that are too strict will definitely accelerate the problem of chronic organ scarcity. It is important that general and organ-specific viability criteria are presented as broadly as possible, but are founded on thorough and clear clinical evaluation tools, giving the different transplant teams the correct information to be able to accept the organ objectively. Between the available information and added clinical analyses, donor teams and transplant coordinators should always balance investment versus outcome parameters to avoid overload and burden on donor hospitals and their teams. Acceptance criteria are based on two factors; donor-recipient compatibility and quality. Quality as such is strongly influenced by experience, and therefore standardised protocols to exclude factors that can influence negative outcomes should be based on extensive experience and exchange between experienced teams.

Topic 2 - General Viability Criteria and Exclusion Criteria

Section 1 - Introduction

In the spirit of maximising the donor pool and avoiding primary triage of potential donors, absolute exclusion criteria should be limited to a minimum. The optimal system is one where the professional (Transplant Procurement Manager – Transplant Coordinator) in collaboration with the different transplant teams, decides on the clinical usability of the potential organ.

Section 2 - General exclusion criteria

- Human immune deficiency virus positive
- Multi-organ failure in the acute and irreversible phase with loss of organ functions
- Acute untreated systemic infection
- Active malignant tumour not curatively treated
- Prion disease (mad cow disease)

In this context all other cases should be considered as potential organ donors and therefore

referred.

Results of transplantation are influenced by various factors, not only donor quality.
The donor quality (determined through co-morbidity factors and donor management) is:

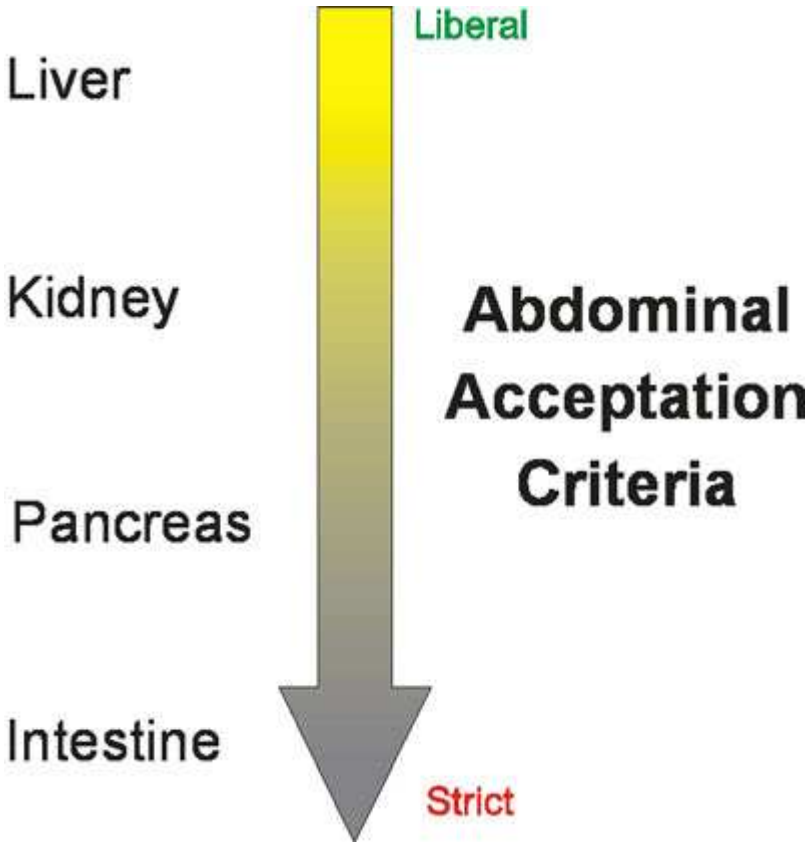
- The quality of the procurement (determined through the surgical and technical aspects - post retrieval viability criteria)
- The medical condition of the organ recipient
- The quality and follow-up of the transplant (surgical–medical)

Topic 3- Abdominal Organs Viability Criteria

Section 1 - Introduction

Based on recent developments and publications, depending on the type of abdominal organ, the approach differs. The most liberal approach is seen in the liver, the strictest is in intestinal organ viability criteria. The balance between life-saving transplant versus life-quality transplant for the recipient is the main drive behind this approach. All the above listed general exclusion criteria are applicable for every organ. We will only focus in detail on each organ separately.

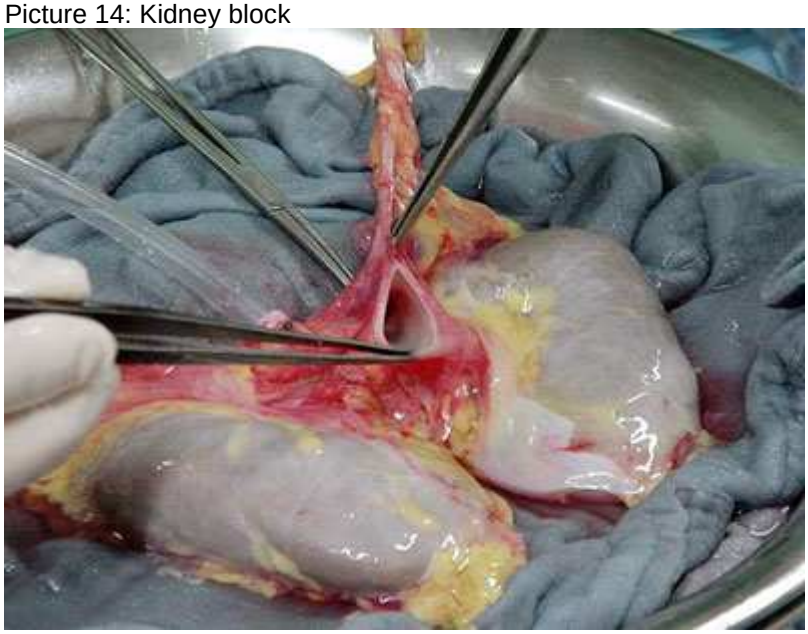
Figure 1: Abdominal organs criteria



Section 2 - Kidney

In addition to the general exclusion criteria applicable to all organs, for the kidneys we have to split the exclusion criteria into absolute and relative exclusion criteria. The concurrence of several relative criteria could become an absolute exclusion criterion.

Picture 14: Kidney block



(Tab 1) Absolute exclusion criteria

- Chronic renal insufficiency which means chronic and irreversible structural damage
- Malignant kidney tumour

(Tab 2) Relative exclusion criteria

Relative kidney exclusion criteria are (more than 1 = consider absolute criteria):

- Over 70 years
- Arterial hypertension >10 years, without adequate treatment
- Diabetes mellitus type I and II
- Acute tubular necrosis
- Suboptimal and prolonged preservation (Heartbeating donors and non-heartbeating donors)
- Hepatitis B- or C- positive patients (in many hospitals this is not contraindication criteria)
- Technically damaged kidneys (encapsulated, vessel damage, ureter damage)

This means that, for example, a kidney procured from a 75-year-old donor with >15 years arterial hypertension and 32 hours of cold ischemia becomes a contraindicated kidney graft. On the other hand, a young, 25-year-old donor in acute renal failure due to haemorrhagic shock is a kidney graft that is very likely to recover from this acute phase. More and more, we see a need for greater preservation techniques (machine-perfusion) in order to evaluate and create a safety window for those organs where we need more evaluation *ex vivo*. In particular, kidneys originating from donors with relative contraindications could be indicated for this type of preservation. Recovery of kidneys with ischaemic lesions can be successful. This has recently been proven in the larger series now available in non-heart-beating donors (Donation after Cardiac Death donors).

(Tab 3) Lab tests

In evaluating kidney function, there should be always a balance between the different tests available. A factor that increases with age is glomerulosclerosis. Although kidney function is normal, there may be underlying damage to the kidney. General testing includes:

- Serum creatinine and urea
- Microscopic urinalysis for glucose and protein
- Urine output / 24 hrs and last hr

(Tab 4) Macroscopic evaluation

Macroscopic evaluation in combination with the clinical evaluation and the general evaluation based on laboratory analysis will result in the most accurate policy to accept a kidney or not. This point is strongly influenced by the experience of the retrieval team. Warning signs in macroscopic evaluation are:

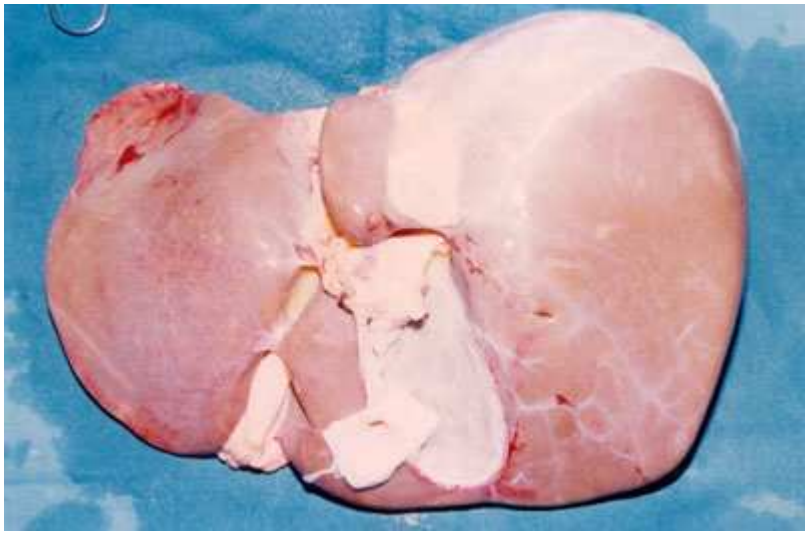
- Polycystic kidneys (multiple large cysts in both kidneys)
- Hypoplastic kidneys in combination with severe arteriosclerosis of the renal artery
- Diffuse calcifications along the entire renal artery
- Suspicious lesions suggestive of malignant tumour
- Marbled kidney after flush (bad organ preservation)

In case of doubt, a biopsy should be done to assess organ viability.

Section 3 - Liver

In addition to the general exclusion criteria applicable to all organs, for the liver there are specific exclusion criteria as well. The liver is possibly the most resistant abdominal organ. Age is not a contraindication and often donors with extended age (up to 90 years of age) are seen as suitable liver donors, whereas kidney function and quality are often poor in these donors. In these donors absolute attention goes to the combination of risk factors that could influence outcome.

Picture 15: Liver



(Tab 1) Absolute exclusion criteria

- Malignant liver tumour
- Hepatic failure
- Acute hepatitis (HbsAg-positive)
- Steatotic hepatitis with steatosis (above 60% micro/macro-vesicular)
- Multiple lesions based on severe trauma

(Tab 2) Relative exclusion criteria

- Ischaemic damage or long warm ischaemia (in case of NHBD/DCD)
- Steatotic hepatitis with steatosis between 30 and 60%
- Acute hepatitis (serology and biopsy may be necessary)
- Prolonged cold ischaemia >14 hours

Combination of relative contraindications leads to increased risk of primary non-function. Therefore a clear evaluation process and standardised approach are necessary in order to properly evaluate hepatic function.

(Tab 3) Liver tests

- SGOT
- SGPT
- Gamma GT (GGT)
- Bilirubin (total and direct)
- Alkaline phosphate
- INR/PT/aPTT (donor clotting parameters)
- Sodium
- Lipases
- Amylases

In the evaluation process, attention should focus on hypernatraemia. In case of brain death, many donors slip into a condition called diabetes insipidus, which often leads to massive free water loss through urine output, causing hyperosmolarity in the serum. This increases ions such as sodium. Severe hypernatraemia (>160 mmol/l) can cause primary non-function after transplant when not corrected. Correction through dilution by glucose and insulin is necessary. Elevated enzymes (SGOT/SGPT) following a period of ischaemia such as CPR in the donor or a long hypotensive period are not contraindicated but should be evaluated at different time points. High enzyme levels but with a decreasing trend after a peak, is a graft that is recovering from hypoxaemia. GGT is a predictive parameter in cases of alcohol damage to the liver. Elevated GGT in combination with elevated enzymes should be thoroughly evaluated in combination with the macroscopic appearance of the liver. On the other hand, elevated GGT as such can be caused by prolonged donor admission in ICU (> one week) in combination with TPN (parenteral nutrition). Increased bilirubin without any other possible parameters suggesting impaired liver function can be caused in trauma patients who recently received packed cells or if the patient has Gilbert's disease (familial non-haemolytic hyperbilirubinaemia with jaundice). In these cases the liver is suitable for transplant. In case of any elevated parameters without an immediate possible cause, they should always be checked by an abdominal ultrasound or CT in order to evaluate the parenchyma of the liver. Especially in the case of abdominal trauma or obesity or alcohol abuse, which is often associated with steatosis, this additional diagnostic test can be valuable.

(Tab 4) Macroscopic evaluation

- Colour (rosy/brown homogenic)
- Soft
- Smooth surface
- Sharp edges
- % of steatosis (frozen section to determine % of steatosis)
- Trauma
- Tumour
- Anatomical variances

Macroscopic observation and histological analysis are crucial to the final acceptance of a liver graft. If the macroscopic parameters are dubious, a liver biopsy will rule out severe hepatic steatosis, ischaemic damage with hepatocyte necrosis and possible malignant tumours. In the case of liver donors, the gold standard is not to combine multiple possible risk factors. Especially in very old liver donors, attention should focus on macroscopic evaluation by experienced procurement teams in combination with short cold ischaemia times. An absolute luxury for such extended grafts would be for these organs to be allocated as the centre offers, so that the graft can be transplanted in patients with clinical reserve capacity, recovering more easily when the graft functions suboptimally.

Section 4 - Pancreas

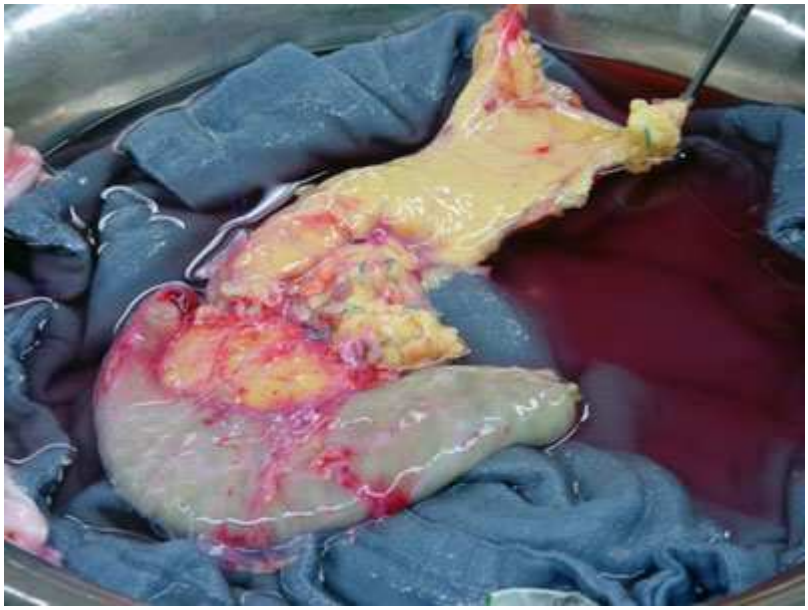
In addition to the general exclusion criteria applicable to all organs, for the pancreas there are

specific exclusion criteria. A pancreas transplantation is a quality-of-life transplantation, and more strict criteria are applicable compared to liver or kidney. In particular, the pancreas with its microvascular structure is more influenced by hypoperfusion and peripheral vasoconstriction.

There are no specific biochemical analyses to determine whether a pancreas is suitable or not for transplantation. In general, the reasoning that is followed by pancreas transplant teams is that when the general liver parameters are impaired, this will impact the pancreas as well. Amylases and HbA1C are additional analyses that could predict some pancreatic function. The best evaluation tool is admission data in combination with the haemodynamic situation of the donor. An extensive need for high doses of catecholamine (>0.1 µg/kg/min noradrenaline – >10 µg/kg/min of dopamine or dobutamine) with low blood pressure can seriously harm pancreatic cells.

Therefore, macroscopic evaluation is the best way to ultimately determine whether a pancreas is suitable or not. Guidance in the final decision can always be supported by previous ultrasound of the abdomen or CT.

Picture 16: Pancreas



(Tab 1) Absolute contra-indications

- Malignant tumour of the pancreas
- Acute or chronic pancreatitis
- Prolonged haemodynamic instability > 12hrs
- Age > 55 yrs and < 10 yrs (vascular diameter)
- BMI > 29
- Admission > 10 days
- Chronic alcohol abuse
- Prolonged cold ischaemia > 12 hours

(Tab 2) Macroscopic evaluation

- Absence of oedema
- Absence of contusion and/or subcapsular haematoma
- Soft
- No lipomatosis

Section 5 - Intestine

Intestinal transplantation was controversial until long-term outcomes slowly improved. Still, chronic rejection and low patient survival in the long term are determining factors in small bowel

transplantation. Therefore, strict criteria are absolutely necessary to guarantee optimal outcome in such patients.

The intestine is a not sterile environment and is directly open to the outside world. Billions of bacteria are active inside the bowel. Any low perfusion-oxygenation can cause severe inflammatory reactions within the bowel causing graft dysfunction post-transplant.

Macroscopic evaluation and procurement should be performed by the transplant team responsible for the transplant procedure. These procedures are rare and not standardised, which makes procurement by the transplant teams essential. Short cold ischaemia times and optimal time coordination of the procedure are pivotal to guarantee success.

(Tab 1) Acceptance criteria

In addition to the general exclusion criteria, small bowel specific acceptance criteria are:

- Donor age < 50 years
- BMI < 27
- No previous or recent history of abdominal trauma – surgery –bowel disease
- No CPR in the past 48 hrs
- Admission < 5 days
- Normal kidney and pancreas function
- Normal oxygenation (PaO_2 > 100 mmHg at normoventilation)
- No cold ischaemia (> 10 hours)

(Tab 2) Lab tests

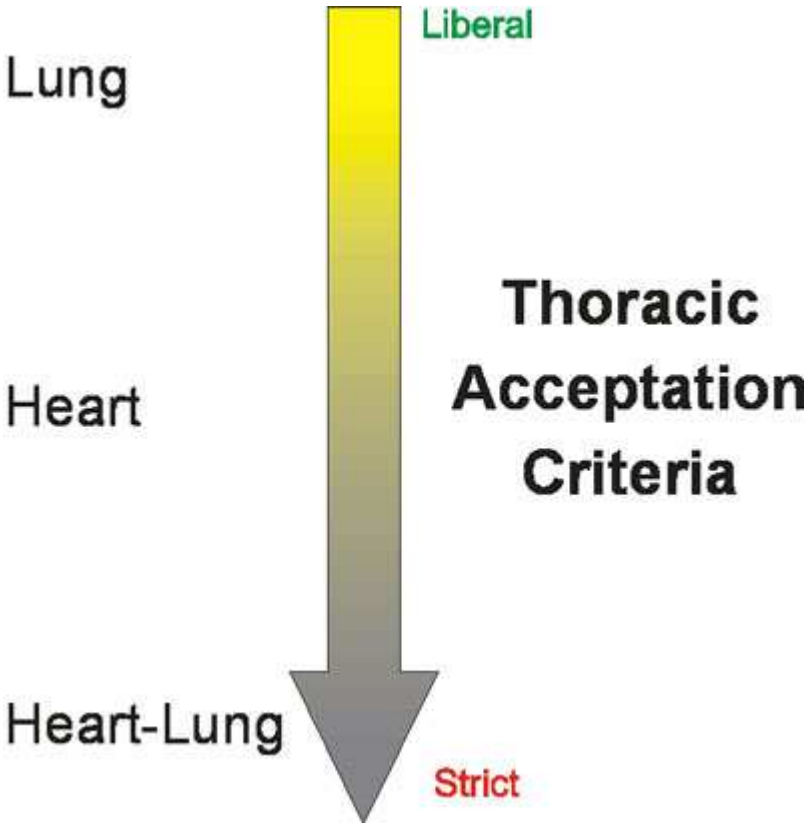
Clinical parameters and biochemical analyses are similar to the liver and pancreas evaluation. These are:

- SGOT
- SGPT
- Gamma GT (GGT)
- Bilirubin (total and direct)
- Alkaline phosphate
- INR/PT/aPTT (donor clotting parameters)
- Sodium
- Lipases
- Amylases
- PaO_2
- pH ≥ 7.4

Topic 4- Thoracic Organs Viability Criteria

Based on recent developments and publications on one hand, and favourable outcomes on the other, the approach differs depending on the type of thoracic organ. The most liberal approach is seen with the lung, and the strictest is with a combined heart-lung block. Thoracic organ transplantations are all life-saving interventions, with the most dramatic impact on patients awaiting a lung transplant. Recent developments and optimisation of heart assist devices have made the approach to heart donors more liberal because there is the possibility of a back-up through a temporary assist device or bridging to re-transplantation.

Figure 2: Thoracic organs criteria



Section 1 - Lung

Lung donors are still a very underused potential group within organ donors. The approaches used are strict, the same as those used in the initial period of lung transplantation, as these criteria became standardised. There was dramatic improvement of results in lung transplantation which made use of more extended lung criteria possible. Comparing different countries and organ allocation organisations, the percentage of lung donors are dramatically different, ranging from 10% up to 50% in some centres. It is often seen that absence of a lung transplant programme has a negative impact on the percentage of available lungs. Therefore, a standardised approach and evaluation is necessary in order to positively impact lung donor availability. In addition to the general exclusion criteria applicable in every donor, there are specific exclusion criteria for the lungs.

Picture 17: Lungs

(Tab 1) Absolute contraindications

- malignant lung tumour
- age > 70 years
- functional damage (fibrosis, emphysema, asbestosis)
- multiple contusions in both lungs

(Tab 2) Relative contraindications

- over 55 years of age in combination with excessive tobacco abuse
- PaO_2 lower than 200 mmHg
- infection
- lung oedema
- ventilation period > 3 weeks
- prolonged cold ischaemia > 8 hours

(Tab 3) Evaluation protocol

When evaluating lungs for transplant, a standardised lung evaluation protocol should be followed. Very often lungs are declined on one-time evaluation data, which can explain the low percentage of lungs available for transplant. Because clinical parameters for lungs are very basic, the protocol to correctly evaluate blood gases becomes essential. Besides a clean chest X-ray, a standardised approach should be followed.

Lung donor lung evaluation protocol:

- PaO_2 on normoventilation
- PaO_2 standardised on 100% FiO_2 and PEEP 5
- calculate percentage of shunting between the 2 values
- 15 minutes of bag squeezing at 100% FiO_2 and aspiration of possible excretions
- PaO_2 standardised on 100% FiO_2 and PEEP 5
- compare both standardised values

If an improvement is seen, the lungs are likely to be suitable for transplant.

(Tab 4) Lung management

If no improvement is seen after the lung protocol application, parameters such as rapid filling due to hypotension, sudden brain death, hypernatraemia and low tidal volumes should be taken into account. In particular, rapid filling in case of brain death (which causes an inflammatory response) and pituitary gland drop-out can cause neurogenic pulmonary oedema. More extensive donor management is necessary in such cases. Simplified protocols with lower filling and less free water loss through urine output are essential key points to optimise gas exchange. Desmopressin or vasopressin, in combination with monitoring of central venous pressure (<8 cm H_2O) and administration of furosemide will treat possible pulmonary oedema.

Atelectasis is another frequent reason for shunting and suboptimal gas exchange. Many patients who are ventilated in ICU show some atelectasis that can be easily blown open at time of management or during the surgical procedure. At the time of surgery, a second evaluation can be done in situ. After bringing the ventilation back to PaO_2 standardised on 100% FiO_2 and PEEP 5, PaO_2 analysis of bilateral pulmonary vena sampling provides gas exchange in the right and left lung and possible calculation of shunting in both lungs. Such an approach can help determine if the lung can go for bilateral transplant or single lung transplant.

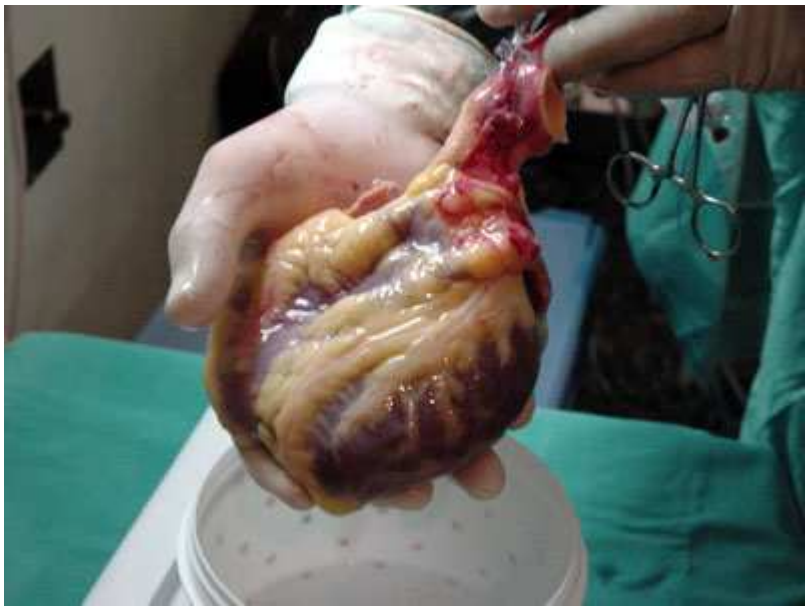
(Tab 5) NHBD

Recently lungs from non-heartbeating donors (NHBD) have been used for clinical transplantation with favourable results. Also, recent developments in machine perfusion suggest that even in suboptimal lungs, treatment and preservation on the machine can help evaluate and optimise lung quality. A more liberal approach is absolutely necessary to optimise the number of available lungs for transplantations.

Section 1 - Heart

In addition to the general exclusion criteria applicable to every organ, for the heart a more liberal approach has been seen in recent years. On the other hand, due to better medical treatment of heart failure, indications for heart transplantations have decreased. As for every other organ, besides clinical and biochemical analysis, the macroscopic appearance of the heart is essential.

Picture 18: Heart



(Tab 1) Absolute contra-indications

- cardiomyopathy
- congenital heart disease
- ischaemic heart disease
- valvular heart disease

(Tab 2) Relative contraindications

- coronary artery disease risk factors (arterial hypertension, age >60 yrs and quickly evolving, diabetes mellitus, obesity, hyperlipidaemia)
- extensive catecholamine use
- extensive hypernatraemia (not corrected)
- prolonged cold ischaemia (>5 hours)

(Tab 3) Clinical evaluation

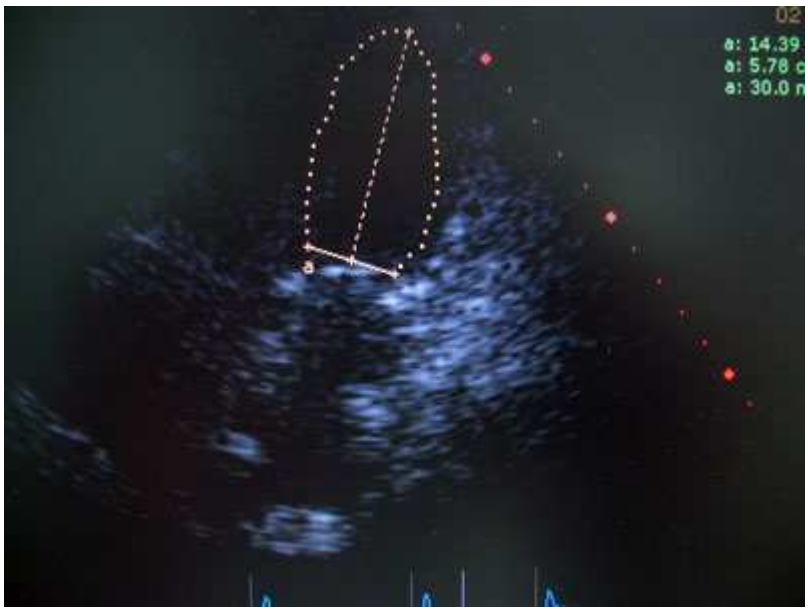
The clinical evaluation parameters are based on a history of hypotension in combination with eventual CPR and laboratory analyses of parameters that suggest possible damage to the heart.

Clinical evaluation and diagnostic evaluation are:

- Sodium
- CPK and CK-MB fraction
- Troponine
- Blood gases

In combination with these parameters, diagnostic analysis such as **12-lead ECG** and **echocardiogram** specifically EF (ejection fraction), valvular appearance and contractility (global as well as regional), are pivotal to evaluate heart function correctly. If a donor shows a higher risk profile for coronary artery disease, a coronarography should be considered. Although this information is essential in such donors, the practical implementation in smaller hospitals is sometimes a difficulty.

Picture 19: Echocardiogram



(Tab 4) Macroscopic evaluation

If heart function is clinically optimal through diagnostic evaluation, macroscopic evaluation is the best approach.

Macroscopic evaluation is based on:

- Haemopericardium or pericardial fluid
- Contractility
- Arteriosclerosis of the coronary branches

Topic 5 - Expanded Criteria Donors

Section 1 - History

Towards the end of the 1990s, the term marginal donors began to appear as a reference to donors who did not meet the classic screening criteria, such as old age or the presence of concomitant diseases.[7] One of the first papers evaluating these donors, published in the mid-1980s, recognised that the results of organs transplants from elderly donors were the same as those with younger donors. These cases demonstrated that with better harvesting techniques, donor maintenance and immunosuppressive treatment, donor acceptance criteria could be expanded.

It was actually the term “marginal” which immediately started to generate conflict, as this term was understood to mean that the results were far inferior, second class, and the benefit was questioned. Around the same time, the term "expanded criteria donors" (ECD) started to be coined, to specifically differentiate those criteria from the classic acceptance criteria.[8]

Section 2 - Definitions

The difficulty with analysing these types of donors is that they comprise many different categories, from cardiac arrest donors and all the variants, including donation after cardiac arrest (donors in whom cardiac arrest was expected in the operating theatre after removal of life support – also called controlled – to differentiate them from unexpected cardiac arrest both in and out of the hospital setting, which is called uncontrolled) to elderly donors or donors with infections or concomitant diseases. It is accepted that the use of cardiac arrest donors is one way of increasing the donor pool

with good results.

Moreover, the concept of ECD with criteria which are universally accepted only applies to kidney transplants, and is not applicable to liver, lung, heart or pancreas transplants.

In the case of ECD for kidney transplantation, an accepted policy was established for the USA in 2002.[10] An ECD is considered if the donor is over the age of 60 or over 50 years and complies with two of the following criteria:

- Arterial hypertension
- Cause of death - cerebrovascular accident
- Creatinine over 1.5

In 1994, the number of donors in the USA who met these criteria was 651 versus 4090 standard criteria donors. In 2003, the ECD were 1169 vs. 4329. In 2004, the kidney ECD were 1341, which was 21% of all renal donors.

There is no unanimous agreement in the published literature on the use of this type of donor, as can be seen below.

There are studies that demonstrate good results with the use of kidneys from this type of donor.[11] The studies show similar results with ECD and standard donors, highlighting that due to the use of ECD alone, the number of renal transplants doubled in one year.[12] This same group subsequently indicated that a better selection of recipients, avoiding those of high immunological risk, improves the results obtained. [13]

Section 3 - Results

But it is also true that we can find articles that question the use of kidneys from these donors. Ojo[14] stressed the worst results obtained and suggested avoiding the use of ECD kidneys in recipients under the age of 40 and in African Americans with a mean waiting list period of less than 1350 days. In a recent article[15] using data from the USA transplant registry, it was observed that repeat transplantation using ECD kidneys did not improve survival versus conventional treatment, although it is true that the group of recipients receiving the re-transplants were older and the rate of diabetes more frequent. Although ECD did not improve survival, it was ultimately considered that a repeat transplant can be used because it could improve the quality of life and there may be a reduction in costs.

What would appear to be clear is that ECD kidney transplantation offers advantages and benefits and undoubtedly the best results are attained by improved selection and definition of the recipient groups to receive the transplant.[16]

There is no such consensus with other organ types, but the use of livers from donors over the age of 65 is becoming more common and this is what is allowing the waiting lists to be maintained. In the case of lung transplants, certain criteria are already being studied.[17]

The debate is open to see what steps may be taken in the future.

Age is not always the criterion that is used in ECD; there are numerous other diseases which, with careful evaluation, would allow more organs to be transplanted.[18] ECD is one of the ways of increasing the number of donors when dealing with an aging population,[19] although it is not free of ethical debates.[20]

Topic 6 - Conclusions

When applying organ viability criteria, it is essential to avoid the loss of potential organs that can be used for transplantation. Criteria that are too strict should not be applied, and therefore standardisation of acceptance criteria is necessary. Although certain clinical and biochemical parameters, regardless of organ, can be unfavourable, the best approach is guaranteed through macroscopic evaluation. To maximise the donor pool, standardised training on evaluating organs is a crucial aspect in evaluating the clinical use of organs for transplantation.

The major drive to accept an organ is the clinical situation of the recipient who will receive the graft. Therefore an organ may be unsuitable for one particular patient, but can be perfectly suitable for another patient. A gold standard is to maximise independent investigation into the organ type the moment a donor enters an extended criteria profile. This will be the best and safest way for clinical transplantation teams to properly accept an organ for transplant. This approach will give the donor hospital an advantage in that thorough examination will positively influence the time of acceptance by the organ allocation teams. In this new era when we are seeing a more liberal approach including extended criteria donors or non-heartbeating donors, standardised analyses of clinical parameters and

protocols of evaluation of viability criteria are necessary.

Figure 3: Balancing risk and benefit

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