Anaesthesia for organ transplantation

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Advances in surgical, anaesthetic, and immunosuppressive techniques as well as increased public awareness have made organ transplantation a well accepted therapeutic modality. Transplantation has become the treatment of choice for selected patients with end-stage cardiac, liver, or kidney failure. The number of potential recipients has increased steadily. For example, at University Hospital the number of recipients has increased more than ten times over the past ten years. During the first eleven months of 1986, 90 kidneys, 43 hearts, 33 livers, and two heart-lungs were transplanted. Judging by the length of current waiting lists it is likely that other institutions will soon enjoy a similar experience.

Anaesthetists may become involved in the the transplantation process in one of three situations: (1) organ donor management, (2) anaesthesia for organ transplantation, and (3) anaesthesia of a transplant recipient having unrelated surgery.

Donor management

Donor organs may be divided into the perfusable organs (kidney, liver, heart, lung, and pancreas) and the non-perfusable organs and tissues (eyes, skin, bone, heart valves, and dura mater). Anaesthetists will be involved in the management of perfusable organ donors as these patients need to have ventilation and organ blood flow maintained until the moment of harvesting. Anaesthetists have no direct role in the removal of non-perfusable tissues.

Declaration of brain death

The first step in donor management is the declaration of brain death. There are no statutory definitions of brain death in Canada. The Canadian Congress of Neurological Sciences has recently published new guidelines on the declaration of brain death.¹ It is hoped that these will be nationally accepted and used. A declaration of brain death is usually based on clinical criteria. When the organs are to be donated for transplantation, at least two physicians not involved in the care of the recipient should certify that brain death has occurred. Special tests such as the electroencephalogram (EEG) or cerebral blood flow measurements are not usually required except in special circumstances.

Organ donor maintenance

After the declaration of brain death, the organ functions of a suitable donor must be maintained as carefully as prior to death (Table I). Without properly cared-for donors, transplantation of perfusable organs would not be possible. It may be useful to think of the organs as already belonging to the recipient and to accord to them all the therapeutic modalities, no matter how costly, that would be offered the recipient.

SPECIFIC PROBLEMS

Hypotension Hypovolaemia develops insidiously with brain death and accounts for most cases of haemodynamic instability. Causes include therapeutic dehydration in an effort to decrease cerebral oedema, blood loss through haemorrhage, diabetes insipidus, osmotic diuresis due to hyperglycemia, and progressive reduction in systemic vascular resistance as a result of defective vasomotor control.

Aggressive fluid resuscitation should be monitored by intra-arterial and central venous (CVP) or pulmonary wedge pressure measurements. CVP or pulmonary wedge pressure should be kept in the 10–15 mmHg range. Infusions of blood and blood products should be used when necessary. Vasopressors should only be used after adequate rehydration has been achieved. Dopamine is the agent of choice because it has the least detrimental effects on renal and splanchnic blood flow.

Arrhythmias. Atrial or ventricular arrhythmias may result from electrolyte imbalance, hypotension, vasopressors, and increased intracranial pressure. Therapy is as usual. Even with the most rigorous efforts, the inevitable deterioration of the brain-dead patient may lead to cardiac arrest. Cardiopulmonary resuscitation should be instituted in an attempt to re-establish cardiac rhythm and output. If the cardiac arrest occurs in the operating room, it may be feasible to remove the kidneys and liver during CPR.

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TABLE 1 Absolute and relative contraindications to organ donation

Age > 65 years
Systemic sepsis
History of Hepatitis B
Acquired Immune Deficiency Syndrome (AIDS)
Intravenous drug user
Malignancy, except skin and CNS
Severe hypertension prior to brain injury
Prolonged high dose vasopressors
Prolonged hypotension
Prolonged anuria
Prolonged hypoxaemia
Donor organ disease or trauma

Transplant programs differ in the criteria used. Check with your regional transplant coordinator.

Diabetes insipidus. This is frequently seen in brain-dead donors and is usually accompanied by hypernatremia and hypovolaemia. If left untreated, urine output can rise to several litres per hour. Such polyuria may dilute the renal medullary concentrating gradient and reduce the responsiveness to subsequently administered Pitressin.

Urine output must be replaced hourly with intravenous crystalloid on a millilitre for millilitre basis. The electrolyte makeup of the fluid is dictated by the donor's serum electrolytes. If the urine output exceeds $300 \text{ ml} \cdot \text{hr}^{-1}$, Pitressin should be used. A continuous intravenous infusion provides the greatest control and reduces the likelihood of complete renal shutdown. Start at a rate of $0.1 \text{ units} \cdot \text{min}^{-1}$ and titrate as needed.

Oliguria. Low urine output (less $50 \text{ ml} \cdot \text{hr}^{-1}$) is initially treated with rehydration. If this is not successful, low-dose dopamine ($2\text{--}3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) is used and failing that furosemide $1 \text{ mg} \cdot \text{kg}^{-1}$.

Electrolytes. Serum electrolytes should be measured frequently so as to avoid hypernatremia and hypokalaemia especially in those patients with diabetes insipidus. If large volumes of dextrose containing solutions are used, then blood glucose should also be frequently measured.

Arterial blood gases. PaO_2 should be kept between 70 and 100 mmHg. If the lungs are to be used for transplantation, then the lowest possible FiO_2 without excessive positive end-expiratory pressure should be used.

PaCO_2 and pH should be kept within the normal range by manipulation of the minute ventilation or the administration of sodium bicarbonate.

Hypothermia. Brain-dead patients are poikilothermic and may need very aggressive warming to maintain a temper-

ature above 34°C . Temperatures below this increase the likelihood of arrhythmias and make the declaration of brain death difficult.

Intraoperative management

Removal of the organs may be performed by a surgeon from one's own hospital or by an itinerant retrieval team. In the latter situation, the timing of the procedure may be dictated by flight schedules and weather conditions rather than the convenience of one's operating room.

The responsibilities of the anaesthetist are no different from those that usually pertain in the operating room – the maintenance of tissue blood flow and oxygenation together with fluid, electrolyte, and acid base balance. Obviously, no drugs need to be given to ensure unconsciousness. The usual meticulous attention to circulatory and ventilatory homeostasis is required. The patient should be ventilated on at least the same FiO_2 as used in the intensive care unit and vasopressors and Pitressin titrated as needed. Depending on the number of organs to be removed, the donor procedure may last from two to five hours.

It must be borne in mind and pointed out to ancillary operating room staff that the declaration of brain death does not require the loss of all reflexes, only the cerebral and brain stem reflexes. Reflex responses should therefore be expected. This can be most disconcerting and staff require frequent re-assurance that the donor is indeed brain-dead. The twitching of muscles or frank contraction may necessitate the use of non-depolarizing neuromuscular blocking drugs. Reflex haemodynamic responses to painful stimulation frequently occur.² This may be due to reflexes involving the brain stem vasomotor areas which may still be intact, spinal reflexes, or adrenal medullary stimulation by a reflex arc. Therapy includes the weaning of vasopressors and on occasion the use of a vasodilator such as an inhalational anaesthetic or sodium nitroprusside.

Heart transplantation

After the first human heart transplant in 1967, the initial enthusiasm for the procedure was followed by profound disappointment because of the high mortality. The development of new immunosuppressive agents, especially cyclosporine, has reduced the mortality so that one-year survival is now in excess of 80 per cent and five-year survival in excess of 50 per cent.^{3,4} This has once again stimulated interest in the procedure. At the beginning of 1986, there were approximately 120 centres world wide (75 per cent in North America) performing this procedure. By the end of 1986 there were another 170 North American institutions planning heart transplant programs.⁴

TABLE II Potential adverse effects of immunosuppressive drugs

Medications	Adverse effect
Antilymphocyte globulin (ALG)	Allergic reactions, hypotension, thrombophlebitis, thrombocytopenia
Azathioprine	Leukopenia, thrombocytopenia, hepatic dysfunction. Inhibits phosphodiesterase and may increase requirements for non-depolarizing muscle relaxants
Cyclosporine	Nephrotoxic, hypertension (especially heart transplants), hepatic dysfunction, hyperkalaemia, hypomagnesaemia, lymphoproliferative diseases
OK T3 monoclonal antibody	Fever, chills, tremor, chest pain, wheezing, pulmonary oedema

Current waiting lists are relatively short (38 Canadians at the time of writing) but the National Heart Transplantation Study estimates that there are at least 14,000 North Americans who could be considered suitable for a transplant. It is therefore highly likely that many more anaesthetists will be involved with heart transplant patients either as part of the transplant team or caring for a transplant recipient having some unrelated surgery.

Anaesthesia for heart transplantation

The anaesthetic management is the same as that used for any patient with a severe cardiomyopathy and ventricular dysfunction. A pulmonary artery catheter is not usually placed preoperatively because of the increased risk of infection, arrhythmias, and the need to withdraw it when the recipient's heart is removed. A CVP is inserted using strict aseptic technique but not through the right internal or external jugular veins. The latter vessels are "saved" for the repeated endomyocardial biopsies that will be performed during follow-up. Weaning from cardiopulmonary bypass is usually unremarkable although small doses of inotropes or chronotropes may be needed.

Anaesthesia in a patient with a transplanted heart

A patient with a transplanted heart presents the anaesthetist with an unusual combination of problems which relate primarily to the use of immunosuppressive drugs and the altered cardiovascular responses to stress. Patients may present for the surgical correction of complications of their transplant e.g., abscess drainage or wound debridement, or for a totally unrelated surgical procedure.⁵ In the Pittsburgh experience, 28 per cent of their patients required a general surgical consultation and half of these patients required an operative procedure.⁶

Immunosuppressive drugs. The sequelae of long-term steroid administration are known to most anaesthetists. Complications of interest to anaesthetists from other immunosuppressive agents are shown on Table II. Anaesthetic drugs or techniques that reduce liver blood flow or that result in enzyme induction will have profound effects on cyclosporine blood levels.

Infection. Sepsis still remains the major cause of death in transplant recipients. All manipulations (IV access, intubation, plexus blockade) should be performed with an aseptic technique and as atraumatically as possible. Urinary catheterization should be avoided if possible.

Cardiovascular response. Many patients make a good functional recovery after heart transplantation although measured cardiac output is often lower than expected. The denervated heart does not respond to neurally mediated stimuli and does not give rise to ischaemic pain. The latter is an important consideration as accelerated atherosclerosis occurs in these patients. Although the heart does not respond to neurally mediated stimuli, the cardiac adrenergic receptors remain intact and respond normally to circulating catecholamines and receptor blockers.⁷ Post-denervation hypersensitivity does not seem to be a clinical problem. Because of the denervation, no heart rate response is seen with atropine, neostigmine, digoxin, gallamine, and pancuronium.⁵

The response to stress follows a sequential pattern.⁸ Initially the left ventricular end diastolic volume increases which results in an increase in stroke volume by means of the Frank-Starling mechanism. This is not sustained but the increased cardiac output is maintained by an increase in heart rate which occurs over about five minutes. This is due to an increase in circulating catecholamines and the heart rate response tends to continue for a while after the period of stress. This relatively slow heart rate response makes tachycardia a poor indicator of depth of anaesthesia. Because the immediate response to stress is critically dependent on preload, these patients are profoundly sensitive to hypovolaemia.

Both atrial and ventricular arrhythmias are common in the recently transplanted patient but the incidence decreases with time. The rhythm disturbances usually respond normally to conventional antiarrhythmics but the negative inotropic effects of many of these drugs are exaggerated in the transplant patient. Cardioversion may therefore be safer.

Liver transplantation

The anaesthetic considerations for hepatic transplantation have recently been reviewed extensively.⁹⁻¹² For

the patient with a transplanted liver having unrelated surgery, the anaesthetic approach is identical to that used in any patient with liver disease. It appears that a normally functioning transplanted liver handles anaesthetic drugs normally. However, there have been no formal or extensive studies of pharmacokinetics and pharmacodynamics in transplant patients.

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