ANAESTHESIA FOR PATIENTS WITH TRANSPLANTED HEARTS AND LUNGS UNDERGOING NON-CARDIAC SURGERY

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Organ transplantation has become an established form of surgical management in a patient with selected end-stage chronic disease not amenable to conventional medical or surgical treatment. Heart and lung transplantation is performed by a few National centres in the United Kingdom often some distance from the patient’s home. The national figures for cardiopulmonary transplantation in the United Kingdom and Eire during 1989, as notified to Transplant U.K., were: heart 302; heart-lung 94; lung 39. Worldwide, 2450 transplantsations were performed during 1988 [15].

Medical attendants should be alert to recognizing problems caused by the presence of infection in immunosuppressed patients, modes of presentation of rejection phenomena and how transplanted organs, notably significantly denervated ones, may behave and respond under the pathophysiological circumstances that arise during surgery, resuscitation and intensive care.

BACKGROUND

Type of transplant

Heart. Heart transplantation is suitable only for a highly selected group of patients in end-stage cardiac failure, the majority of whom suffer from ischaemic heart disease or cardiomyopathy [15]. Contraindications vary from centre to centre. Relative contraindications and risk factors include: age more than 60 yr; increased pulmonary vascular resistance; peripheral vascular disease; diabetes mellitus; neoplastic disease; renal dysfunction; hepatic disease; acute infection; multi system disease; adverse social conditions; adverse psychiatric conditions.

The International Society for Heart Transplantation reported that 83% of patients are male in the age range 34–55 yr.

The diseased heart is removed during bypass, leaving right and left atrial remnants. Consequently, the postoperative ECG may exhibit two P waves [12]. The impulse generated by the atrial remnant is inconsequential.

Combined heart–lung (HLT). Originally applied to primary pulmonary hypertension and Eisenmengers’ Syndrome, HLT has expanded to include parenchymal lung diseases, predominantly septic lung conditions such as cystic fibrosis and bronchectasis. Generally, patients undergoing HLT are younger than those having heart transplants, with a mean age of 29 yr.

Single lung (SLT). SLT is performed for isolated pulmonary disease with minimal cardiac involvement. Since the first successful SLT was performed in 1983, it has developed as an acceptable surgical treatment for suitable patients in respiratory failure. Most experience to date has been with pulmonary fibrosis, but the indications are widening on an experimental basis to include emphysema and pulmonary vascular diseases.

Where appropriate, SLT has several advantages in comparison with HLT. Three recipients can benefit from a single organ donor. This is particularly important as the number of patients awaiting transplantation increases. Cardiopul-
Table I. Survival rates of patients who underwent heart, heart-lung and lung transplantation

<table>
<thead>
<tr>
<th>Organ transplanted</th>
<th>Survival</th>
<th>%</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart-lung</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>81.2</td>
<td>[15]</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>55.7-61.1</td>
<td>[15]</td>
<td></td>
</tr>
<tr>
<td>5 year</td>
<td>55.4</td>
<td>[15]</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>91.1</td>
<td>[15]</td>
<td></td>
</tr>
<tr>
<td>5 year</td>
<td>73.9-81.9</td>
<td>[15]</td>
<td></td>
</tr>
<tr>
<td>10 year</td>
<td>73.3</td>
<td>[15]</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>65.0</td>
<td>[J. D. Cooper, personal communication]</td>
<td></td>
</tr>
</tbody>
</table>

Survival

Better patient selection, improved surgical and anaesthetic techniques and the introduction of cyclosporin as part of triple immunosuppressive regimens have led to improved survival for transplant patients. The first year after transplantation appears to be the most critical, with the greatest mortality, particularly from rejection and infection. The nature of the immunosuppressive regimen seems to have an influence on survival; those receiving corticosteroids, azathioprine and cyclosporin have the best outcome. The sex and age of the patient do not appear to be significant factors. Table I gives the current survival rates for cardiopulmonary transplantation.

Morbidity and mortality

Recipients of transplanted hearts and lungs are prone to several major problems, the foremost of which are organ rejection and opportunistic infection. Rejection is discussed later.

Arrhythmias. An increased frequency of arrhythmias after cardiac transplantation has been reported by several workers [1,14], in particular, ventricular premature beats. Exercise has been demonstrated to increase the frequency of arrhythmias [29].

Providing the heart functions well, and in the absence of rejection, these arrhythmias are thought to be benign. However, ventricular tachycardia has been reported also and may be responsible for sudden death in patients with transplants [24]. Several mechanisms have been postulated for these frequent arrhythmias, including hypersensitivity to circulating catecholamines, loss of vagal tone and ischaemia secondary to graft coronary atherosclerosis [29].

Infection. Infection presents a major risk to immunosuppressed patients and is a significant cause of morbidity and mortality [15]. In one series [12], it was reported that 16 of 33 patients who had undergone heart transplantation died from infection.

Infections seem to be commonest during the first 3 months after transplantation [8,13]. The lung is the organ affected most commonly. A multitude of micro-organisms have been isolated, but the most common viral agents are Cytomegalovirus and Herpes simplex. Protozoal and fungal infections also occur, most notably Pneumocystis carinii pneumonia.

The incidence of opportunistic infection appears to decline 6 months after transplantation [22], but as long as the patient continues to receive immunosuppressants and corticosteroids, the risk of infection persists.

Neoplasia. Immunosuppressed patients are known to have a greater incidence of malignant
neoplasms [23] and lymphoma [25] than the general population. Cardiac transplant patients appear to be at a greater risk in this respect compared with renal transplant patients, possibly because the former have a more intense immunotherapy regimen [20]. A second transplantation appears to enhance further the risk of subsequent malignancy [13].

Psychological problems. Psychological problems associated with organ transplantation have been reviewed [18]. In general, the psychological status of most patients improves after cardiac transplantation, although transient psychiatric disorders are not uncommon in the early postoperative period [10]. Organic mental disorders were the most frequent observation and thought to be associated with drug therapy or other metabolic derangements. Chronic psychiatric conditions such as anxiety and depression occur and appear to correlate with preoperative psychological status. Depression and anxiety may lead to non-compliance with drug therapy, a problem shared by many chronically ill patients. Drug non-compliance is thought to be a significant factor in many cases of organ rejection.

Nature of the presenting illness

Isolated reports of anaesthesia in patients with transplanted hearts have appeared in the literature for a wide variety of non-cardiac procedures including total hip replacement, laparotomy, removal of infected toe nails, aortic aneurysm repair and lumbar laminectomy [2,7,9,19,28].

Steed and colleagues [30] noted a greater incidence of general surgical complications in post-transplant patients compared with other post-cardiopulmonary bypass patients, and that these complications were associated with a greater than expected mortality rate. Colon and colleagues [4] reported that biliary and pancreatic disorders were a common cause of surgical intervention in post-transplant patients. An increased risk of serious complications was noted also in those patients who underwent surgery.

Because of the smaller number of successful lung transplants, reports in the literature of subsequent anaesthesia are uncommon unless associated with a heart transplant.

Heart

Acute allograft rejection is a serious complication in the post-transplantation period and a major cause of mortality and morbidity [15]. The long-term results of heart transplantation are marred by the complication of accelerated coronary atheroma, thought to be a manifestation of chronic rejection. In one series [13], it was reported that 46% of transplant patients had angiographic evidence of graft coronary artery disease 2 years after transplantation, increasing by a further 1% after 4 years. Graft atherosclerosis is not infrequently associated with haemodynamic abnormalities.

The patient with the denervated heart does not experience angina or cardiac chest pain, the usual hallmarks of myocardial ischaemia. The only warning of impending rejection or ischaemia may be a complaint of excessive tiredness and dyspnoea which in time may manifest as heart failure [3]. Therefore, it is policy in most units to perform coronary angiography on an annual basis. Atrial arrhythmias were observed in 40% of patients during an episode of rejection, the frequency declining in response to antirejection therapy. Bradycardia and small ECG complexes should also alert the physician to the possibility of impending rejection, as should an increased frequency of transient ischaemic attacks [17].

Lungs

Early lung transplants were troubled with rejection and breakdown of the bronchial anastomosis, usually within 4 weeks of transplantation. This has been overcome partially by the technique of wrapping a pedicle of omentum, pulled through a hole in the diaphragm, around the anastomosis [6]. The steroid sparing effect of cyclosporin A has also had a beneficial effect on healing.

Detecting rejection of a transplanted lung can often be difficult, as the symptoms may mimic those of a chest infection. Typically, rejection is associated with fatigue, dyspnoea, sudden arterial desaturation, pyrexia and leucocytosis. Perihilar infiltration or graft opacification on the chest x-ray [5,32] may be preceded by a decrease in \( D_1 \)CO and FEV\(_1\) [16]. Pulmonary blood flow decreases as detected by isotope perfusion scan [6]. Although these non-invasive investigations are useful indicators, it is imperative to differentiate between infection and rejection using the relatively simple techniques of bronchoalveolar lavage and transbronchial lung biopsy. The
predominant pathological finding in acute lung rejection is of perivascular or peribronchial infiltration by mononuclear cells.

Heart–lung

Heart–lung allograft rejection is similar to that described for the individual organs. In practice, pulmonary rejection precedes cardiac rejection and it is rare for cardiac rejection to occur in the absence of lung rejection.

Obliterative bronchiolitis appears to be more common in lungs which have rejected when the transplant was in conjunction with a heart transplant than in isolated lungs [6].

If the anaesthetist suspects an episode of rejection, surgery should be postponed and the patient referred to the transplantation centre, as anaesthesia in the presence of ongoing rejection presents formidable management problems and may necessitate full inotropic and mechanical support.

DENERVATION

Heart

*Physiology.* The physiology of the transplanted heart has been discussed by several authors [9, 12, 26]. The denervated heart has a greater resting rate in the absence of vagal tone, generally 90–100 beat min⁻¹. No autonomic reinnervation takes place in humans after transplantation, therefore the normal sympathetic responses to laryngoscopy and intubation are absent. The heart does respond to circulating catecholamines, although this response may take 5–6 min to manifest. The normal baroreceptor reflexes are absent and carotid sinus massage and Valsalva manoeuvre have no effect on heart rate.

Of concern to the anaesthetist is the absence of tachycardia in response to light anaesthesia or hypovolaemia. Increases in cardiac output are achieved by increasing stroke volume rather than heart rate. Modulation of cardiac output is dependent, therefore, on intrinsic mechanisms. The anaesthetized patient with a heart transplant may show exaggerated responses to hypovolaemia, sudden changes in posture or decreases in systemic vascular resistance. Care should be taken, therefore, to avoid excessive loss of volume, dehydration or significant peripheral vasodilatation. Consequently, it is desirable to maintain an adequate preload at all times.

*Pharmacology.* In the denervated heart, drugs with autonomic activity, such as atropine, neostigmine, suxamethonium and pancuronium, have little effect on heart rate. Glucagon and digitalis exhibit inotropic effects, although the latter has no significant influence on heart rate or AV nodal conduction [21, 24, 26]. The heart receptors remain responsive to drugs, and sympathomimetic amines such as isoprenaline, adrenaline, dopamine and dobutamine respond in the normal manner.

Reflex tachycardia, often seen with vasodilator drugs such as hydralazine, glycerin trinitrate and sodium nitroprusside is absent and hypotension may be exaggerated.

Anti-arrhythmic drugs act in the normal manner and cardioversion remains effective.

Lung

*Physiology.* The transplanted lung is denervated distal to the bronchial anastomosis. Modulation of the mechanics of breathing is regarded generally as being under brainstem control, and respiratory and apneustic centres receive peripheral information from chemo- and stretch receptors via the vagus nerve. As with the denervated heart, no functional reinnervation takes place. Rhythmic disturbances of breathing have been reported in the early postoperative period, but the normal pattern appears to return quickly [27]. The lung responds normally to exercise and carbon dioxide.

Several workers have described transient reduction in lung volume secondary to changes in the rib cage and vertebral column [16]. The FEV₁ increases progressively to reach preoperative values by 6 months [31].

Of concern to the anaesthetist is the cough reflex. This is initiated by stimulation of receptors in the trachea, bronchi and bronchioles. Stimulation of any airway distal to the anastomosis does not elicit a cough reflex. In single lung transplants, the carina remains intact, consequently carinal stimulation elicits a cough reflex. Extubation of the trachea of lung transplant patients should be delayed until the patient is sufficiently awake to co-operate and respond to verbal commands to cough. Expectoration from the transplanted lung has to be encouraged by postural drainage and physiotherapy.

Although regarded as having some advantages over heart–lung transplants [6], single lung transplants give rise to an imbalance of perfusion. The transplanted lung is often perfused preferentially by virtue of its lesser vascular resistance compared with the remaining diseased lung. Anaesthesia should therefore avoid manoeuvres that give rise
to excessive increases in pulmonary vascular resistance.

**Pharmacology.** It has been noted that some heart–lung transplant patients have an increased P\textsubscript{aco}\textsubscript{2} in the postoperative period. In time, the P\textsubscript{aco}\textsubscript{2} decreases to within normal limits. In animals, vagotomy has been shown to reduce the ventilatory response to hypercapnia. Finch and Jamieson [9] have expressed fears that drugs which depress ventilation may further obtund the response to carbon dioxide. The clinical significance of this observation is not clear.

Despite denervation, bronchoconstriction has been described in a patient with a transplanted lung which subsequently rejected [9]. Interestingly, there was a poor response to bronchodilators such as isoprenaline, aminophylline and adrenaline.

**DRUG THERAPY**

Heart and lung transplant patients receive a wide variety of drugs, many of which are familiar to the anaesthetist. The complex drug regimens are essential for the maintenance of the allograft. In addition to immunosuppressive drugs such as azathioprine, cyclosporin and corticosteroids, these patients are often receiving antihypertensive agents, diuretics, histamine-2 blockers, antifungal and antiviral agents. A full discussion of these drugs is beyond the scope of this article, but several points are of concern to the anaesthetist in relation to cyclosporin A, the cornerstone of antirejection therapy.

Cyclosporin A has been reported to have a wide variety of drug interactions and side effects, particularly nephrotoxicity and hepatotoxicity. In one study after heart transplant, all patients receiving cyclosporin A demonstrated chronic nephrotoxicity within 2 years of transplantation [13]. Hypertension is associated not infrequently with nephrotoxicity. In experimental animals, cyclosporin infusions have been shown to potentiate the neuromuscular blocking effects of atracurium and vecuronium. Cremophor EL, the solubilizing agent of cyclosporin, further enhanced this effect [11]. The clinical significance of this finding is uncertain.

### TABLE II. Postoperative modulation of immunosuppression therapy in transplant patients undergoing surgery unable to take medication orally

<table>
<thead>
<tr>
<th></th>
<th>Before operation</th>
<th>After operation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Route</strong></td>
<td><strong>Drug</strong></td>
<td><strong>Route</strong></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Oral</td>
<td>Methylprednisolone</td>
<td>I.v. Given at a ratio of 0.8 of the dose of prednisolone</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Oral</td>
<td>Azathioprine</td>
<td>I.v. Given as the same dose as orally</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Oral</td>
<td>Cyclosporin</td>
<td>I.v. Given as 25% of the oral dose over 6h twice daily at 08.00 and 20.00. Monitor blood concentrations</td>
</tr>
</tbody>
</table>

**Preoperative drug therapy**

All medication should be continued as prescribed up to the day of operation. This is essential for immunosuppressive therapy. A supplementary dose of steroids is given usually during anaesthesia.

**Postoperative drug therapy**

After operation, the drug regimen should continue. Where possible, medication should be given orally. Following gastrointestinal surgery, or when the patient is unable to take enteral medication, modulation of the immunosuppressive regimen is necessary (table II). It is our practice to continue steroids i.v. as methylprednisolone in an equivalent dose. Azathioprine may be given i.v. at the same dose as given orally. Changes in cyclosporin dose necessitate monitoring blood concentrations after operation in order to maintain them within the therapeutic range of 150–250 mg ml\textsuperscript{-1}.

**PREOPERATIVE EVALUATION**

The approach to the preoperative assessment of a patient with a transplanted heart or lung should not differ from that of any other patient. Transplant patients are issued with a record book which provides the anaesthetist with the latest infor-
mation obtained at the last hospital visit. The record notes details of drug therapy, biopsy results, electrocardiograms, chest x-rays and any other relevant details, including the phone number of the transplant centre. Early communication with the transplant centre is desirable, particularly regarding any peroperative changes in immunosuppressive therapy.

The usual preoperative investigations should be conducted: review patient’s record book; perform full blood count; measure haemoglobin, urea, electrolyte and creatinine concentrations; perform liver and pulmonary function tests; chest x-ray; ECG; sputum microbiology. If an indwelling pacemaker has been fitted, the usual assessment of its function should be made.

**ANAESTHETIC TECHNIQUE**

After the patient is assessed before operation and it has been established that there is no rejection, the patient should be premedicated with the usual premedication of choice.

A wide variety of general anaesthetic techniques have been described in the literature, all of which have been successful. In general, an i.v. induction followed by tracheal intubation and ventilation using a neuromuscular blocking agent, an opioid and an inhalation agent, or spontaneous breathing with an inhalation agent, seem to be the most popular.

Several authors have expressed concern at the use of spinal or extradural anaesthesia in cardiac transplant patients because of exaggerated hypotensive responses [2,9]. Firestone [personal communication] has reviewed 127 post-transplant procedures and found that 20% were performed under regional anaesthesia and 30% under i.v. sedation. Recently, we have used extradural anaesthesia for postoperative pain control over a 2-day period in a post cardiac transplant patient who had undergone oesophagogastrectomy. The patient was hydrated adequately and changes in haemodynamic state were minimal.

All peripheral, central and arterial cannulae should be sited under full aseptic techniques. Disposable sterile tracheal tubes should be used and all i.v. infusions fitted with bacterial filters and injection ports kept capped and sterile.

Of greatest concern is the development of peroperative bradycardia in a patient with a transplanted heart. As atropine is ineffective in increasing heart rate, an infusion of isoprenaline should be readily available for administration through a peripheral cannula.

In patients with isolated lung allografts, care should be taken to avoid excessive airway pressures which may stress the bronchial anastomosis. A transplanted lung is deprived of lymphatic drainage and great care should be taken to avoid fluid overload in these patients. It has been postulated [19] that potentially noxious stimuli, such as prolonged increased oxygen concentrations, may be deleterious to the graft.

Appropriate antibiotic cover is essential in all transplant patients undergoing surgery. The normal regimen used for non-transplant patients should be adopted, the choice of antibiotic prophylaxis being dictated by the nature of the surgery. It is prudent also to include a single dose of an anti-staphylococcal agent, such as flucloxacillin, to cover the insertion of all percutaneous cannulae.

**Monitoring**

Standard peroperative monitoring of the ECG, arterial pressure, oxygen saturation and end-tidal carbon dioxide concentration may be all that is required in a well patient. The nature of the peroperative monitoring should be decided after consideration of the patient’s preoperative condition and the proposed surgery.

The risk of infection is such that the use of invasive monitoring should be avoided unless it is felt to be absolutely necessary. When central venous pressure monitoring is necessary, the catheter should be inserted via the antecubital fossa or the left internal jugular vein, as routine cardiac biopsies are performed usually via the right internal jugular vein.

**POSTOPERATIVE CARE**

Postoperative care should be routine, but extra vigilance should be exerted to detect infection. Any evidence of infection must be investigated early and treated accordingly. Fluid balance must be monitored carefully to avoid excessive positive balances, particularly in patients with transplanted lungs. Lung transplant patients should be encouraged to cough and expectoration promoted by physiotherapy and postural drainage where possible.

**SUMMARY**

Heart and lung transplantation is now accepted as
a means of treating some end-stage cardiopulmonary diseases. These patients may present with a wide variety of non-cardiopulmonary conditions requiring anaesthesia and surgery, possibly at a place distant from their original transplant centre. In general, for much elective, acute or even emergency surgery, if the allograft is functioning satisfactorily, these patients should present few problems during anaesthesia, provided the anaesthetist has some understanding of the pathophysiology of the transplanted organ and recognizes the differences (potential and specific to cardiopulmonary transplantation) between such patients and any other subject.

REFERENCES