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Clinical heart and lung transplantation

Patients with end stage parenchymal lung disease or pulmonary vascular disease present a difficult therapeutic problem, for these conditions are ultimately fatal and conventional treatment is no more than palliative. Transplantation of the lung or combined transplantation of the heart and lung offer the only chance of cure.

Over the past 20 years repeated efforts have been made to transplant single lungs and until 1980 there had been three attempts at combined heart and lung transplantation.[1-3] Nevertheless, between 1963 and 1980 experience with isolated transplantation of the lung was disappointing, and only two of about 38 patients survived more than one month.[4] One of these lived for six months and the other 10 months; but apart from a two week period in the second case both remained in hospital throughout their postoperative course. All three recipients of the combined heart and lung transplants died within a few days.

Improved results of cardiac transplantation at Stanford with the use of cyclosporin,[5] and long term survival after combined heart and lung transplantation in primates,[6] encouraged further efforts, and in March 1981 the world's fourth heart and lung transplant operation was carried out. The patient, a 45 year old woman with primary pulmonary hypertension, remains alive and well 45 months later. Twenty two patients have now undergone 23 combined operations in the Stanford series with one, two, and three year actuarial survivals of 71%, 58%, and 58% respectively. Comparable figures for survival after isolated cardiac transplantation were 82%, 75%, and 68%.[7] The total period of follow up of recipients of combined heart and lung transplants is 332 months (mean 16 months, range 4-45 months). Early mortality was 26% which largely reflects the initial surgical experience, and there has been only one early death in the last eight patients.

Neither the operation nor the postoperative management of these patients is straightforward. Adhesions from previous cardiac surgery (common in those with Eisenmenger's syndrome), exacerbated by a hypocoagulable state due to hepatic congestion, and prolonged periods on cardiopulmonary bypass increase the operative risk and have contributed to three of the six early deaths. Furthermore, as the transplanted lungs are denervated there is no cough reflex, so the patients need vigorous postoperative physiotherapy to the chest including instruction on how to achieve postural drainage.

Early diagnosis of rejection of the lung is difficult. The hypothesis that pulmonary and cardiac rejection occur simultaneously—and therefore that rejection of both organs may be diagnosed by endomyocardial biopsy—is no longer tenable, for isolated lung rejection has occurred after combined heart and lung transplantation in primates and in one patient.[8 8a] Chest radiographs show diffuse opacification but this appearance may be confused with cardiac failure or infection and thus there is no satisfactory non-invasive way to diagnose lung rejection.

The 16 patients in the Stanford series who were discharged from hospital had normal exercise tolerance and normal gas exchange four weeks after operation.[9] Cardiac catheterisation, performed in 13 patients after one year and in five after two years, showed normal haemodynamic values, including pulmonary artery pressure and pulmonary vascular resistance. The appearances on coronary arteriography were normal apart from the development of extensive coronary mediastinal collateral vessels. One of two patients studied at three years had triple vessel coronary artery disease and raised pulmonary artery pressure as a result of recurrent pulmonary vascular disease; both the pulmonary and coronary vascular disease were probably the result of immune mediated injury. This patient was given a second transplant and has since made a full recovery and left hospital.

There have been two late deaths at 14 and 15 months from acute anterior myocardial infarction and respiratory failure respectively. Six of the long term survivors, including the two who died, have developed late pulmonary complications. Symptoms have included progressive breathlessness, cough (often productive), and fever, with signs of diffuse crepitations and expiratory rhonchi.[10] Serial tests of lung function have shown an obstructive pattern in all six patients with superimposed restrictive changes in three. Histological examination of tissue from open lung biopsy or necropsy has shown obliterative bronchiolitis in five of these six patients. This syndrome has been unresponsive to treatment with antibiotics, bronchodilators, or physiotherapy. A course of corticosteroids was given in four patients, late in the course of their deterioration, but no sustained response was obtained. Four of these six patients remain alive, one remains dyspnoeic on moderate exertion, one has undergone successful retransplantation, and two await a repeat operation.

The development of late respiratory dysfunction is worrying, but this may be due to inadequate immunosuppression and thus may be avoidable in the future. In support of this view a seventh patient who recently presented with this syndrome was given early augmented immunosuppression and this resulted in resolution of his symptoms and a return to normal values of lung function. Most patients, however, have had no late complications and the remaining 10 patients are now fully rehabilitated and able to choose their own lifestyle—a remarkable achievement, especially in those with Eisenmenger's syndrome who are born severely incapacitated and have never before been able to exercise normally.

Recent results of combined heart and lung transplantation are considerably better than those for isolated lung transplan-

tation, where there is only one long term survivor (J Cooper, personal communication). The main advantage of the combined operation is that all diseased tissue is removed and so recurrent infection and an imbalance of ventilation and perfusion from the remaining lung are avoided. In addition, coronary bronchial vascular collaterals, shown at coronary arteriography in these patients, may aid healing of the trachea. Thus no early or late complications have occurred as a result of problems with the tracheal anastomosis after heart and lung transplantation in the Stanford series, which is in sharp contrast to the experience after isolated lung transplantation.[4]

But perhaps the most important practical problem for the future of combined heart and lung transplantation is the lack of suitable donors. Pulmonary changes occur early in patients with brain death as a result of aspiration or infection or both and may be complicated by the development of neurogenic pulmonary oedema. Satisfactory preservation and storage of the heart and lung block have not been achieved, and the donor must be moved to the recipient hospital before the organs are removed. This may result in emotional and logistical difficulties but donors with normal lung function are rare and suitable cases should perhaps be considered for heart and lung donation as a priority. This does not of course preclude the donation of other organs.

It is not only patients with pulmonary hypertension who might benefit from combined heart and lung transplantation. Advances in the diagnosis and treatment of lung rejection should make the procedure a realistic treatment for many other patients with pulmonary failure—especially when improved techniques for preserving the integrity of the lungs result in an increased number of suitable donors.

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Regular Review

Therapeutic ranges in anticoagulant administration

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Clinicians around the world have reawakened their interest in the use of anticoagulants as less intense ("low dose") therapeutic regimens have come into use. Among the factors that have contributed to this change of attitude have been cumulative experience with national systems of anticoagulant control (particularly in Britain and the Netherlands[1]), new clinical trials, and the wide availability of a standardised thromboplastin, British comparative thromboplastin and its routine counterpart Manchester comparative reagent.

Therapeutic ranges of anticoagulation can be established only by planned randomised clinical trials in the prevention or treatment of the relevant thrombotic disorder. These must be of sufficient size and duration to assess the clinically relevant end point. Many of the early clinical trials overlooked the methods used for laboratory control. The effects on the anticoagulant dose of the technique used for measuring prothrombin time and its method of reporting are of paramount importance. Regimens based on techniques relatively insensitive to the coumarin dependent clotting factors II, VII, and X invariably result in a more intense coagulation defect.[2 3]

A recent international survey of current practice showed that physicians tend to be conservative in dosage with more intense regimens, while important differences in mean dosages may still be seen among countries (see figure).[2] This review will look at current techniques for monitoring anticoagulant treatments and at the main clinical indications.

Therapeutic ranges

The lower limit of a therapeutic range should be the minimum coagulation defect necessary for the prevention of recurrence or extension of an established thrombotic episode. There is no virtue in choosing a coagulation defect