Coronary artery disease after heart transplantation: clinical aspects

Oclusive coronary artery disease is now the main complication limiting long-term survival after heart transplantation and also the most common indication for retransplantation. The reported angiographic prevalence ranges from 2% to 28% one year after transplantation, increasing to 40–70% by five years. Most of these patients, however, have only minor coronary stenoses or minimal luminal irregularities. There are as yet few data available about the rate of progression and clinical significance of these minor changes. In this issue (pages 260–5) Mullins et al report a three year survival of 60–80% after first diagnosis of coronary disease, which depends on the number of vessels involved. When the disease is more advanced survival rates are poor. Keogh et al report actuarial three year survival rates of 6% and 22% for advanced (>40% stenoses) triple and single vessel disease respectively.

The clinical presentation of oclusive coronary disease in transplant recipients is very different from that in other patients. The importance of relatively minor coronary oclusive disease can be substantially increased by a tendency to increased platelet aggregation and blood hypercoagulability caused by high serum concentrations of fibrinogen and factors VIIIC and VIIIIC. Although a few transplant patients probably do experience angina most will have silent ischaemia because of autonomic denervation after surgery. As with conventional coronary disease, advanced disease in the transplanted heart is associated with frequent multifocal and complex ventricular activity and sudden death. Progressive heart failure caused by recurrent infarction or progressive ischaemia can develop. Acute myocardial infarction in transplant recipients is usually painless although they may report dyspnoea, palpitation or sudden weakness. The electrocardiographic changes may be slight because of the diffuse and atypical pattern of infarction.

Because there is no effective treatment for established coronary oclusive disease in transplant recipients prevention is an important priority. Existing studies have been retrospective and have used widely differing diagnostic criteria. They have produced few data that are directly applicable to the management of patients being given transplants today.

Effective future research will require the best methods of diagnosis and assessment of transplant related coronary disease. Existing studies have relied heavily on conventional coronary arteriography which has very serious limitations. It consistently underdiagnoses coronary disease in transplant recipients and underestimates its severity. Quantitative angiography has improved sensitivity particularly in detecting smooth concentric vessel narrowing. Intracoronary ultrasound also enables more accurate assessment of smooth concentric stenoses but the size of the probe restricts its use to large epicardial vessels. The widespread involvement of small vessels in transplant related coronary oclusive disease probably limits the usefulness of these methods of assessment that are solely anatomical.

Functional assessment by non-invasive techniques has proved disappointing with too low a sensitivity for routine use. Intracoronary Doppler measurement of blood flow can be readily combined with conventional angiography and this approach may provide a more comprehensive evaluation of the oclusive disease. Although there are few good data on which to base recommendations about patient management it seems prudent to treat hypertension vigorously, to advise patients to eat a diet low in saturated fat, and to avoid cigarette smoking and excessive weight gain. Despite these measures many recipients will continue to have "atherogenic" lipid profiles, and this raises the question of drug treatment for hyperlipidaemia. Unfortunately, when the very effective hydroxymethylglutaryl co-enzyme A reductase inhibitors are used in combination with cyclosporin they can occasionally cause rhabdomyolysis and renal failure and therefore may be too hazardous to be recommended for widespread use. The effectiveness of aspirin in other patients may encourage its use in established coronary disease but it is probably not widely appreciated that its effectiveness is seriously limited by changes in platelet aggregation in transplant patients.

Some centres have advocated steroid-free maintenance immunosuppression to reduce coronary disease. It may be particularly effective in children and is also desirable for their optimum growth. In adults, however, its effectiveness is unproven, and given the suspected immunological nature of the process this approach may be deleterious. The preliminary results of a randomised trial of diltiazem in the prevention of graft coronary disease from the Stanford group are encouraging but further data are needed before it can be recommended for routine practice. In animal models low molecular weight heparin, which reduces smooth muscle cell proliferation, has been shown to reduce the severity of oclusive disease.

What are now required are large scale, multicentre, randomised, prospective trials of management strategies with clearly defined end points. Advanced assessment techniques such as those discussed would be preferable. Intensive drug treatment of hyperlipidaemia, steroid-free maintenance immunosuppression, and the prophylactic use of calcium antagonists or low molecular weight heparin would be suitable for this type of study. The role of cardiac autograft rejection also needs to be investigated further particularly with reference to the question of maintenance steroid therapy. Because the United Kingdom has a relatively small number of centres, each performing substantial numbers of transplants, we are in an ideal administrative position to undertake such studies.

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