Editorial

Long-term complications of cardiac transplantation

Cardiac transplantation has evolved over the past 27 years from a procedure with a one year survival of 20% to an accepted treatment for end stage heart failure with over 26 000 recipients in 251 centres around the world.[1] Today the one year survival at Papworth, as in most established centres, is nearly 90% and five year survival and 10 year survival are 65% and 52% respectively. The cardiac transplant programme at Papworth Hospital started in 1979 and 600 patients have now undergone the procedure. These patients have been closely followed at the hospital and over the years the long-term problems in this population have gradually become clear.

Rejection

Acute rejection remains the most important clinical problem in the first year after transplant but in patients on stable immunosuppressive treatment it is an infrequent long-term problem.[2] Endomyocardial biopsy remains the reference standard for the diagnosis of acute rejection and like most centres we perform "surveillance" biopsies during the first year. We have recently discontinued the common practice of performing annual surveillance biopsies after the first two years but we selectively perform biopsy when clinically indicated. Endomyocardial biopsies are performed as an outpatient procedure via the internal jugular vein; the mean procedure time is 10-15 minutes. When performed by an experienced operator complications seldom occur: they include pneumothorax, haematoma from accidental puncture of the carotid artery, and rarely cardiac tamponade. Numerous non-invasive markers of acute rejection have been described but none has proved sensitive, specific, and reproducible enough to supplant endomyocardial biopsy.

Other complications

There are three important long-term complications associated with cardiac transplantation. In decreasing order of importance they are (*a*) the development of coronary artery disease, (*b*) the increased risk of malignancy, and (*c*) progressive renal dysfunction owing to cyclosporin. Coronary artery disease in the allograft (also referred to as coronary occlusive disease or cardiac allograft vasculopathy) has emerged as the most important long-term problem in the management of these patients. Allograft coronary disease is believed to be immunologically mediated[3] and is a diffuse process affecting epicardial and intramyocardial vessels with poor collateral flow.[4] Coronary angiography underestimates disease prevalence and severity[5]; at Papworth the prevalence of angiographically determined disease (of any severity) 5 years after transplant is 40%.[6] Intracoronary ultrasound has shown intimal thickening in most patients by the end of the first year[5] and we have seen extensive coronary disease at necropsy in a patient who died suddenly 4 months after transplant. Coronary flow reserve is impaired in patients with vessels that are angiographically normal or minimally diseased, indicating involvement of distal vessels.[7] The relative importance of these investigative techniques in evaluating cardiac allograft vasculopathy remains unclear.

Though it is believed to be an immunological disease, conventional risk factors such as hyperlipidaemia may contribute to the development of cardiac allograft vasculopathy.[8] There may be an increased incidence of side effects (myalgia, rhabdomyolysis) from lipid lowering drugs in patients taking cyclosporin, but we have had relatively few problems with HMG CoA reductase inhibitors (statins) and fibrates.[9] Initially it was thought that angina would not occur in the cardiac transplant recipient (because of denervation), however, angina is now well recognised in a few patients, which suggests that reinnervation may occur.[10] In most patients the angina is not severe; none the less, two of our patients presented with unstable angina (one had a left main stem lesion).

The natural course of the disease has been well documented by the practice of annual coronary angiography at many centres and lesions progress more rapidly than in conventional coronary artery disease.[4,6] Treatment options are limited; the diffuse nature of the disease makes revascularisation impractical in most patients. Though symptoms are rare we have treated selected patients with proximal lesions and evidence of reversible myocardial ischaemia on perfusion scanning. Coronary angioplasty has been performed on 20 patients with an initial success rate and restenosis rate similar to those in conventional coronary artery disease.[11] The impact on prognosis is as yet unclear because new lesions often appear on follow up angiograms. The role of coronary artery bypass grafting is also unclear; at Papworth it has been performed in five patients with two operative deaths (both patients had unstable angina).[11] Surgery can, however, relieve symptoms of angina and dyspnoea and may have a role in carefully selected patients with proximal stenoses in multiple vessels and good run-off on angiography. Cardiac retransplantation is the only definitive treatment for allograft coronary artery disease. To maximise the benefit achieved from a scarce pool of donor organs it is important that candidates for retransplantation are selected carefully. Our current practice is to consider for retransplantation patients who have good renal function and no evidence of generalised vascular disease. Only 16 patients (2·7%) have undergone retransplantation at Papworth over the 16 years of the programme. Future research must focus on the development of new immunosuppressive drugs to prevent the onset or slow the progression of allograft vasculopathy.

An inevitable consequence of long-term immunosuppressive treatment is the increased incidence of malignancy. There seems to be a correlation between the doses of immunosuppressive agents used and the risk of malignancy.[12] Data from large tumour registries suggest that the incidence of malignancies commonly seen in the general population (lung, breast, prostate, colon, uterine cervix) is not increased whereas that of squamous cell carcinoma of the skin and lymphoma is.[13] At Papworth the incidence of

malignancy in patients surviving 3 months or more after transplantation is 11·6% (59 of 495 patients). The median interval between transplantation and appearance of malignancy was 48 months. A third of these were skin cancers (predominantly squamous cell carcinoma) and just under 30% of the tumours have been lymphomas (17 patients); the incidence of lymphomas may be significantly higher in centres using OKT3 as part of the immunosuppressive regime.[12 13] Most lymphomas in organ transplant recipients are B cell non-Hodgkin tumours. There is an association between post-transplant lymphoma and infection with the Epstein-Barr virus[14] though the exact relation is not clear.[15] The only useful predictor of a favourable outcome is a response to reduced immunosuppression. In three of our 17 patients the lesions regressed completely in response to a reduction in cyclosporin dose and treatment with high doses of oral acyclovir. Patients with a large tumour mass usually need chemotherapy along with a reduction in conventional immunosuppression but the prognosis is generally poor.

Though cyclosporin has revolutionised organ transplantation nephrotoxicity has been a major problem with its use.[16] Acute cyclosporin nephrotoxicity is reversible[17] but chronic toxicity may lead to end stage renal disease necessitating dialysis or renal transplantation.[16] Most patients on cyclosporin also develop hypertension[18] which may contribute to renal dysfunction. The incidence of end stage renal disease (requiring chronic dialysis) in our patients is 3·4% (17 of 495 patients survived 3 months or more after transplant) and the median interval between transplant and dialysis is 67 months. Four patients have undergone renal transplantation: one died soon after operation. While the dose of cyclosporin commonly used now is considerably less than that used in the early 1980s the improved long-term survival in these patients (with the cumulative exposure to cyclosporin) may result in this complication being seen more frequently. It must be emphasised that the morbidity from nephrotoxicity caused by cyclosporin is more than offset by the improvement in early survival.

Conclusions

We believe it is important that patients referred for transplantation (and their families) are made aware of the potential complications, and in our assessment programme we take great care to discuss these issues at some length. It is important, however, to place these problems in perspective. The transformation in the quality of life of a patient with severe heart failure after cardiac transplantation is dramatic; most patients can now also hope to survive 10 years or more. In carefully selected symptomatic patients with a poor prognosis cardiac transplantation remains the best treatment.

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