Transplant Int (1992) 5 [Suppl 1]: S238–S241

TRANSPLANT
International

Determinants of graft arteriosclerosis after heart transplantation

C. D. Scott, I. W. Colquhoun, K. Gould, J. Au, and J. H. Dark

Cardiothoracic Centre, Freeman Hospital, Newcastle-upon-Tyne, UK

Abstract. Accelerated graft coronary artery disease (TxCAD) is now the most common complication limiting long-term survival after heart transplantation. This study examines its association with several potentially causative factors. The study population comprised all 73 transplants recipients at this centre between May 1985 and June 1989 who survived at least 2 years. Coronary angiography was performed in every patient at 2 years after transplantation and annually thereafter. All angiograms were retrospectively examined for any evidence of TxCAD. The number of rejection episodes and history of cytomegalovirus (CMV) infection were determined from patient records. Fasting serum triglycerides, and total and HDL cholesterol were measured at between 18 and 60 months after transplantation. Patients with advanced TxCAD (> 70% stenoses) had a mean of 1.4 ± 1.4 rejection episodes in the first year compared with 0.5 ± 0.8 episodes in those without TxCAD ($P < 0.05$). The mean number of episodes in all patients with any evidence of TxCAD was 0.8 ± 1.1 which was not significantly different from those without TxCAD. There were no association between exposure to CMV infection and TxCAD or between hyperlipidaemia and TxCAD. We conclude that frequent episodes of allograft rejection are associated with the development of advanced TxCAD. Hyperlipidaemia is not associated with the development of TxCAD in the first 5 years after transplantation. A history of exposure to CMV is not associated with TxCAD in our patients possibly because of our routine use of anti-CMV hyperimmune globulin in CMV-mismatched patients.

Key words: Heart transplantation – Graft arteriosclerosis

Accelerated coronary artery disease is now the most common complication limiting long-term survival after heart transplantation [2, 4]. Suggested causes of this phenomenon include those common to patients with native coronary artery disease such as hyperlipidaemia, hypertension and diabetes [6, 11] and those peculiar to heart transplant recipients such as allograft rejection and transplant related cytomegalovirus infection or reactivation [10, 11, 15, 16, 19, 20].

The results of previously published studies have been contradictory with regard to the importance of hyperlipidaemia after transplantation [6, 8]. A consensus has emerged that allograft rejection and cytomegalovirus infection are associated with accelerated coronary artery disease [10, 15, 16, 19, 20] although it is not unanimous [1, 8].

This angiographic study of both early and advanced coronary artery disease in transplant recipients re-examines several of these potential associations.

Methods

The study population comprised all 73 adult transplant recipients at this centre between May 1985 and June 1989, who survived at least 2 years after surgery. The operative technique was as described by Lower et al. [14]. All patients were immunosuppressed with cyclosporin, azathioprine and prednisolone. Aspirin was given routinely only to those patients with angiographically demonstrated coronary artery disease. Those recipients who were CMV-antibody-negative at the time of transplantation with a CMV-positive donor (CMV mismatch) were given prophylactic anti-CMV hyperimmune globulin. Full details of the protocol employed have been published previously [7].

Coronary angiography

Coronary angiography was performed in all patients, first at 2 years after transplantation and then annually. All coronary angiograms were reviewed by two of the investigators independently and consensus was then reached. Coronary artery disease was said to be present if any irregularity of coronary vessels was detected. The severity of stenoses was visually estimated. Advanced coronary artery disease was defined as a stenosis of 70% or greater in any major epicardial coronary artery or occlusion of any visible vessels.

Offprint requests to: Dr. C. D. Scott, Cardiothoracic Centre, Freeman Hospital, High Heaton, Newcastle-upon-Tyne, NE7 7DN, UK

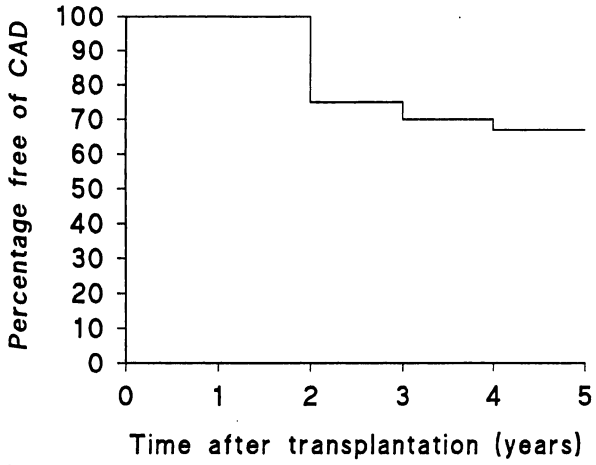

Fig. 1. A survival curve representing those transplant recipients free of proven coronary artery disease at the indicated time after transplantation

Hyperlipidaemia

All transplant patients at this centre are encouraged to eat a low-fat diet with a high polyunsaturated to saturated fat ratio. Blood lipid profiles were obtained at a minimum of 18 months after transplantation. Total cholesterol, HDL cholesterol and triglycerides were measured in each patient after a 16-h fast.

CMV infection

CMV infection was determined by donor-recipient mismatch (defined above) or by the presence of CMV IgM antibody and/or isolation of CMV from the urine from a patient with an otherwise unexplained pyrexial illness.

Allograft rejection

Each patient underwent routine endomyocardial biopsies weekly until 6 weeks after transplantation, fortnightly until 3 months, monthly until 6 months and 3-monthly thereafter. Additional biopsies were performed as clinically indicated. A rejection episode was defined by a biopsy indicating moderate or severe rejection according to the Billingham classification [3].

Statistical analysis

Results are expressed as mean ± 1 standard deviation. Comparative analyses were performed using the Student's *t*-test, Mann-Whitney *U* test and Fisher's exact test. A probability $p < 0.05$ was considered significant.

Results

A survival curve was constructed by the Kaplan-Meier technique [13] showing the percentage of transplant patients free of proven coronary artery disease as a function of time after transplantation (Fig. 1). The percentage of patients free from proven coronary artery disease was 75% at 2 years, 70% at 3 years ($n = 42$), 67% at 4 years ($n = 16$) and 67% at 5 years ($n = 8$).

Of a total of 25 patients with coronary artery disease, ten have advanced disease, the majority of the remaining 15 have only minor luminal irregularities.

There have been three deaths in the study population, one due to malignancy in a patient with no coronary disease and two due to coronary disease. One of these patients had advanced disease identified angiographically ante-mortem, the other had only minor disease documented. Post-mortem examination subsequently proved this to be a considerable underestimade of the severity of disease.

Rejection

Patients with coronary disease had a total of 0.8 ± 1.1 episodes of rejection in the first year after transplantation compared with 0.5 ± 0.8 episodes in those without. This difference was not statistically significant. However those with advanced disease had significantly more episodes (1.4 ± 1.4) than those with no disease ($P < 0.05$, Mann-Whitney). No patient had any rejection episode after the first postoperative year.

Hyperlipidaemia

The lipid profiles of the study patients are detailed in Table 1. There were no significant differences in serum levels of triglycerides, or total or non-HDL cholesterol between any of the groups with severe, mild or no coronary disease.

Cytomegalovirus infection

Of 25 patients with coronary artery disease, four (16%) were CMV mismatched or had reactivation/reinfection compared with nine (19%) of 48 patients with no evidence of coronary disease. This difference was not significant ($P = 0.52$).

Discussion

Limitations of the study

Coronary angiography is currently the best method available for studying coronary artery disease in transplant patients but it is less than ideal. It is not able to distinguish

Table 1. Blood lipid profiles of patients with severe, mild or no coronary disease. Values are expressed as mean ± 1 standard deviation

	Coronary disease	No coronary disease	Significance
Total cholesterol (mmol/l)	7.4 ± 1.4	7.3 ± 2.0	NS
Non-HDL cholesterol (mmol/l)	5.9 ± 1.5	6.2 ± 2.1	NS
Triglycerides	2.42 ± 1.23	2.37 ± 1.50	NS

different underlying pathological processes [12] and it also probably underestimates the severity of disease [9].

The serum lipid levels in this study were based on single samples. However they were all performed at least 18 months after transplantation when serum lipids can be expected to be more stable than in the immediate perioperative period [6].

Prevalence of graft arteriosclerosis

The prevalence of graft coronary disease in our patients is comparable with that found in other studies [1, 6, 8, 17, 22]. There were however some differences in diagnostic criteria. In common with most other studies [1, 8, 16, 20], we accepted any luminal irregularity as indicative of coronary disease. Pascoe et al. [17] recorded only lesions causing greater than 30% stenosis of any vessel. Eich et al. [6] identified coronary disease by evidence of perfusion defects or impaired left ventricular function using isotope techniques and confirmatory coronary angiography. The prevalence of disease diagnosed by routine angiography would probably have been higher.

Rejection

We have confirmed, in our patients, previous findings that frequent episodes of allograft rejection [16, 20] are associated with graft arteriosclerosis. This association was limited, however, to those with advanced disease and was not significant for all patients with coronary artery disease. Some previously published studies have also found limited [16] or no such associations [8].

The underlying reason for this variation in the apparent importance of allograft rejection is probably that current techniques only indirectly assess the immune process responsible for coronary disease. The standarad technique of surveillance endomyocardial biopsy assesses only cell-mediated myocardial rejection. Antibodies reactive against vascular endothelium have been shown to be associated with atherosclerosis in non-transplant patients [5]. Several studies have indicated the importance of antibody-mediated rejection in the development of graft coronary disease [11, 18]. Although acute antibody-mediated rejection is often accompanied by cell mediated rejection the processes may differ in severity and response to treatment [21].

Hyperlipidaemia

We have found no association between blood lipids and the development of coronary disease in our patients. Gao et al. [8] reported an association with plasma triglycerides at 1 year after transplantation but it was not consistent over time. Hess et al. [11] reported a clear association between coronary disease and hypercholesterolaemia in combination with cytotoxic B-cell antibodies but there were only 14 patients in the study. In a larger study of 38 patients Eich et al. [6] also found an association with hypercholesterolaemia. However, the frequency of rejection episodes in each group was not stated. The overall incidence of coronary artery disease may have been abnormally high in this study [6] given that the diagnostic techniques would have missed minor coronary artery disease and that the stated incidence was similar to other series [1, 8, 17, 22].

The lack of association between blood lipids and transplant-related coronary disease may seem surprising in view of the well-known association of hyperlipidaemia and coronary atheroma in the general population. This may be due to the aetiological dominance of relatively rapid immunological processes in the first years after transplantation. The effects of hyperlipidaemia in these patients may only become apparent over a much longer period.

Cytomegalovirus infection

Our finding of no association between CMV infection and coronary disease is in contrast to several large published studies [10, 15, 19]. At this centre routine surveillance of anti-CMV IgG levels amongst asymptomatic seropositive patients is not performed. Thus some patients classified in other studies [10, 15] as having had CMV infection would not be in this analysis. Another centre using routine anti-CMV hyperimmune globulin [1] has reported similar findings to our own although the criteria for CMV infection were not stated in this report. We have found that anti-CMV hyperimmune globulin prevents or greatly ameliorates clinical CMV illness in mismatched patients; it may also prevent CMV-related graft coronary disease in this group.

Conclusion

We have confirmed that frequent allograft rejection is associated with the development of advanced graft coronary disease. In contrast to other studies, we have not demonstrated any effect of CMV exposure, we believe that our use of anti-CMV hyperimmune globulin in all CMV-mismatched recipients may be protective in this respect. In common with many other studies, we have found no association between blood lipids and accelerated coronary disease. The effects of hyperlipidaemia may only become apparent over a much longer period after transplantation.

References

1. Balk AHMM, Linden MVD, Meeter K, et al (1991) Is there a relation between transplant coronary artery disease and the occurrence of CMV infection (abstract). J Heart Lung Transplant 10: 188
2. Bieber CP, Hunt SA, Schwinn DA, et al (1981) Complications in long term survivors of cardiac transplantation. Transplant Proc 13: 207–211
3. Billingham ME (1985) Diagnosis of cardiac rejection by endomyocardial biopsy. J Heart Transplant 1: 25–30
4. Billingham ME (1989) Graft coronary disease: the lesions and the patients. Transplant Proc 21: 3665–3666

5. Cerilli J, Brasile J, Sosa J, et al (1987) The role of autoantibody to vascular endothelial cell antigens in atherosclerosis and vascular disease. Transplant Proc 14 [Suppl V]: 47–49
6. Eich D, Thompson JA, Ko D, et al (1991) Hypercholesterolaemia in long term survivors of heart transplantation: An early marker of accelerated coronary artery disease. J Heart Lung Transplant 10: 45–49
7. Freeman R, Gould FK, McMaster A (1990) Management of CMV antibody negative patients undergoing cardiac transplantation. J Clin Pathol 43: 373–376
8. Gao SZ, Schroeder JS, Alderman EL, et al (1987) Clinical and laboratory correlates of accelerated coronary artery disease in the cardiac transplant patient. Circulation 76 [Suppl V]: 56–61
9. Gao SZ, Johnson D, Schroeder JS, et al (1988) Transplant coronary artery disease: histopathologic correlations with angiographic morphology (abstract). J Am Coll Cardiol 11: 135A
10. Grattan MT, Moreno-Cabral CE, Starnes VA, Oyer PE, Stinson EB, Shumway NE (1989) Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. JAMA 261: 3561–3566
11. Hess MJ, Hastillo A, Mohanakumar T, et al (1983) Accelerated atherosclerosis in cardiac transplantation: role of cytotoxic B-cell antibodies and hyperlipidaemia. Circulation 68 [Suppl II]: 94–101
12. Johnson DE, Gao SZ, Schroeder JS, DeCampli W, Billingham ME (1989) The spectrum of coronary artery pathologic findings in human cardiac allografts. J Heart Transplant 8: 349–359
13. Kaplan EL, Meier P (1958) Nonparametric estimation for incomplete observations. Am Stat Assoc 10: 457
14. Lower RR, Stofer RC, Shumway NE (1961) Homovital transplantation of the heart. J Thorac Cardiovasc Surg 41: 196–202
15. McDonald K, Rector TS, Braunlin EA, Kubo SH, Olivari MT (1989) Association of coronary artery disease in cardiac transplant recipients with cytomegalovirus infection. Am J Cardiol 64: 359–362
16. Narrod J, Kormos R, Armitage J, et al (1989) Acute rejection and coronary artery disease in long term survivors of heart transplantation. J Heart Transplant 8: 418–421
17. Pascoe EA, Barnhart GR, Carter WH, et al (1987) The prevalence of cardiac allograft arteriosclerosis. Transplantation 44: 838–839
18. Rose EA, Smith CR, Petrossian GA, Barr ML, Reemtsma K (1989) Humoral immune responses after cardiac transplantation: correlation with fatal rejection and graft atherosclerosis. Surgery 106: 203–207
19. Stovin PGI, Sharples L, Hutter JA, Wallwork J, English TAH (1991) Some prognostic factors for the development of transplant related coronary artery disease in human cardiac allografts. J Heart Lung Transplant 10: 38–44
20. Uretsky B, Murali S, Reddy S, et al (1987) Development of coronary artery disease in cardiac transplant patients receiving immunosuppressive therapy with cyclosporine and prednisone. Circulation 76: 827–834
21. Yowell RL, Hammond EH, Bristow MR, Watson FS, Renlund DG, O'Connell JB (1988) Acute vascular rejection involving the major coronary arteries of a cardiac allograft. J Heart Transplant 7: 191–197
22. Zusman DR, Stinson EB, Oyer PE, et al (1985) Determinants of accelerated graft atherosclerosis in conventional and cyclosporin treated heart transplant recipients (abstract). J Heart Transplant 4: 587