Editorial Comment

Investigation of Heart Transplant Coronary Atherosclerosis

Stuart W. Jamieson, MB, FRCS

More than 17,000 orthotopic heart transplants have been performed, and the results of all centers reporting to the International Registry show a 1-year survival rate of more than 80%. Heart transplantation has become a routine and effective method for the treatment of end-stage heart disease.

Acute cellular rejection or infection are the most common causes of death within the first year after transplantation. However, because of the progressive adaptation that occurs by the host to the transplanted organ, the incidence of cell-mediated rejection diminishes with time. Immunosuppression can thus be reduced after the first few months, and the incidence of infection therefore also lessens. The predominant cause of graft loss after the first year is the progressive development of graft atherosclerosis. Because of the denervated state of the transplanted heart, it is most unusual for transplant patients to experience angina, and regular monitoring for this condition must be carried out.

The precise etiology of graft atherosclerosis has been hard to determine. It is probably the result of endothelial injury by antibody directed against the graft, and similar lesions can be generated by direct injection of antibody in the vessels of experimental animals or in experimental cardiac grafts in inbred rats, in which it is absent in isograft controls. All organ grafts are affected, but nowhere is the effect as serious as in cardiac transplantation, with the myocardium particularly dependent on an unimpeded blood supply and the patient on the graft.

Analysis has been made of various characteristics of both donor and recipient to attempt to identify predisposing causes. This has been unrewarding. In the experience of most centers, donor age or sex appears to be unrelated to the late development of vascular disease.

Early in the clinical experience of heart transplantation, it was noted that graft atherosclerosis equally affected those recipients whose presenting illness was cardiomyopathy and those who suffered from end-stage coronary artery disease, and this has since been confirmed. Therefore, as one might suspect, a relation to plasma triglyceride and cholesterol levels is tenuous. There are some experimental data, however, that demonstrate that in the presence of continued immunological injury to the graft, high-fat diets will accelerate the development of graft atherosclerosis. The combination of hyperlipidemia and cytotoxic B-cell antibodies has also been found to predispose to coronary artery disease in human transplant recipients, and elevated total cholesterol and low density lipoprotein levels together with rejection episodes have been identified as risk factors in retransplantation for accelerated graft atherosclerosis. It would thus seem prudent to minimize the effect of cholesterol and triglycerides in transplant recipients by dietary restriction and treatment as indicated.

The age of the recipient is not an independent risk factor, and graft atherosclerosis is now emerging as a limiting factor in the long-term survival of children after cardiac transplantation. Because the presence of antibody has been linked to the development of graft coronary disease in animals, it might be expected that the degree of host-graft mismatch and the number of rejection episodes after transplantation would be linked to the development of atherosclerosis, but this is not the case. Experimentally, very little antibody will cause graft atherosclerosis, and this may explain the relative lack of effect of overt rejection episodes on this condition in the clinical situation.

Cyclosporine was first used in heart transplantation immunosuppression in December 1980, and this drug became available for general use in 1983. Graft atherosclerosis was the major cause of late death in the precyclosporine era, and its impact has not lessened with newer immunosuppressive regimens. The reverse may be the case. A review of the series from Stanford, one of the few centers with significant numbers of patients treated before the use of cyclosporine, showed that with the use of cyclosporine, the rate of vessel stenosis nearly doubled. The explanation is not clear. It may be that antibody production still occurs with cyclosporine therapy. On the other hand, cyclosporine increases total cholesterol in nontransplanted subjects. A decrease in total cholesterol and triglyceride levels has also been observed in renal transplant patients converted from cyclosporine therapy to azathioprine. Cyclosporine has also been related to postoperative hypertension in transplant recipients, but...
hypertension as such is unlikely to be the cause of graft atherosclerosis, because vascular changes have been seen in long-term lung transplants, in which the pulmonary vasculature is exposed to a low pressure.16

The use of antilymphocyte globulins or OKT3 may be related to graft vasculitis17 and thus the long-term development of graft atherosclerosis, through either the development of serum sickness with the development of immune complexes,10,15,16 hypersensitivity,17 or the predisposition to viral illness that is associated with specific anti-T cell therapy. That human atherosclerotic disease may be associated with viral infection19 has lead some investigators to investigate a correlation of viral infection, particularly with cytomegalovirus, with posttransplantation atherosclerosis. A relation has been noted by some groups8,20 but not by others.9 Although it is difficult to isolate viral infection as a single factor, because it often is the result of augmented immunosuppression after severe and persistent rejection or the use of OKT3 therapy, there is evidence to suggest that the cytomegalovirus can persist in the vessel wall, and this may be a stimulus for progressive intimal thickening.21 If this should be the case, the newer antiviral agents being increasingly used as prophylaxis against cytomegalovirus after transplantation may make a difference in the occurrence of graft atherosclerosis.

Noninvasive tests have proved relatively insensitive in the detection of graft atherosclerosis. This is probably because of the characteristically diffuse nature of the disease. Therefore, regular coronary angiography is performed (at least annually). The incidence of graft atherosclerosis as detected by angiography has varied from 2% to 25% at 1 year and may be as high as 50% at 5 years.8,18,22 As might be expected, the severity of angiographic disease correlates with survival.23 However, angiography is insensitive in the detection of early graft disease and tends to underestimate the degree of narrowing of the vessels.4 This is because the lesions are rarely localized, being diffuse and concentric. Comparison with prior films is therefore important in the assessment of angiography, although in the later stages the changes are obvious, the picture being that of a “leafless tree” often with the loss of major branches.

In this issue of Circulation, St. Goar et al24 compare intracoronary ultrasound in heart transplant patients to conventional angiography. The left anterior descending coronary artery was studied in 80 patients to midlevel in vessels more than 2 mm in diameter. This test was found to be more sensitive than angiography. With the limitations imposed by the size of the coronary probe at the present time, isolated vessel disease of small vessels will be missed with this technique, and this is often the cause of sudden death, presumably through arrhythmias when the blood supply to a critical area of myocardial conduction tissue is jeopardized. The potential use of this technique in donors is limited because of the absence of supportive technology in many donor hospitals. Earlier diagnosis of graft atherosclerosis may not be beneficial if specific treatment is not available.

However, despite these obvious disadvantages, any new information on this matter will be helpful. Earlier recognition conceivably will give additional insight into etiological factors. It may be helpful to monitor progress of the disease to determine timing of retransplantation. Perhaps dependable recognition of those susceptible to graft atherosclerosis might encourage the early conversion to immunosuppressive regimens avoiding the use of cyclosporine and the strict avoidance of other possible contributing factors.

The lesions in transplant coronary atherosclerosis differ from that of naturally occurring coronary artery disease in that they affect the whole length of the vessel and its branches, including small penetrating intramyocardial tributaries.25 The disease is a panvasculitis affecting venules and even the endocardium. Calcification and atherosclerotic plaques are rare. Although the smaller vessels are not invariably involved, a correlation of the clinical course with autopsy studies showed that patients with diffuse narrowing involving both large and small vessels were at greater risk for myocardial infarction, death, or retransplantation than if either of the two lesions occurred separately.26 Small-vessel disease can occur without large vessel involvement and may be a significant cause of mortality after transplantation.27

Attempted prevention of the onset of graft atherosclerosis has been unsuccessful. Because platelets are integrally involved with endothelial injury in both the acute and chronic forms of antibody damage to the vessel wall,10,28 it seemed reasonable to attempt to treat grafts with platelet-active agents, although this had not been effective in experimental grafting.29 Initial reports of the efficacy of dipyridamole and warfarin in a very small group of patients6 were later found to be premature. Nonetheless, most centers still treat all transplant recipients with some type of platelet-active agents, although the use of dipyridamole has been largely abandoned.

Angioplasty has been attempted, although the lesions are generally diffuse and always progressive. It is now recognized that angioplasty is palliative and only reasonably used for the occasional localized lesions30 as a temporizing measure. The only definitive therapy is retransplantation. However, the results of retransplantation for graft failure are not as good as for the primary procedure,7 and it might be questioned whether this is the best use of scarce donor organs. Because only 2,000 donor hearts are available annually in the United States and there is an increasing number of cardiac transplant survivors, retransplantation would ultimately absorb a significant percentage of donor hearts.

The outlook on the development of graft atherosclerosis is not altogether bleak. This complication is not invariably, and some patients are now alive 20 years after surgery. There seems little doubt that with the great experience presently being accumulated in heart transplantation, increased familiarity with this frustrating complication of transplantation will ultimately lead to its effective prevention or treatment.

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S W Jamieson

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