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Low Clinical Utility of Routine Angiographic Surveillance in the Detection and Management of Cardiac Allograft Vasculopathy in Transplant Recipients

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Summary

Background: Cardiac allograft vasculopathy (CAV), a form of accelerated atherosclerosis, is the major cause of late death in heart transplant recipients. Routine annual coronary angiography has been used as the standard surveillance technique for CAV in most transplant centers.

Hypothesis: The aim of this study was to investigate the clinical utility of routine angiographic surveillance in the detection and management of CAV in transplant recipients.

Methods: We reviewed the case notes and angiograms of 230 patients who underwent cardiac transplantation in our unit between January 1986 and January 1996 and survived beyond the first year post transplantation.

Results: Significant complications secondary to angiography arose in 19 patients (8.2%). Cardiac allograft vasculopathy was present on none of angiograms performed 3 weeks post transplantation, but was identified in 9 patients (4%) at the first annual angiogram and an additional 25 patients by the fifth annual angiogram. A target lesion suitable for angioplasty was only identified in two patients, and only limited procedural success was achieved in both cases. Twenty-five patients (11%) died during the study period, and the most common cause of late death was graft failure which occurred in 10 patients. All patients who died from graft failure had significant CAV at autopsy, but the most recent coronary angiogram had been normal in eight of these patients.

Conclusions: These data clearly illustrate the limited clinical utility of routine angiographic surveillance for CAV in heart transplant recipients and prompted us to abandon this method of surveillance in our unit.

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Introduction

Cardiac allograft vasculopathy (CAV), a form of accelerated atherosclerosis, is the major cause of late death in heart transplant recipients.[1, 2] It differs from traditional atherosclerosis in that it is a concentric and diffuse intimal hyperplastic process in which the internal elastic lamina remains intact and calcification is rare. Although the exact mechanisms underlying CAV are not fully understood, it is believed to be a response to repetitive endothelial injury, and both immunological and infective processes have been implicated.[1–3] Routine annual coronary angiography has been used as a surveillance technique for the early detection of CAV in most transplant centers. However, histopathologic studies have demonstrated that coronary angiography is a relatively insensitive technique for detecting CAV[4] and this finding has been confirmed by more recent investigations employing intracoronary ultrasound imaging.[5] In this paper, we present the results of a survey performed at our institution to assess the clinical utility of routine annual coronary angiography in a large cardiac transplant population over a 10-year period.

Methods

Patient Population

In all, 280 patients underwent cardiac transplantation in our institution between January 1986 and January 1996. The indications for transplantation included ischemic left ventricular disease (n = 176), dilated cardiomyopathy (n = 94), and congenital heart disease (n = 10). A total of 230 patients survived at least 1 year following transplantation. Patients routinely underwent coronary angiography 3 weeks after transplantation and on an annual basis thereafter.

Post Transplantation Management

After transplantation, patients were routinely immunosuppressed with cyclosporin A (Cy A, aiming to achieve whole

blood trough levels of 500 ng/ml in the first month, 150–250 ng/ml in the first year, and 100–150 ng/ml thereafter) and azathioprine 2 mg/kg/day. Steroids were only prescribed for treatment of allograft rejection or in patients who were unable to tolerate Cy A because of renal dysfunction. Endomyocardial biopsies were performed weekly for the first 6 postoperative weeks, every 2 weeks for the next 6 weeks, and every 6 weeks for the first postoperative year. Additional biopsies were performed if rejection was suspected and 1 week following the treatment of episodes of rejection. The diagnosis of rejection was made according to standard histopathologic criteria.[6]

The cytomegalovirus (CMV) IgG antibody status of donors and recipients were checked, and CMV-negative recipients of donor hearts from CMV-positive donors received intravenous hyperimmunoglobulin. Symptomatic CMV infection was treated with ganciclovir.

Angiographic Surveillance

Coronary angiography was performed 3 weeks following transplantation and then yearly; in excess of 1,000 angiograms were performed. The case records and angiograms were retrospectively analyzed, the latter by two experienced cardiologists. Angiographic CAV was judged to be present when a >50% stenosis was present in any segment of the coronary tree using orthogonal views. Selective coronary angiography was performed via the femoral approach using 6 or 7 French catheters. A standard series of orthogonal views (left coronary artery 5 views, right coronary artery 3 views) with additional views as required according to individual variations in coronary anatomy. Each angiogram was analyzed by two experienced cardiologists blinded to the clinical history. Final interpretation was based on consensus, and angiographic CAV was defined by the presence of one or more lesions of >50% lumen diameter stenosis in any segment of the coronary tree. Direct quantitative angiographic measurements were not performed.

Intracoronary Ultrasound

Five patients with normal angiograms underwent intracoronary ultrasound (ICUS) imaging of one or more coronary arteries as part of a separate research protocol. Imaging was performed with a 20 MHz phased array system (Endosonics, Inc., Rancho Cordova, Calif., USA) employing a slow manual pullback technique. Intimal thickening was scored according to the Stanford system[7] at the most diseased segment.

Results

During the study period, 230 patients survived for at least 1 year following transplantation. A total of 220 patients (96%) underwent angiography 1 year post transplantation and 165 patients (72%) had angiography 5 years post transplantation. Complications of coronary angiography occurred in 19 patients (8.2%) and consisted of major hematoma formation in 14 patients, pseudoaneurysm of the femoral artery in 4 patients (treated by ultrasound-guided compression in all cases), and serious anaphylaxis due to contrast in 1 patient. All patients who suffered groin complications had undergone at least three coronary angiograms. No patients died as a consequence of complications due to angiography.

Incidence of Angiographic Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy was present on none of the angiograms performed 3 weeks post transplantation but was identified in nine patients (4%) at the first annual angiogram (Fig. 1). By the fifth year post transplantation, CAV was detected angiographically in an additional 25 patients who had normal 1-year angiograms. Only two patients had disease deemed suitable for percutaneous intervention. One patient had a discrete, proximal stenosis in the left anterior descending (LAD) artery which was treated by percutaneous balloon angioplasty and deployment of a 15 mm Palmaz-Schatz intracoronary stent. The final result was satisfactory, but subsequent coronary angiograms demonstrated that, although the stented segment remained widely patent, significant CAV developed at other sites. A second patient with more diffuse LAD disease was also treated by percutaneous balloon angioplasty. An unsatisfactory angiographic result was obtained, but the disease was considered too extensive and the artery too small for stent implantation. Repeat angiography 1 year post intervention demonstrated diffuse CAV involving all three epicardial vessels and significant left ventricular dysfunction. None of the patients underwent coronary artery bypass surgery or retransplantation for CAV in our series. No significant difference in the incidence of angiographic abnormalities was detected between patients with ischemic and nonischemic cardiomyopathy as the indication for transplantation.

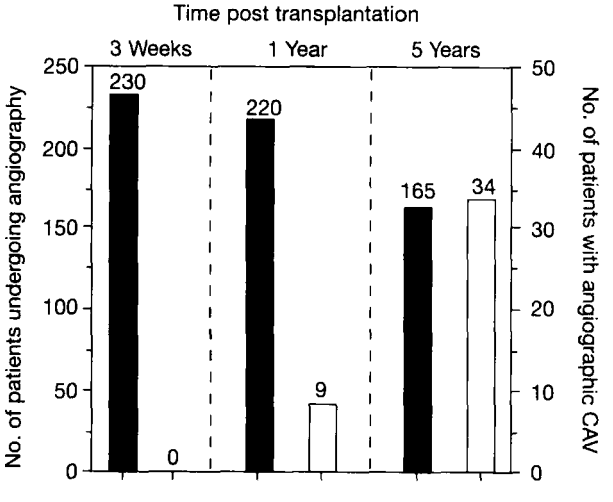

FIG. 1 Bar chart summarizing the number of patients undergoing angiography (black bars) and the cumulative incidence of angiographic cardiac allograft vasculopathy (CAV) (white bars) at 3 weeks, 1 year, and 5 years post transplantation.

Causes of Death

During the 10-year study period, 25 patients (11%) who survived to 1 year post transplant have died. The causes of late death included graft failure (n = 10), acute rejection (n = 6), renal failure (n = 4), pulmonary embolism (n = 1), septicemia (n = 1), stroke (n = 1), ruptured abdominal aortic aneurysm (n = 1), and pneumonia (n = 1). The most recent coronary angiogram had been normal in 8 of the 10 patients who died of graft failure, although all of these patients had significant CAV at autopsy as defined by the presence of diffuse fibrous intimal thickening, focal atherosclerotic plaques, or a mixture of both according to previously published criteria.[8] All the other patients had also undergone coronary arteriograms in the year prior to their death and this had been normal in every case. No relationship was detected between the incidence of angiographic CAV and either episodes of acute rejection or CMV infection.

Intracoronary Ultrasound

A total of five patients with normal coronary angiograms underwent ICUS examination as a part of a separate research protocol (informed consent was obtained and the research protocol was approved by the hospital ethics committee). Significant intimal thickening was present in all patients examined. Two patients had moderate (grade III) intimal thickening and three had severe (grade IV) intimal thickening at the most diseased segment. An example of a patient who had significant intimal thickening despite having a normal coronary angiogram is shown in Figure 2. No major complications occurred as a result of the use of ICUS. Coronary vasospasm occurred during examination of the LAD coronary artery of one patient; this was treated with intracoronary nitrates with no adverse sequelae.

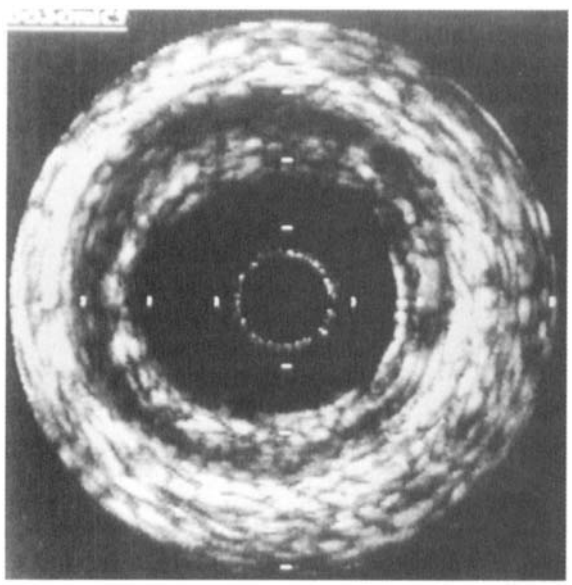

FIG. 2 Intracoronary ultrasound image from the left anterior descending artery of a transplant recipient in our series. The severity of disease in this patient was graded as class IV (>0.5mm, >180°) according to the Stanford classification system.[6]

Discussion

Incidence of Cardiac Allograft Vasculopathy

In this large series including over 1,000 angiograms over a 10-year period, CAV was detected by routine angiography in 4% of patients at 1 year post transplantation and in 15% of patients at 5 years post transplantation. Other authors[9–11] have documented a higher incidence of CAV at around 10% at 1 year and 40% by 3 years post transplantation. This discrepancy may be explained by differences in the angiographic criteria applied for the diagnosis of CAV. In particular, minor lumenal irregularities and distal tapering on angiography were not recorded as CAV in our series as such features are prone to much greater interobserver variability than clearcut angiographic stenoses. The incidence of CAV recorded in our study also does not include the presence of histopathologic changes at autopsy, as is the case in many other series.

After transplantation, the patients in our series were routinely immunosuppressed with cyclosporin A (aiming to achieve whole blood trough levels of 500 ng/ml in the first month, 150–250 ng/ml in the first year, and 100–150 ng/ml thereafter) and azathioprine 2 mg/kg/day. Steroids were only prescribed for treatment of allograft rejection or in patients who were unable to tolerate Cy A because of renal dysfunction. Consequently, the incidence of steroid usage within our patient group was relatively low compared with other series in which patients have routinely received a standard triple therapy regimen including cyclosporin, azathioprine, and prednisolone. This may also have contributed to the relatively low incidence of CAV in our series, since steroid usage has been identified as a potential risk factor for the development of CAV.[12]

Relative Insensitivity of Angiography for Detecting Cardiac Allograft Vasculopathy

The ICUS and autopsy findings in our series highlight the relative insensitivity of angiography for detecting CAV which appears to be due to the diffuse concentric and longitudinal distribution of intimal thickening and the presence of adaptive remodeling which minimizes the effect of intimal thickening on angiographic lumenal geometry.[13] Although ICUS screening in transplant recipients provides superior sensitivity for detecting CAV[7] and appears to be safe,[14] this method is limited to the major epicardial vessels and is more expensive and time consuming than simple angiography. Furthermore, skilled operators are required for both the manipulation of the ICUS catheter and interpretation of the images. Other noninvasive methods including exercise electrocardiography and radionuclide scintigraphy have also proved unsatisfactory[15] although some authors have suggested that dobutamine stress echocardiography may provide a reasonable alternative.[16]

Low Clinical Utility of Angiographic Surveillance

Successful therapeutic approaches to the treatment of CAV remain elusive. Although there is some evidence that revascularization may be an effective palliative therapy in some cases of CAV,[17] the results of conventional revascularization techniques and even the radical approach of retransplantation have, in general, been disappointing.[1] In this series, a target lesion suitable for angioplasty was only identified in two patients and only limited success was achieved in both cases. None of the patients was referred for coronary bypass surgery. This is not surprising since CAV is generally a diffuse process and, therefore, does not lend itself readily to treatment by conventional revascularization techniques. In this respect, transmyocardial laser revascularization has been proposed as an alternative method for improving myocardial perfusion in transplant patients with CAV which is not amenable to other modes of therapy.[18]

Conclusion

The data presented in our study clearly demonstrate the limited clinical utility of routine angiographic surveillance for CAV in heart transplant recipients. Furthermore, significant complications secondary to angiography arose in 8.2% of patients, with a particularly high incidence of peripheral vascular complications arising after multiple femoral artery punctures. As a result of these findings, routine annual angiography was abandoned at our institution and angiography now is only performed in transplant recipients for specific clinical indications, for example, poor graft function despite a normal endomyocardial biopsy. Improvements in the methods available for the detection of CAV are crucial to allow for further advances in our understanding of the underlying pathophysiology and the development of more effective treatment strategies.

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