Coronary Angioplasty in Cardiac Transplant Patients
Results of a Multicenter Study

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Background. Accelerated allograft atherosclerosis is the main cause of death of cardiac transplant recipients after the first year after transplantation. Because no medical therapy is known to prevent or retard graft atherosclerosis and retransplantation is associated with a shortened allograft survival, alternative, palliative therapy with percutaneous transluminal coronary angioplasty (PTCA) has been attempted. Because no single medical center has performed angioplasty in a large number of cardiac transplant recipients, representatives of 11 medical centers retrospectively analyzed their complete experience of coronary angioplasty in cardiac transplant patients to determine the safety, efficacy, limitations, and long-term outcome of angioplasty in allograft coronary vascular disease.

Methods and Results. Thirty-five patients underwent 51 angioplasty procedures for 95 lesions 46±5 months (mean±SEM) after transplantation. The primary indications for angioplasty included angiographic coronary disease in 22 cases (43%) and noninvasive evidence of ischemia in 18 procedures (35%). Angiographic success, defined as ≤50% post-PTCA stenosis, occurred in 88 of 95 lesions (93%). Mean pre-PTCA stenosis was 85±1.1%; mean post-PTCA stenosis was 29±2.1% (p < 0.0001). Periprocedural complications included myocardial infarction and late in-hospital death in one patient and three groin hematomas. Twenty-three of the 35 patients (66%) had no major adverse outcome such as death, retransplantation, or myocardial infarction at 13±3 months after angioplasty. Four patients died less than 6 months after angioplasty, and four died more than 6 months after angioplasty (range, 6–23 months). Two patients had retransplantation 2 months after PTCA, and one patient had retransplantation 18 months after angioplasty.

Conclusions. Coronary angioplasty may be applied in selected cardiac transplant recipients with comparable success and complication rates to routine angioplasty. Whether angioplasty prolongs allograft survival remains to be determined by a prospective, controlled trial. (Circulation 1992;86:458–462)

Key Words • heart transplantation • percutaneous transluminal coronary angioplasty • coronary arteriosclerosis

Coronary vascular disease is the leading cause of death after the first year after cardiac transplantation,1,2 whereas acute rejection and infection are the overall leading causes of death after transplantation.3 The incidence of allograft coronary artery disease as determined by angiographic and autopsy studies is between 1% and 18% at 1 year and 40% and 50% at 5 years.4–6 The pathogenesis of accelerated atherosclerosis after cardiac transplantation is unresolved. Important clinical manifestations of coronary artery disease after cardiac transplant include symptoms of congestive heart failure, ventricular arrhythmias, sudden death, and silent myocardial infarction7; typical angina pectoris7–9 may infrequently occur. Analysis of coronary arteriograms of patients with cardiac allografts demonstrates a mixture of diffuse arterial narrowing of mid and distal vessels with distal vessel obliteration in addition to proximal discrete stenoses similar to typical atheromatous plaques.10 There is no known effective medical therapy for the prevention or retardation of transplant atherosclerosis. Retransplantation has been successfully used, although survival after retransplantation is shorter than after first transplants, and the incidence of recurrent atherosclerosis is high.11 Recently, percutaneous transluminal coronary angioplasty (PTCA) has been attempted as palliative therapy in a few cardiac transplant patients.12–15 There are no data on the long-term outcome of angioplasty in cardiac transplant recipients.

Because no single medical center has performed angioplasty in a large cohort of post–cardiac transplant
patients, representatives from several transplant centers agreed that a collaborative effort should be made to describe their complete experience with angioplasty in cardiac transplant patients to determine the safety, efficacy, and limitations of angioplasty as well as the long-term outcome after angioplasty. We herein present the results and analysis of the collective experience.

Methods

Patient Population

Representatives of 11 medical centers retrospectively reviewed the medical records and cineangiograms of all cardiac transplant recipients who had subsequent coronary angioplasty and completed a data form collaboratively determined before the study. The clinical profile, primary indication for angioplasty, angiographic features, procedural results, and late outcome were documented by the investigators.

A primary angioplasty procedure that was performed in two stages was regarded in this analysis as one revascularization procedure. A subsequent angioplasty was considered as a separate procedure. Patients who underwent repeat transplantation after angioplasty were assessed only by mortality outcome after retransplantation.

Statistical Methods and Measurements

Mean values and standard errors of the means were calculated and expressed as mean±SEM. The Student’s t test was performed to determine significant differences between mean values.

Results

Clinical Characteristics

Of 2,678 cardiac transplants performed from January 1968 to May 1990 at the 11 contributing centers, 35 patients underwent PTCA. Table 1 illustrates the patients’ clinical characteristics. Potential risk factors for transplant atherosclerosis were analyzed and included a history of hypertension in 29 of 34 (85%), a history of treated acute rejections in 28 of 33 (84%), chronic prednisone immunosuppression in 25 of 34 (73%), positive cytomegalovirus serology in 17 of 26 (65%), cigarette smoking in 12 of 30 (40%), serum cholesterol >300 mg/dl in four of 33 (12%), and positive posttransplant allogeneic antibodies of no identifiable specificity in two of 27 patients (7%). Two cardiac donors who were older than 40 years of age had pretransplant coronary arteriography. One donor had a 20–30%

narrowing of the mid left anterior descending artery that became 75% 4 years after transplantation. The other donor heart had a 50% narrowing of the first diagonal artery that did not progress after transplant.

There were 51 angioplasty procedures performed in the 35 patients. Four patients had multivessel angioplasty performed in two stages. Table 2 lists the primary indications for angioplasty. Table 3 categorizes the number of angioplasty procedures per patient as well as the type and number of vessels dilated per procedure.

Angiographic Characteristics

The locations of the 95 lesions treated with angioplasty are illustrated in Table 4. Eight total and four subtotal (99% stenosis) occlusions were attempted. Sixty-eight of 81 lesions (84%) were <10 mm in length, 11 of 81 (14%) were 10–20 mm, and two of 81 (3%) were >20 mm. Lesion length was unavailable or not applicable (such as total occlusion) in 14 lesions. In 25 of 51 procedures (49%), there was nondilated proximal coronary artery disease; in 35 of 51 procedures (69%), there was nondilated distal coronary artery disease.

Angiographic Results

Angiographic success, defined as luminal diameter stenosis ≤50%, was achieved in 88 of 95 lesions (93%). The mean pre-PTCA stenosis was 83±1.1%; the mean post-PTCA stenosis was 29±2.1% (p<0.0001). In the seven unsuccessful angioplasty attempts, the reasons for failure were inability to cross a total occlusion in four
Ten patients underwent 16 subsequent angioplasty procedures (Table 3). Seventeen of 30 lesions (57%) were restenoses; thirteen (43%) were previously nondilated sites. The angiographic success was 100% (30 of 30). Five of the patients who had repeat angioplasty were alive 32±5 months (range, 11–71 months) after their initial angioplasty. Of the five patients who died, two had retransplantation 2 months after the third and fourth angioplasty procedures, respectively. The three other patients died 8, 9, and 23 months after their second angioplasty procedure.

There was no difference in procedural success or late outcome (restenosis, death, retransplantation) based on the primary indication for angioplasty or the duration from transplantation to angioplasty. Restenosis tended to occur in allografts with a longer interval between transplant and PTCA. The mean duration between transplant and angioplasty of allografts with subsequent restenosis was 67 months compared with 50 months, the mean duration between transplant and PTCA of allografts without restenosis (p = 0.15).

**Discussion**

**Allograft Atherosclerosis**

Accelerated graft atherosclerosis is a major limitation to the long-term survival of cardiac transplant recipients. Allograft vasculopathy was the cause of death in 24% of 3-month survivors after transplantation.

The definition of coronary artery disease in transplant recipients is variable. Most observers underestimate the presence and severity of allograft coronary artery disease because of its diffuse, concentric nature and because of the inherent limitations of coronary arteriography providing only a "lumogram." Gao et al have detailed the angiographic findings of coronary vascular disease in heart transplant recipients that have been confirmed by autopsy and from explanted hearts. These studies indicate that allograft coronary artery disease is a mixture of typical atheromatous lesions and a diffuse progressive vasculopathy that predominantly affects mid and distal vessels, including small vessels such as penetrating intramyocardial branches and collateral vessels.

Therapies to prevent or retard allograft atherosclerosis in humans have been ineffective. Attempts at modification of risk factors that have been established for nontransplant coronary artery disease may be less rewarding in transplant recipients. An effort is made to control lipid profiles, optimize blood pressure, and discourage smoking. The role of immunosuppression and cellular rejection in relation to the development of this disease remains unclear. There is preliminary evidence that dehydroepiandrosterone, \( \alpha \)-polysaturated fatty acids, and angiopentin in animal models and calcium blockers in humans retard graft atherosclerosis. Definitive therapy with repeat cardiac transplantation has been used in patients with advanced transplant coronary artery disease. Gao et al found the second graft survival rate to be 55%, 25%, and 10% at 1, 2, and 5 years, respectively, after transplantation, which was significantly lower than after the first transplant. Given the limited number of donors, these data have dissuaded many centers from recommending retransplantation in view of the rapidly increasing number.

**Table 4: Lesion Location**

<table>
<thead>
<tr>
<th>Lesion Location</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal LAD</td>
<td>14</td>
</tr>
<tr>
<td>Mid LAD</td>
<td>19</td>
</tr>
<tr>
<td>Distal LAD</td>
<td>4</td>
</tr>
<tr>
<td>First diagonal</td>
<td>10</td>
</tr>
<tr>
<td>Second diagonal</td>
<td>2</td>
</tr>
<tr>
<td>Proximal Cx</td>
<td>5</td>
</tr>
<tr>
<td>Distal Cx</td>
<td>5</td>
</tr>
<tr>
<td>First obtuse marginal</td>
<td>12</td>
</tr>
<tr>
<td>Second obtuse marginal</td>
<td>5</td>
</tr>
<tr>
<td>Third obtuse marginal</td>
<td>1</td>
</tr>
<tr>
<td>Proximal RCA</td>
<td>5</td>
</tr>
<tr>
<td>Mid RCA</td>
<td>4</td>
</tr>
<tr>
<td>Distal RCA</td>
<td>3</td>
</tr>
<tr>
<td>Acute marginal</td>
<td>1</td>
</tr>
<tr>
<td>Posterior descending</td>
<td>3</td>
</tr>
<tr>
<td>First posterolateral</td>
<td>1</td>
</tr>
<tr>
<td>Second posterolateral</td>
<td>1</td>
</tr>
</tbody>
</table>

LAD, left anterior descending artery; Cx, circumflex artery; RCA, right coronary artery. See Reference 36, coronary artery surgery classification.

Cases, failure to traverse a lesion with a guide wire in two cases, and inability to dilate to ≤50% in one case. The angiographic success rate for total occlusions was 50% (four of eight); the angiographic success rate for subtotal (99% stenosis) occlusions was 100% (four of four). Lower success rates generally occurred in angioplasty of distal vessels or distal branches.

**Complications**

Procedural complications included a myocardial infarction and subsequent death 1 week after angioplasty in one patient because of left main coronary dissection by an Amplatz left coronary guiding catheter. There were three groin hematomas and one exacerbation of renal insufficiency.

**Late Outcome**

The late outcome of patients treated with angioplasty was available for all patients discharged from the hospital for a mean of 13±3 months after angioplasty (range, 1 week to 71 months). Twenty-three of 35 patients (66%) are alive and have not had retransplantation or myocardial infarction. Fifteen of 35 patients (43%) are free from late adverse events including repeat angioplasty, death, retransplantation, or myocardial infarction during 8±1 months of follow-up (range, 2 weeks to 48 months). Four patients died less than 6 months after angioplasty, and four patients died more than 6 months after angioplasty (range, 6–23 months). Three patients had retransplantation; two were performed 2 months after angioplasty, and one had retransplantation 18 months after angioplasty. These patients died 3 weeks, 4 months, and 10 months after repeat transplantation.

Angiographic follow-up was obtained in 30 of 51 procedures (60%) and 53 of 95 lesions (56%) at a mean of 8 months after angioplasty (range, 3 weeks to 19 months). Restenosis, defined as return of ≥50% stenosis, was present in 29 of 53 lesions (55%) 7 months (range, 1.5–19 months) after angioplasty.
of patients awaiting their first heart transplant who have a greater chance of survival.\textsuperscript{20}

\textbf{Percutaneous Transluminal Coronary Angioplasty}

The main objectives of coronary angioplasty after cardiac transplantation are to reduce coronary morbidity and mortality. The role of PTCA in the asymptomatic patient without objective evidence of ischemia is controversial because in many transplant recipients, symptoms and signs of ischemia may be subtle or absent. Noninvasive studies including standard exercise testing with thallium scintigraphy,\textsuperscript{29} rest and exercise gated wall motion studies, echocardiography, and Holter monitoring, either alone or in combination, are not adequately sensitive to detect obstructive coronary arteriopathy.\textsuperscript{30} Thus, PTCA may be considered on the basis of coronary angiographic findings.

The current study demonstrates that angioplasty may be used in suitable patients with initial success and complication rates comparable to routine angioplasty.\textsuperscript{31} Furthermore, this study extends previous observations that angioplasty also can be successfully attempted in midvessel and selected, discrete, distal vessel stenoses as well as total or subtotal occlusions. These findings undoubtedly relate to the widening applications of angioplasty to distal vessel disease in general and to refinements in angioplasty technology (e.g., lower profile catheters).

The low incidence of procedural complications in this series may be attributed to careful patient selection because of concern regarding management of acute occlusion and limitation of revascularization in many cases to major ischemic zones supplied by discrete stenoses with a high probability of angioplasty success. The case of traumatic left main coronary artery dissection may have been due to a diffusely diseased and perhaps friable vessel. This underscores the necessity of operator care in catheter and guide wire manipulations. A drawback of angioplasty in post--cardiac transplant patients is that surgical support for emergent coronary artery bypass surgery in the event of a major complication is very judiciously considered. Coronary artery bypass surgery is rarely performed in these patients\textsuperscript{32} because of the diffuseness of allograft atherosclerotic disease. In the event of a life-threatening complication, hemodynamic support such as intra-aortic balloon pumping can be available while such a patient is listed for emergent retransplantation. Based on this limited experience with predominantly proximal vessel disease, angioplasty cannot be suggested as treatment for distal small vessel disease.

Although the precise rate of restenosis cannot be determined from our data because of incomplete angiographic follow-up, the incidence of restenosis is higher than after routine angioplasty.\textsuperscript{17,33,34} The explanation for the higher restenosis rate is unknown; underlying aggressive arteriopathy and the diffuseness of the disease process may be responsible. Manifestations of ischemia may be absent; therefore, angiographic follow-up is recommended in cardiac transplant recipients after angioplasty. Repeat angioplasty procedures may be required in some patients for restenoses or progressive disease in other areas. This may retard the need for retransplantation, which is vital when there are limited cardiac donors.

\textbf{Impact on Survival}

Based on actuarial survival analysis, Grattan et al\textsuperscript{35} documented the rate of death caused by graft atherosclerosis to be 0.4\% at 1 year and 9.8\% at 5 years after transplantation in patients treated with cyclosporine. It is difficult to compare the data on long-term outcome in the current study with the cohort of Grattan et al because the severity and extent of atherosclerotic disease of the patient populations may differ. A prospective, controlled study will be necessary to determine whether or not angioplasty prolongs cardiac allograft survival.

\textbf{Study Limitations}

The limitations of this study are that it is a retrospective study in which patient selection was variable, and angiographic interpretation was by individual center and not centrally reviewed. However, the study was inclusive of all cardiac transplant patients treated by angioplasty in each center. Despite these limitations, this is the largest published series of angioplasty applied in allograft atherosclerosis.

\textbf{Summary}

In summary, this collaborative experience indicates that PTCA can be safely and successfully performed as palliative therapy in suitable cardiac transplant recipients. Repeat angioplasty procedures may be required in some patients for restenoses or progressive accelerated atherosclerosis in other areas.

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\textbf{Appendix}

The following persons and institutions participated in this study.

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