Coronary Stenting in Cardiac Allograft Vasculopathy

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Objective. The purpose of this study was to evaluate acute angiographic success, in-hospital complications and long-term outcome after intracoronary stenting in patients with cardiac allograft vasculopathy.

Background. The application of conventional interventional modalities to treat discrete lesions in patients with cardiac allograft vasculopathy is associated with higher procedural morbidity, mortality and higher restenosis compared to atherosclerotic coronary artery disease. Elective coronary stenting has been shown to lower restenosis rates and improve long-term outcome in selected patients with native coronary artery disease; however, its safety and efficacy in reducing restenosis in patients with cardiac allograft vasculopathy is unknown.

Methods. Ten patients with 19 discrete lesions in a major coronary artery without diffuse distal disease underwent intracoronary stenting using Palmaz-Schatz stents. The average stent size was 3.4 mm, and the stent/artery ratio was 0.99 ± 0.07. Eight of ten (80%) patients received antiplatelet therapy (aspirin plus ticlopidine) only.

Results. Procedural success was 100% with no in-hospital stent thrombosis, Q-wave myocardial infarction or death. Minimal luminal diameter increased from 0.83 ± 0.38 mm to 3.23 ± 0.49 mm after stenting. Diameter stenosis decreased from 74.91 ± 11.52% to 5.90 ± 4.09% after stenting. Follow-up angiography was performed in 8 of 10 (80%) patients and 16 of 19 (84%) lesions. Target lesion revascularization was required in 2 of 10 (20%) patients and 3 of 16 (19%) lesions. Allograft survival was 7 of 10 (70%) at the end of 22 ± 11 months follow-up.

Conclusions. Intracoronary stenting can be performed safely with excellent angiographic success in selected patients with cardiac allograft vasculopathy. The restenosis rate appears to be low despite the aggressive nature of the disease. A multicenter study with a larger number of patients is required to assess its efficacy in reducing restenosis and improving allograft survival.

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Cardiac allograft vasculopathy (CAV) represents an accelerated form of obstructive coronary artery disease and remains an obstacle to the long-term survival of cardiac transplant recipients (1-5). Unlike atherosclerotic coronary artery disease, treatment options are limited due to the progressive and diffuse nature of CAV. Retransplantation was initially used in patients with severe CAV; however, with a 55% survival at 1 year and a 46% incidence of recurrent CAV in those who survived, it is no longer recommended in many centers (6). Pharmacologic interventions to prevent CAV progression have been unsuccessful, with the exception of diltiazem, a calcium channel blocker (7). Recently, two studies have shown that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (pravastatin and simvastatin) can reduce the incidence of CAV and graft rejection and can increase long-term survival in cardiac transplant recipients (8,9). Balloon angioplasty, directional atherectomy and coronary bypass grafting have been used as palliative measures to reduce CAV-related morbidity and mortality (10-12). However, all these techniques have higher procedural morbidity and mortality and higher restenosis compared to atherosclerotic coronary artery disease.

Elective coronary stenting has been shown to achieve excellent angiographic success, to lower the restenosis rate and to improve long-term outcome compared to balloon dilatation alone in selected patients with native coronary artery disease (13,14); however, its safety and efficacy in reducing cardiac morbidity and mortality in patients with CAV is unknown. The purpose of this study was to evaluate acute angiographic success, in-hospital complications and long-term efficacy of intracoronary stenting in patients with CAV.

Methods

Patient population. The study group consisted of 10 patients who underwent intracoronary stenting for CAV between March 1994 and April 1997. These patients were selected from 34 of 120 (28.3%) cardiac transplant recipients who were found to have lesions suitable for percutaneous revascularization. Patients with discrete lesions (>50% diameter stenosis, lesion length <12 mm, a vessel diameter ≥3.0 mm) in the
proximal or midvessel without diffuse distal disease were selected for intracoronary stenting. Clinical and demographic characteristics of the patients are shown in Table 1. All patients received immunosuppression with cyclosporine, azathioprine and prednisone. Eight of the 10 patients were also receiving HMG-CoA reductase inhibitor. Indications for coronary angioplasty were angiographic stenosis ($n=3$) with provokable ischemia in the vascular territory of the stenotic artery, angina pectoris ($n=5$) and following myocardial infarction in two patients with severe residual stenosis.

**Procedural details.** All patients underwent balloon angioplasty and stent implantation according to the standard clinical practice by the femoral approach. A bolus of 10,000 units of intravenous heparin was given at the beginning of the procedure and further supplemented to maintain an activated clotting time of 250 to 300 s. Selection of the balloon catheter was at the discretion of the operator. Stent size was selected based on the diameter of the proximal reference vessel. Primary stenting was performed in seven patients, and three patients had stenting for the suboptimal results following directional atherectomy ($n=2$) and balloon angioplasty ($n=1$). A total of 19 lesions were treated. Lesion locations are shown in Figure 1. Poststent balloon dilatation was performed at a mean of 14 ± 4 atm (range 8 to 20 atm). Poststent antithrombotic regimens at discharge included a combination of aspirin (325 mg/day), dipyridamole (75 mg three times/day) and coumadin for 2 months and then aspirin alone indefinitely in two patients. The remaining eight patients received a combination of aspirin (325 mg/day) and ticlopidine (500 mg/day) for 1 month, and then aspirin indefinitely. None of the patients received abciximab during the procedure. Twelve-lead electrocardiograms were recorded before, immediately after and 24 h after the procedure. Serum creatinine kinase (CK) and myocardial band isoenzyme levels were measured before the procedure and repeated at 8-h intervals for 24 h.

**Definitions.** A significant lesion was defined as >50% diameter stenosis in either the left anterior descending artery, left circumflex, right coronary artery or a major branch. Distal vessel disease was defined as the presence of diffuse concentric narrowing or diffusely diseased irregular and nontapered lesion of a tertiary vessel as defined by Gao et al. (15). Procedural success was defined as ≤20% residual diameter stenosis without in-hospital stent thrombosis, Q-wave myocardial infarction, emergency bypass surgery or death. Q-wave myocardial infarction was diagnosed by appearance of new pathologic Q waves in two contiguous electrocardiographic leads and a CK level greater than twice the upper limit of normal. Non-Q-wave myocardial infarction was defined as greater than or equal to a twofold increase in total CK level without pathologic Q waves. Vascular complications were defined as a hematoma requiring blood transfusion or pseudoaneurysm diagnosed clinically and/or by color Doppler ultrasound.

**Angiographic analysis.** An automated edge detection technique was used for quantitative angiographic analysis from a diastolic cine frame which included measurements of reference vessel diameter, minimal luminal diameter (MLD), lesion length and percent diameter stenosis. The acute gain was defined as the difference between the MLD after stenting and the MLD at baseline. The late loss was defined as the difference between the poststent MLD and the MLD at the follow-up angiography.

**Follow-up.** All patients were followed in the outpatient clinic. Follow-up angiography was performed at 6 to 12 months or earlier when indicated. The primary end point was angiographic evidence of restenosis (≥50% diameter stenosis) within the stent. Allograft survival was defined as the absence of retransplantation or death.

**Statistical analysis.** Continuous variables were expressed as mean ± SD. Discrete variables were expressed as percentages. The cumulative frequency curve for MLD was processed as mean ± SD. Discrete variables were expressed as percent-ages. The cumulative frequency curve for MLD was processed using JMP software version 3.2.2 (SAS Institute, Inc., Cary, North Carolina).

**Results**

**Procedural success and complications.** Twenty-one 15 mm Palmaz–Schatz (Johnson and Johnson Interventional Systems, Warren, New Jersey) stents were placed in 19 lesions. The average stent size was 3.4 mm, and the stent/artery ratio was 0.99 ± 0.07. Procedural success was achieved in all (100%) lesions (Fig. 2). One patient developed a non-Q-wave myocardial infarction following occlusion of a small side branch at the stent site. None of the patients had a Q-wave myocardial infarction, in-hospital stent thrombosis, emergency bypass surgery or a vascular complication.

**Quantitative angiography.** The reference vessel diameter was 3.41 ± 0.48 mm and mean lesion length was 6.94 ± 1.88 mm. Baseline MLD was 0.83 ± 0.38 mm, which increased

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**Table 1. Demographic and Clinical Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age*</td>
<td>57 ± 6 years</td>
</tr>
<tr>
<td>Time since transplantation*</td>
<td>5 ± 2 years</td>
</tr>
<tr>
<td>Male</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Hypercholesterolemia (&gt;200 mg/dl)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>LVEF (%)*</td>
<td>49 ± 11</td>
</tr>
</tbody>
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*Mean ± SD. LVEF = left ventricular ejection fraction.
to 3.23 ± 0.49 mm after stenting, thus giving rise to an acute gain of 2.39 ± 0.69 mm. Similarly, percent diameter stenosis was reduced from 74.91 ± 11.52% to 5.90 ± 4.09% after stenting.

**Angiographic follow-up.** Follow-up angiography was performed in 8 (80%) patients (symptomatic = 2, asymptomatic = 6) and in 16 of 19 lesions at 8.5 ± 3.7 months. The mean late loss (the decrease in absolute diameter from immediate post-stenting to follow-up angiography) was 1.06 ± 0.8 mm, resulting in an average late luminal diameter of 2.21 ± 0.67 mm. The corresponding mean diameter stenosis was 28.81 ± 19.28%. The cumulative frequency distribution curve of the MLD measured before and after stenting and at follow-up is shown in Figure 3. In-stent restenosis was noted in 2 of 10 (20%) patients and in 3 of 16 (19%) lesions. All three restenotic lesions were successfully dilated using balloon angioplasty.

**Long-term follow-up.** Clinical follow-up was available in 10 of 10 (100%) patients. Seven (70%) of the 10 patients were alive without bypass surgery/retransplantation at a mean duration of 22 ± 11 months (range 9 to 45) after stenting. One patient died at 9 months from intractable congestive heart failure and follow-up angiography was not available. Two patients underwent bypass surgery in combination with transmyocardial laser revascularization and retransplantation for progression of CAV 16 and 17 months after stenting, respectively. The stent site was patent in both of these patients.

**Discussion**

Cardiac allograft vasculopathy morphology and limitations of conventional angioplasty modalities. Cardiac allograft vasculopathy is a heterogeneous disease with varied morphologic expression ranging from concentric, diffusely obliterative lesions of distal vessels and branches to focal stenoses involving proximal vessels (16). Histopathologic studies have demonstrated that discrete stenoses are more likely to consist of lipid-rich atheromatous plaques, whereas diffuse disease typically is characterized by severe fibrous intimal thickening (17). The morphologic features of these lesions as assessed by coronary angioscopy and intravascular ultrasound also differ

![Figure 1. Lesion location of the stented arteries. LM = left main coronary artery (n = 1); LAD = left anterior descending artery (n = 8); diagonal artery (n = 3); LCx = left circumflex artery (n = 2); RCA = right coronary artery (n = 5).](image1)

![Figure 2. Upper panel demonstrates stenting of a mid left anterior descending artery (LAD) lesion in a patient who is 4 years posttransplant; (A) Baseline angiogram showing a severe stenosis (arrow) in the midLAD region; (B) Poststent angiographic frame showing no residual stenosis (arrow); (C) Angiographic follow-up (F/U) at 6 months shows a patent lumen (arrow) without any restenosis. Lower panel demonstrates stenting of a left main coronary lesion in a patient who presented with unstable angina 6 years after cardiac transplant; (A) Baseline angiogram showing a severe stenosis in the body of the left main coronary artery; (B) After placement of a 4-mm stent; (C and D) Follow-up angiography at 6 months and 2 years, respectively, showing minimal luminal narrowing within the stent.](image2)
significantly (18). The presence of isolated discrete stenoses (>50%) in the proximal or midvessel have been shown to adversely affect long-term survival (4). Therefore, traditional interventional modalities, such as balloon angioplasty and directional atherectomy, have been used in cardiac transplant patients with discrete lesions (10–12). In contrast to native coronary arteries, procedural morbidity, mortality and restenosis rates are significantly higher in patients with CAV, thereby limiting the long-term benefits in terms of repeat revascularization and graft survival (10–12).

Rationale for stenting: a comparison with previous studies. Data regarding the role of intracoronary stenting in CAV is limited to a single case report and, therefore, has not been systematically explored (19). This study is the first series to demonstrate that intracoronary stenting is a safe and feasible alternative to balloon angioplasty and directional atherectomy in selected patients with CAV. Procedural success was 100% with no periprocedural death, stent thrombosis, Q-wave myocardial infarction or emergency bypass surgery. The residual diameter stenosis was 6 ± 4%, and only 19% of the lesions developed restenosis. In contrast, procedural success with balloon angioplasty has varied from 85% to 94%, with a 3% incidence of periprocedural death due to myocardial infarction (10–12). The average residual diameter stenosis following balloon angioplasty is 30% (range 8% to 46%) (10–12). In the multicenter study report by Halle et al. (12), 55% of the lesions (65% angiographic follow-up) developed restenosis. Intracoronary stenting of discrete lesions in CAV appears to be associated with excellent procedural success without any major complications, a larger acute gain in luminal diameter and a lower restenosis rate than balloon angioplasty. By providing a metallic “scaffold” to the coronary lumen, intracoronary stenting minimizes plaque disruption which can lead to abrupt closure, myocardial infarction and death, as noted in CAV patients undergoing balloon angioplasty and directional atherectomy (10–12). The acute gain (2.39 ± 0.69 mm), late loss (1.06 ± 0.8 mm) and restenosis (20%) following stenting in our series are comparable to those reported for native coronary artery stenting (13–14). Thus, it appears that the reduction in restenosis in our group of patients was due to a larger acute gain following stenting. During the clinical follow-up, 70% of the patients were free from retransplantation or death at a mean duration of 22 months following stent implantation, a promising result when compared to those reported in prior studies of balloon angioplasty (10–12). By preserving luminal patency and reducing the rate of repeat revascularization, stenting may improve allograft survival in patients with discrete lesions.

Influence of HMG-CoA reductase inhibitors. In the present study, 8 of 10 patients were on HMG-CoA reductase inhibitors, which may have contributed to the overall improved long-term outcome. Two prospective, randomized studies have shown that HMG-CoA reductase inhibitors can reduce the incidence of CAV and prolong graft survival in cardiac transplant recipients independent of plasma cholesterol levels (8,9). Both studies demonstrated a significant reduction in intimal proliferation by intravascular ultrasound studies in patients receiving HMG-CoA reductase inhibitors. The various mechanisms by which HMG-CoA reductase inhibitors prevent CAV progression and prolong graft survival include a decrease in natural-killer-cell cytotoxicity (8,20) and inhibition of farnesylation of ras-proteins which are essential for the induction of cell growth by fibroblasts and smooth muscle cells in the allograft arteries (21,22). It is likely that these mechanisms may have retarded intimal proliferation within the stented sites and may be partly responsible for the lower late loss observed in the present series despite the aggressive nature of CAV.
Study limitations. The present study has several limitations. First, it is a single center, nonrandomized, uncontrolled observational study. Second, the number of patients is small; however, the population of cardiac transplant recipients with discrete lesions without distal disease is also limited. Third, angiographic follow-up was available in only 84% of the lesions. Lastly, the average vessel size was >3.0 mm, which may have contributed to the reduced restenosis rate and therefore these results may not be applicable to patients with smaller vessel size. Despite these limitations, this is the first study to show that intracoronary stenting can be used safely and effectively in treating discrete stenoses in CAV.

Conclusions. This preliminary study shows that intracoronary stenting in selected patients with cardiac allograft vasculopathy is safe, technically feasible and provides excellent immediate angiographic results. The acute gain and late loss are similar to those reported for native coronary artery stenting. The restenosis rate appears to be low despite the aggressive nature of the disease. Concomitant treatment with HMG-CoA reductase inhibitors may be beneficial in terms of reducing in-stent intimal proliferation and may act synergistically in prolonging graft survival. A multicenter study with a larger number of patients is needed to validate the long-term efficacy of intracoronary stenting in reducing restenosis and in improving graft survival.

References
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