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Usefulness and safety of percutaneous coronary interventions for cardiac transplant vasculopathy.

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Journal

The American journal of cardiology, 97(8)

ISSN

0002-9149

Authors

Tanaka, Koji
Li, Haiyan
Curran, Peter J
et al.

Publication Date

2006-04-01

DOI

10.1016/j.amjcard.2005.11.038

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Peer reviewed

Usefulness and Safety of Percutaneous Coronary Interventions for Cardiac Transplant Vasculopathy

Koji Tanaka, MD, Haiyan Li, MD, Peter J. Curran, MD, Yuzuru Takano, MD, PhD, Boris Arbit, BS, Jesse W. Currier, MD, Lawrence A. Yeatman, MD, Jon A. Kobashigawa, MD, and Jonathan M. Tobis, MD*

Late morbidity and death as a result of progressive coronary vascular obliteration remains a major unsolved problem after orthotopic heart transplantation. Various percutaneous catheter intervention (PCI) methods have been used to treat transplant coronary artery disease (CAD), but few reports have assessed the longitudinal results of these procedures. Of 1,440 cardiac transplant patients at University of California, Los Angeles, Medical Center, treated between 1984 and 2004, 65 patients who had undergone orthotopic heart transplantation underwent PCI on a total of 156 coronary artery lesions because of transplant CAD between July 1993 and August 2004. The procedural success rate was 93%. Angiographic follow-up was available for 42 patients and 101 lesions 9.5 $\pm$ 5.8 months after PCI. The global restenosis rate was 36%. Multivariate analysis was used to assess 49 clinical, angiographic, and immunologic variables per lesion. The use of a cutting balloon increased the risk of restenosis (odds ratio 11.5, $p < 0.01$) and the use of stents decreased the risk of restenosis (odds ratio 0.34, $p < 0.05$) compared with other PCI methods. The restenosis rate with drug-eluting stents was 19%, lower than that with bare metal stents (31%). Of the 65 patients, 20 (31%) died within 1.9 $\pm$ 1.8 years after PCI. The actuarial survival rate was 56% at 5 years after the first PCI. In conclusion, although the restenosis rate after PCI was higher than that in nontransplant patients with CAD, the immediate and long-term results were acceptable in this high-risk population. Despite the intense inflammation associated with transplant CAD, drug-eluting stents appeared to reduce the occurrence of restenosis. Compared with historical controls, PCI may also improve the actuarial survival rate of patients undergoing orthotopic heart transplantation. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;97:1192–1197)

Transplant coronary artery disease (TCAD) remains the limiting factor in the survival of orthotopic heart transplantation (OHT) recipients.^{1–3} The process is characterized by diffuse and multifocal heterogeneous myointimal hyperplasia.⁴ The only effective treatment for such diffuse disease is retransplantation. However, retransplantation is limited by the scarcity of donor organs, and the survival rate after retransplantation is worse than that after initial transplantation.^{5,6} Coronary artery bypass grafting is seldom possible because of the diffuse nature of the disease, and the long-term results have been disappointing.⁷ Pharmacologic interventions to prevent TCAD development have been unsuccessful, but some agents, such as pravastatin^{8–10} or simvastatin,¹¹ may prolong the event-free interval. No therapy has been shown to reverse TCAD after it develops.

Although focal stenosis due to TCAD can be treated with percutaneous coronary intervention (PCI), the restenosis rate is higher than when treating native CAD.^{12–17} Advances in immunosuppressive therapy, including rapamycin, and PCI technology with drug-eluting stents (DESs) may be expected to reduce the restenosis rate in TCAD.^{18,19} The objective of this study was to analyze the outcome of OHT patients in whom a PCI procedure had been performed at our hospital for treatment of TCAD.

Methods

Study population: The study group consisted of 65 patients who underwent PCI for treatment of TCAD between July 1993 and August 2004 at the University of California, Los Angeles, Medical Center (Los Angeles, California). A total of 156 allograft coronary artery lesions were treated during 93 PCI procedures. The clinical and demographic characteristics of the patients and donor information are listed in Table 1. Allograft coronary angioplasty was performed according to standard clinical practice by the femoral approach with a 6Fr or 8Fr catheter. A bolus of 100

University of California, Los Angeles, Center for Health Sciences, Los Angeles, California. Manuscript received July 5, 2005; revised manuscript received and accepted November 8, 2005.

*Corresponding author: Tel: 310-794-4797; fax: 310-267-0384.

E-mail address: jtobis@mednet.ucla.edu (J.M. Tobis).

Table 1
Patient characteristics and donor information (n = 65)

Variable	
Recipient	
Age at OHT (yrs)	48 ± 16
Age at PCI (yrs)	55 ± 17
Men	46/65 (71%)
Cytomegalovirus infection before OHT	34/44 (77%)
Diabetes mellitus	12/56 (21%)
Total cholesterol (mg/dl)	186 ± 43
Triglycerides (mg/dl)	187 ± 137
High-density lipoprotein cholesterol (mg/dl)	47 ± 15
Low-density lipoprotein cholesterol (mg/dl)	102 ± 37
Smoker	22/55 (40%)
Original heart disease	
Idiopathic cardiomyopathy	18/56 (32%)
Ischemic cardiomyopathy	27/56 (48%)
Other	11/56 (20%)
Donor	
Age (yrs)	31 ± 13
Men	44/56 (79%)
Cytomegalovirus infection	27/41 (66%)
Hypertension	6/23 (26%)
Diabetes mellitus	0/24 (0%)
Smoker	9/22 (41%)
ABO nonidentical	4/54 (7%)
Cytomegalovirus mismatch	18/40 (45%)
Gender mismatch	18/55 (33%)
Ischemic time (min)	192 ± 61
Interval between OHT and PCI (yrs)	7.2 ± 4.0

Data are expressed as numbers of lesions (percentages) or mean ± SD.

U/kg of intravenous heparin was given at the beginning of the procedure and further supplemented to maintain an activated clotting time of 250 to 300 seconds. Intracoronary injection of nitroglycerin (100 to 200 μ g) was given to avoid vascular spasm during angioplasty. Selection of the angioplasty method was determined by each operator and varied during the study period depending on the availability of new technologies. Procedural success was defined as postprocedural lumen diameter stenosis of <50% without creatine phosphokinase elevation, Q-wave myocardial infarction, emergency bypass surgery, or death related to the present PCI.

Follow-up angiography was evaluated at the next annual catheterization or earlier when indicated. Angiographic restenosis at follow-up was defined as the return of >50% diameter stenosis. Allograft survival was defined as the absence of repeat transplantation or death. Quantitative coronary angiography was performed.²⁰ Right ventricular myocardial biopsies to evaluate rejection were performed on all patients a minimum of every year. The myocardial biopsy specimen was classified by standard methods.²¹

Results

Procedural success and complications: Of the 156 target lesions from 65 patients, procedural success was achieved in 145 (93%). Of the 11 unsuccessfully treated

Figure 1. (A) Baseline angiogram showing severe stenosis (arrow) in proximal right coronary artery. Lumen diameter stenosis was 71%. (B) After 3.5 × 10-mm cutting balloon angioplasty and a NIR, 4.0 × 15-mm stent (Boston Scientific, Natick, Massachusetts) was deployed, final lumen diameter stenosis was 3.6%. (C) Complete occlusion at stent site in proximal right coronary artery 6 months later. In addition, rest of artery was diffusely diseased.

Figure 2. (A) Baseline angiogram showing severe stenosis at proximal site (arrows) of left anterior descending artery. Lumen diameter stenosis was 65%. (B) After 2 stents (3.0-mm Palmaz-Schatz, Johnson & Johnson, New Brunswick, New Jersey) were deployed, final lumen diameter stenosis was -1.3%. (C) No restenosis 3 years later.

lesions, a guidewire or balloon catheter could not pass through 10 lesions (8 were chronic total occlusions and 2 were tortuous arteries). One patient had a myocardial infarction during PCI that required intubation and intra-aortic balloon pump assistance, but the patient survived.

PCI methods: Of the 145 successfully treated lesions, 29 were treated with conventional balloon angioplasty alone. Coronary stents have been used routinely for OHT patients since 1995. A total of 128 coronary stents were placed in 106 lesions (Figures 1 and 2). These stents included 31 DESs (27 sirolimus-eluting stents, Cypher, Cordis, Miami Lakes, Florida, and 4 paclitaxel-eluting stents, Taxus, Boston Scientific, Natick, Massachusetts). The mean stent diameter was 3.0 ± 0.5 mm, and the mean stent length was 17.4 ± 7.4 mm. Rotational atherectomy was performed on 8 lesions, but no directional atherectomy cases occurred. Cutting balloon (Boston Scientific) angioplasty was used on 18 lesions; 10 of the cutting balloon cases also received a stent.

The coronary lesion characteristics and angiographic results are listed in Table 2.

Follow-up angiography: Follow-up coronary angiography was obtained in all eligible 101 lesions from 42 patients at a mean duration of 9.5 ± 5.8 months. Of the remaining 44 lesions, 26 did not have follow-up angiography because a repeat OHT was performed (n = 11) or the patient had died (n = 15) before follow-up, and 18 lesions were not yet eligible for 1-year follow-up angiography. The mean percent diameter stenosis at follow-up was 39.8 ± 35.6%, and the minimal lumen diameter (MLD) was 1.6 ± 1.1 mm.

Table 2
Coronary lesion characteristics and angiographic results

No. of narrowings	156
Vessel	
Left main trunk	2
Left anterior descending artery	69
Left circumflex artery	48
Right coronary artery	34
Saphenous vein graft	3
Lesion type*	
A	15
B1	35
B2	47
C	59
Angiographic results	
No. of narrowings	156
Proximal reference diameter (mm)	2.6 ± 0.6
Lesion length (mm)	22.8 ± 22.2
Baseline MLD (mm)	0.6 ± 0.4
Final MLD (mm)	2.4 ± 0.8
Baseline percent diameter stenosis	77.9 ± 15.1
Final percent diameter stenosis	14.4 ± 16.6

Data are expressed as numbers of lesions (percentages) or mean ± SD.

* Modified America Heart Association/American College of Cardiology criteria.

Table 3
Predictors of restenosis by multivariate logistic regression analysis

Variable	Odds Ratio	95% CI	p Value
Per lesion (n = 101)			
Cutting balloon	11.52	2.29–57.85	0.003
Stent	0.34	0.13–0.89	0.028
Per patient (n = 42)			
Cutting balloon	8.44	1.37–52.06	0.022

CI = confidence interval.

Angiographic restenosis was present in 36 lesions (36%). The average late loss of lumen diameter was 0.8 ± 1.0 mm, and the average loss index was 0.44 ± 0.61 .

The concordance rate for restenosis of lesions in the same patient was 10% (3 of 30). Of the 42 patients with follow-up angiography, 30 (87 lesions) had ≥ 2 lesions at risk. Of these 30 patients, 3 (10%) had restenosis in all their treated sites, 12 (40%) had no restenosis in any of their treated lesions, and 15 (50%) had treated sites with restenosis and no restenosis.

Predictors for restenosis: The 101 lesions with follow-up were classified into 2 groups: no restenosis (n = 65) and restenosis (n = 36). A total of 49 clinical, angiographic, and immunologic variables were analyzed. The restenosis group had donors with a greater frequency of smoking, recipients with a lower incidence of any stent use, a higher incidence of cutting balloon use, a smaller final MLD, a higher incidence of type C lesions, a shorter ischemic time, and a shorter time between OHT and PCI.

Twelve variables with $p < 0.15$ from the univariate analysis per lesion were entered into a multivariate logistic regression model for the binomial variable of angiographic restenosis. Only 2 variables were independent predictors for

Table 4
Follow-up results between bare metal stent and nonstent lesions

Variable	Bare Metal Stent	Nonstent	p Value
No. of narrowings	58	27	
Mean follow-up time (mo)	8.6 ± 3.7	11.7 ± 8.8	0.08
Angiographic results at follow-up			
Minimum lumen diameter (mm)	1.9 ± 1.2	0.9 ± 0.7	<0.0001
Percent diameter stenosis	35.0 ± 36.3	58.6 ± 30.3	0.004
Late loss	0.8 ± 1.0	0.9 ± 0.9	0.8
Loss index	0.43 ± 0.58	0.60 ± 0.71	0.2
Restenosis rate (%)	18/58 (31%)	15/27 (56%)	0.03

Data are expressed as numbers of lesions (percentages) or mean ± SD.

angiographic restenosis: recipients who did not receive a stent and the use of a cutting balloon (Table 3). The risk of restenosis increased 11.5 times with the use of a cutting balloon and decreased 66% with the use of a stent.

To account for the nonindependence of multiple lesions per patient, a similar multivariate logistic regression analysis per patient was performed for the binomial variable of angiographic restenosis. The most severe baseline percent diameter stenosis lesion was selected from each patient. In this per patient analysis, only 1 variable was an independent predictor for angiographic restenosis. The use of a cutting balloon increased the risk of restenosis 8.4 times (Table 3).

Comparison between bare metal–stented and non–stented lesions: A bare metal stent was placed in 81 lesions (56%). Compared with the 39 lesions without a stent, no differences were found in baseline percent diameter stenosis, lesion length, or baseline MLD. Type B1 lesions (47% vs 8%, $p < 0.05$) and right coronary artery location (37% vs 8%, $p < 0.05$) were more prevalent in the bare metal–stented lesions than in the nonstented lesions. The reference diameter was significantly larger in the bare metal–stented lesions (3.0 ± 0.6 mm) than the lesions that did not receive a stent (2.3 ± 0.7 mm, $p < 0.001$).

After PCI, the MLD was larger (2.7 ± 0.7 vs 1.7 ± 0.6 mm, respectively; $p < 0.001$) and the percent diameter stenosis was smaller ($7.6 \pm 14.4\%$ vs $27.3 \pm 15.8\%$, respectively; $p < 0.001$) in the stented lesions than in the nonstented lesions. Angiographic follow-up was performed on 58 bare metal–stented lesions and 27 nonstented lesions (Table 4). The percent diameter stenosis at follow-up was significantly smaller and the MLD was significantly larger in the bare metal–stented lesions than in the nonstented lesions. The restenosis rate was significantly lower in the bare metal–stented lesions (31%) than in the nonstented lesions (56%, $p < 0.05$).

Comparison between lesions with DESs and bare metal stents: A DES was used in 25 lesions (17%). Compared with the 81 lesions (56%) treated with bare metal stents, no differences were found in the lesion location,

Table 5
Influence of rejection on restenosis (n = 101)

Variable	Restenosis		p Value
	No (n = 65)	Yes (n = 36)	
Total biopsy score	16.3 ± 10.2	16.7 ± 8.8	0.8
Average of biopsy score	0.5 ± 0.3	0.6 ± 0.3	0.1
Biopsy score before PCI	15.8 ± 9.7	16.3 ± 8.3	0.8
Average biopsy score before PCI	0.5 ± 0.3	0.6 ± 0.3	0.1
ISHLT grade 3A or more	30/52 (58%)	22/52 (42%)	0.1

Data are expressed as numbers of lesions (percentages) or mean ± SD.
ISHLT = International Society for Heart and Lung Transplant.

lesion type, or reference diameter. The lesion length and baseline percent diameter stenosis were significantly larger in the bare metal–stented lesions (24.9 ± 2.6 mm, $79.4 \pm 14.2\%$) than in those stented with a DES (17.2 ± 12.0 mm, $p < 0.05$ vs $70.8 \pm 15.2\%$, $p < 0.05$, respectively). The baseline MLD was significantly smaller in the bare metal–stented lesions (0.6 ± 0.4 mm) than in the DES lesions (0.8 ± 0.5 mm, $p < 0.05$).

After PCI, the MLD was larger (2.7 ± 0.7 vs 2.3 ± 0.6 mm, respectively; $p < 0.01$) and the percent diameter stenosis was smaller ($7.6 \pm 14.4\%$ vs $16.1 \pm 11.6\%$, respectively; $p < 0.01$) in the DES lesions than in the bare metal–stented lesions. Angiographic follow-up was performed on 16 DES lesions and 58 non-DES lesions. No significant differences were found in MLD, percent diameter stenosis, or restenosis rate (19% vs 31%) between these groups. The late loss was significantly smaller in the DES lesions (0.26 ± 0.75 mm) than in the bare metal–stented lesions (0.84 ± 1.03 mm, $p < 0.05$). Because of the low number of cases, the loss index did not reach statistical significance between the DES lesions (0.15 ± 0.46 mm) and the non-DES lesions (0.43 ± 0.58 mm), but the DES lesions had a trend toward a smaller loss index and restenosis rate.

Comparison of de novo and restenotic lesions: No differences were found between the 124 de novo lesions and 21 repeat PCI lesions in lesion location, reference diameter, baseline MLD, or baseline percent diameter stenosis. The lesion length was larger in the repeat lesions (35.1 ± 22.2 mm) than in the de novo lesions (20.9 ± 21.7 mm, $p < 0.01$). Type C lesions were more prevalent in repeat lesions (71%) than in de novo lesions (27%, $p < 0.01$). Type B1 lesions were less prevalent in repeat lesions (5%) than in de novo lesions (27%, $p < 0.05$).

After PCI, neither the MLD nor percent diameter stenosis was different between de novo and repeat lesions. Angiographic follow-up was performed on 87 de novo lesions and 14 repeat lesions. The percent diameter stenosis at follow-up was significantly smaller and the MLD was significantly larger in de novo lesions ($37 \pm 35\%$, 1.7 ± 1.1 mm) than in restenotic lesions ($58 \pm 37\%$, $p < 0.05$, vs 1.0 ± 1.0 mm, $p < 0.05$, respectively). The late loss and loss index were significantly smaller in the de novo lesions

Figure 3. Kaplan-Meier survival and allograft survival curves after PCIs for 65 heart transplant patients. Actuarial survival rate at 5 years after PCI was 56%. Allograft survival was defined as absence of repeat OHT or death. Allograft survival rate at 5 years after PCI was 39%. Numbers at each period refer to number of patients (Pt) at risk for survival curve.

(0.7 ± 0.9 mm and 0.39 ± 0.61 , respectively) than in the repeat lesions (1.4 ± 1.2 mm, $p < 0.05$, and 0.73 ± 0.55 , $p < 0.05$, respectively). The repeat restenosis rate (57%) in repeat PCI lesions tended to be higher than the restenosis rate in de novo lesions (32%, $p = 0.08$), but the number of lesions was small. Of the 21 lesions with repeat PCI, 11 were because of in-stent restenosis. The 8 in-stent restenosis lesions available for follow-up had 5 repeat restenosis lesions. Of the 3 lesions that had no repeat restenosis at the in-stent restenosis, 1 had received radiotherapy and the others had a DES.

Relation between myocardial rejection and angiographic restenosis: The total biopsy score and the biopsy score before PCI were compared with the presence of restenosis. As shown in Table 5, no significant difference was found between the biopsy scores in these groups. The percentage of having a rejection grade of $\geq 3A$ also was not different for the 2 groups.

Clinical follow-up: Clinical follow-up data were available for all 65 patients. The average follow-up time was 3.0 ± 2.5 years. The total mortality was 31%; 20 patients had died by 1.9 ± 1.8 years after the first PCI or 9.6 ± 4.5 years after the initial OHT. Of the 3 patients who had an unsuccessful PCI, 1 died 1 day after the attempted PCI of acute myocardial infarction that had preceded the PCI and 1 died 29 days after the procedure of congestive heart failure and sepsis. Sixteen patients who had had a successful PCI died within 1.6 ± 1.6 years after the procedure without repeat OHT. Repeat OHT was performed in 16 patients; 5 patients had repeat OHT within 3 months after the PCI procedure, which was performed as a bridge to a planned repeat OHT. The indication for repeat OHT in these 16

patients was heart failure due to diffuse transplant arteriopathy. Four of these 16 patients died (25%) (at 6, 47, 917, and 1,534 days) after the repeat OHT.

For these 65 patients treated with a variety of PCI techniques, the 5-year actuarial survival rate after the first PCI was 56% and the allograft survival rate was 39% by Kaplan-Meier analysis (Figure 3).

Discussion

Late morbidity and death as a result of progressive coronary artery occlusion remains the leading impediment to long-term survival after cardiac transplantation.^{1-3,22,23} TCAD is angiographically detectable in 5% to 10% of OHT recipients each year and affects up to 50% of these patients within 5 years of heart transplant surgery.^{5,24,25} Once TCAD is diagnosed, the 5-year life expectancy of the allograft averages 17% but has varied from 0% to 22%, depending on the presence of diffuse distal arteriopathy.^{1,2} Although various interventional revascularization methods have been used to treat TCAD, it is still unknown whether angioplasty-based therapies prolong cardiac allograft or patient survival.^{12,14}

The procedural success rate was 93% (145 of 156 lesions) in the present study. Previous studies of PCI for TCAD reported a similar initial success rate.^{13,14,16,17,26-28} The most common reason for an unsuccessful PCI was chronic total occlusion. The primary success rate of PCI for TCAD is comparable to that in native CAD for a similar degree of lesion severity. Transplant arteries are more susceptible to intense spasm, but usually respond to intracoronary vasodilators, such as nitroglycerin, calcium channel blockers, or adenosine.²⁹ Without coronary intervention, Keogh et al¹ reported an actuarial survival rate of only 17% at 5 years after disease detection in 54 cardiac transplant recipients with $\geq 40\%$ stenosis. In the present study of 65 patients, the actuarial survival rate from the Kaplan-Meier analysis was 56% at 5 years after PCI. Allograft survival (defined as the absence of retransplantation or death) was maintained in 32 of 65 patients (49%) a mean of 35 ± 30 months after the successful initial PCI. In a multicenter review, Halle et al¹⁴ reported in 1995 that 61% (40 of 66 patients) were alive without repeat OHT at 19 ± 14 months after angioplasty, but the Kaplan-Meier actuarial survival was only 20% at 5 years after angioplasty. Several explanations may exist as to why the actuarial survival was improved in the present study; these include alterations in surgical technique, newer medical regimens, and the use of coronary stents and DESs.

The restenosis rate after PCI for TCAD is high compared with that for native CAD. Explanted hearts demonstrate an intense lymphoproliferation in the adventitia, media, and intima of arteries with TCAD. This intense inflammatory response is believed to play a key role in the vasculopathy of heart transplants and may be responsible for the increased

Figure 4. (A) Ultrasound image of right coronary artery demonstrating adventitia with relative low echogenicity. (B, C) Patient had repeat cardiac transplantation. Histologic examination revealed infiltration of adventitia with lymphocytes and macrophages. This inflammatory cellular response accounted for low echogenicity on the intravascular ultrasound image.

rate of restenosis (Figure 4). Unusually high restenosis rates (55% at 8 months) were reported in the North American Multicenter Registry in PCI without stenting.¹⁴ In the present study, the overall restenosis rate was 36%. However, significant differences were found in the restenosis rate with the various techniques. The concordance rate for restenosis of multiple lesions in the same patient was only 10% (3 of 30) in the present study. This result suggests that restenosis even in the transplant patient milieu is predominantly lesion specific. This implies that a new lesion that appears during follow-up could be appropriate for PCI treatment, even if the previous lesion developed restenosis.

However, no difference was found in late loss of coronary lumen diameter and loss index between the bare metal-stented and nonstented lesions (Table 4). Because the late loss was similar, the reduction in the restenosis rate of bare metal-stented lesions compared with nonstented lesions was a result of the acute gain in lumen diameter after PCI. Although, the restenosis rate with DESs (19%) was lower than with bare metal stents (31%), it did not reach statistical significance because the number of DES patients with follow-up was low. On the basis of the significant reduction in late lumen loss, DESs appear to prevent neointimal proliferation in transplant arteries, but the restenosis rate is higher than in native coronary vessels.

The present study was a single-center, nonrandomized observational study. The patient number was small compared with PCI studies in native CAD; however, the cardiac transplant population is a unique patient group with high mortality despite successful PCI because of the diffuse nature of transplant vasculopathy. The patient and lesion number in the present study were comparable or higher compared with previous single- or multicenter studies of PCI for TCAD. Only a randomized trial can determine whether PCI for TCAD prolongs survival in this high-risk population, but the logistic requirements make it unlikely that a randomized trial will be done.

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