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Long-Term Outcomes of Heart Transplantation Recipients With Transplant Coronary Artery Disease Who Develop In-Stent Restenosis After Percutaneous Coronary Intervention

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Abstract

This retrospective study assessed long-term clinical outcomes of patients with orthotopic heart transplantation (OHT) and transplant coronary artery disease (TCAD) who developed in-stent restenosis (ISR) after percutaneous coronary intervention (PCI). TCAD is a major cause of morbidity and mortality after the first year after OHT. Description of outcomes in patients with ISR after revascularization for TCAD is limited. One hundred five patients underwent PCI with bare-metal stents or drug-eluting stents at the UCLA Medical Center from 1995 throughout 2009, of whom 83 patients (79.0%) underwent repeat angiography for clinical symptoms or surveillance. The primary end point was the composite of death, myocardial infarction, or repeat OHT. ISR occurred in 26 patients (31.3%) who underwent follow-up angiography. Initial treatment strategies for the 26 patients with ISR were target vessel revascularization in 19 (73.1%), repeat OHT in 3 (11.5%), and medical therapy in only 4 (15.4%). At 7 years freedom from the primary end point was lower in patients with ISR compared to patients without ISR (27.9% vs 63.2%, $p = 0.006$, log-rank test) primarily driven by a lower survival rate in patients with ISR (38.5% vs 84.2%, $p < 0.001$, log-rank test). Although numerically smaller in patients with ISR, there were no statistically significant differences in freedom from myocardial infarction (80.8% vs 91.2%, log-rank $p = 0.18$) and freedom from repeat OHT (73.1% vs 84%, $p = 0.22$, long-rank test). In conclusion, patients with OHT who develop ISR after PCI have poor long-term prognosis. Improvements in prevention and treatment of TCAD such as increased pharmacotherapy are needed.

Transplant coronary artery disease (TCAD) commonly occurs after orthotopic heart transplantation (OHT), occurring in 32% of patients at 5 years and 53% at 10 years, and is a major cause of death and allograft loss after the first year after OHT.^{1,2} TCAD is characterized by an aggressive form of diffuse arterial narrowing. Ideal management of TCAD is unknown because treatment options for TCAD are few. Current options are associated with poor long-term success and there is because of limited characterization of outcomes after treatment. Patients after OHT comprise 1 of the highest-risk groups who undergo percutaneous coronary intervention (PCI), with poor long-term angiographic and clinical outcomes.^{3,4} PCI plays a palliative role for treatment of TCAD. There are no published data or recommendations on ideal treatment for in-stent restenosis (ISR) in

TCAD, and descriptions of outcomes after identification and treatment of ISR are sparse. We evaluated outcomes of patients with TCAD who developed ISR after stenting.

Methods

Data on patients with TCAD who underwent PCI with a bare-metal stent or drug-eluting stent from 1996 through 2009 at the UCLA Medical Center and had angiographic evidence of binary restenosis (>50% diameter restenosis on repeat coronary angiogram) were retrospectively analyzed. Data on the first 82 patients in this study have been previously described.³ Approval of the institutional review board was obtained to review the PCI database for this study.

Standard techniques for PCI were used. Choices of anticoagulation and type of stent used were at the discretion of the operator. From 1996 through April 2003, bare-metal stents were used. From May 2003 through November 2009, PCI with drug-eluting stents using sirolimus (Cypher, Cordis, Johnson and Johnson Corporation, Miami, Florida), paclitaxel (Taxus, Boston Scientific Corporation, Natick, Massachusetts), or everolimus (Xience, Abbott Vascular, Santa Clara, California) was the preferred strategy. All patients were treated with a thienopyridine (ticlopidine or clopidogrel) for a minimum of 1 month if PCI with bare-metal stents was used and 6 months if PCI with drug-eluting stents was used and aspirin indefinitely. Management of ISR was based on clinical judgment after discussion with the transplant cardiologist.

The primary end point of this analysis was the composite of death, myocardial infarction, or repeat OHT. Secondary clinical end points were death, myocardial infarction, and repeat OHT. Myocardial infarction was diagnosed according to the universal definition with the detection of an increase and/or decrease of cardiac enzymes with 1 value >99th percentile of the upper limit of normal with evidence of myocardial ischemia and 1 of the following: (1) ischemic symptoms, (2) electrocardiographic changes indicative of new ischemia (new ST-T-wave changes or new left bundle branch block), (3) development of pathologic Q waves on electrocardiogram, or (4) new loss of viable myocardium or new regional wall motion abnormality on imaging.⁵ The Academic Research Consortium definition for definite or probable stent thrombosis was used.⁶

Patient data were collected from medical records or from telephone interviews with physicians who followed them at another institution and recorded into a dedicated database. If repeat PCI was performed, surveillance angiography was performed at 6 months if clinically indicated. Reasons for incomplete follow-up were premature death or patient refusal.

Quantitative coronary analysis was performed with an automated edge detection computer analysis system (GE CA1000 Stenosis Analysis Application, GE Healthcare, Piscataway, New Jersey).

Continuous variables are expressed as mean $\pm$ SD and were compared by Student's *t* tests. Categorical variables are expressed as percentage and were compared by chi-square statistics or Fisher's exact test, as indicated. Time-to-events curves were determined by the Kaplan-Meier method and comparisons were made using log-rank test. A multivariable Cox proportional hazard model was created using baseline clinical and angiographic characteristics and procedure-related variables to identify independent predictors of the primary end point. Variables inserted into the Cox regression analysis included age, male gender, diabetes mellitus, hypertension, treatment with statin, left ventricular ejection fraction, elective PCI, age of allograft, symptom when ISR was detected, intravascular

ultrasound, intra-aortic balloon pump, glycoprotein IIb/IIIa inhibitor, rotational atherectomy, drug-eluting stent, mean stent diameter, and mean stent length. A p value <0.05 was considered statistically significant. Statistical analysis was performed with SAS 9.1 (SAS Institute, Cary, North Carolina).

Results

In total 105 patients underwent first-vessel PCI with bare-metal stents ($n = 47$) or drug-eluting stents ($n = 58$; Figure 1). Of 83 patients (79%) who underwent follow-up angiography, ISR occurred in 26 patients (31%; Table 1). Median time to identification of ISR was 282 days. Mean angiographic stenosis for patients who developed ISR was $85.2 \pm 11.8\%$ (Table 2).

In the 26 patients with ISR, initial treatment strategies were target vessel revascularization (TVR) in 19 (73.1%), repeat OHT in 3 (11.5%), and medical therapy only in 4 (15.4%). Of the 19 patients who underwent TVR, repeat stenting was performed in 16 (84.2%), brachytherapy in 1 (5.3%), balloon angioplasty in 1 (5.3%), and coronary artery bypass surgery in 1 (5.3%). Of the 11 patients who underwent further repeat angiography after TVR, 7 (63.6%) developed recurrent ISR.

Two patients who were initially treated with TVR died from stent thrombosis, although the relation to the restenotic lesion was not definitely ascertained. A 74-year-old man had ISR of a bare-metal stent placed in the right coronary artery and underwent TVR with 2 sirolimus-eluting stents and revascularization of the left anterior descending coronary artery with 2 sirolimus-eluting stents and left circumflex coronary artery with 1 sirolimus-eluting stent. The patient died suddenly 18 days later. A 60-year-old woman had ISR of a sirolimus-eluting stent in the left anterior descending coronary artery and subsequently underwent TVR. Four years later she died from autopsy-confirmed stent thrombosis of a paclitaxel-eluting stent 20 days after undergoing PCI of a de novo lesion in the right coronary artery.

At 7 years, which was the mean duration of follow-up, freedom from the composite end point of death, myocardial infarction, or repeat OHT was lower in patients with ISR compared to patients without ISR (27.9% vs 63.2%, $p = 0.006$, log-rank test; Figure 2) primarily driven by a lower survival rate in patients with ISR (38.5% vs 84.2%, $p < 0.001$, log-rank test; Figure 3). Although numerically smaller in patients with ISR, there were no statistically significant differences between patients with ISR and patients without ISR in freedom from myocardial infarction (80.8% vs 91.2%, $p = 0.18$, log-rank test; Figure 4) and freedom from repeat OHT (73.1% vs 84%, $p = 0.22$, log-rank test; Figure 5).

Logistic regression analysis revealed that for patients undergoing initial PCI for TCAD, ISR (odds ratio [OR] 2.4, 95% confidence interval [CI] 1.1 to 5.7, $p = 0.03$), mean stent diameter (OR 2.8, 95% CI 1.0 to 7.6, $p = 0.048$), and mean stent length (OR 1.0, 95% CI 1.0 to 1.1, $p = 0.02$) were independent predictors of the primary end point. Treatment with statin (OR 0.3, 95% CI 0.1 to 0.9, $p = 0.03$), higher left ventricular ejection fraction (OR 0.9, 95% CI 0.9 to 1.0, $p = 0.005$), and treatment with a drug-eluting stent (OR 0.2, 95% CI 0.1 to 0.5, $p = 0.001$) were negative predictors of the primary end point.

Discussion

In this series that describes the longest and largest follow-up of patients with OHT and TCAD who developed ISR after PCI, the primary end point of death, myocardial infarction, or repeat OHT was higher in patients with TCAD who developed ISR compared to those who did not. The difference was due largely to a high mortality rate in patients with OHT and ISR.

Therapeutic options focusing on the treatment of TCAD are limited. The exact mechanism for increased risk of death, myocardial infarction, or allograft loss in patients with TCAD who develop ISR after PCI is unknown. One possible explanation of the adverse prognosis after ISR for PCI of TCAD may be concurrent long-term rejection leading to increased intimal hyperplasia in remote coronary segments throughout the coronary tree.⁷ Despite the benefit of less restenosis at the target site with drug-eluting compared to bare-metal stents, its clinical impact may be less pronounced because of multiple co-morbidities, diffuse involvement, and rapid progression of TCAD in other areas of the coronary tree. Development of ISR after PCI for TCAD may be a surrogate marker of a more diffuse and aggressive inflammatory response and allograft rejection versus a modifiable risk factor for adverse clinical events, despite optimal PCI techniques and maximal medical therapy.

Intracoronary thrombus is also commonly found in patients with TCAD and may increase the risk of stent thrombosis and sudden death.⁸ Two patients who developed ISR and subsequently underwent repeat PCI had definite and probable stent thrombosis, respectively.

Despite the poorer prognosis of patients with OHT and ISR, most of them were asymptomatic. Surveillance angiography is routinely performed to detect TCAD because these patients may not manifest the classic ischemic symptoms of coronary artery disease because of denervation of the heart. However, almost 1/3 of patients with ISR presented with symptoms such as angina or dyspnea on exertion, myocardial infarction, ventricular tachyarrhythmia, and sudden cardiac death. Previous studies from the bare-metal stent and drug-eluting stent era have suggested that ISR of non-TCAD lesions is not a benign entity, with 10% to 13% of patients presenting with acute coronary syndromes.^{9,10}

The optimal initial treatment strategy for ISR in patients with TCAD is not well established but was based on clinical judgment of the interventionalist and transplant cardiologist. Factors considered when deciding the optimal treatment option included clinical presentation, urgency of revascularization, feasibility of repeat PCI, likelihood of long-term patency, distal run-off, and whether repeat OHT was an option. Patients who presented with acute coronary syndrome owing to ISR were treated with urgent TVR. Patients also were more likely to undergo TVR if the lesions were focal, whereas patients with multiple and diffuse lesions were referred for repeat OHT. Because the recurrent restenosis rate was high (63.6%) after TVR for ISR, judicious patient selection is required if repeat PCI is considered for palliation. Risk stratification with a scoring system would be ideal to identify patients who are likely to benefit from repeat PCI. Patients with diffuse restenosis (in-stent, proliferative, or total occlusion) or poor distal run-off are unlikely to benefit from TVR, whereas patients with focal disease restenosis may have better patency.¹¹ Every attempt should be made to optimize stent deployment during the first PCI, especially with bypass surgery being a poor treatment alternative after OHT, because of high operative mortality rates and poor targets owing to “pruning” of the distal vessels common in TCAD.¹²

Treatment with drug-eluting stents was a negative predictor of the composite end point. Previous studies have demonstrated that drug-eluting stents are associated with lower restenosis rates compared to bare-metal stents and may explain the lower incidence of adverse clinical events.^{4,13,14} Treatment with statins was identified as a negative predictor of the composite end point. A randomized trial found that pravastatin decreased the incidence and progression of plaques in patients with OHT.¹⁵ In addition, statins may inhibit the development of TCAD through their immunomodulatory effects.¹⁶

The limitations of this study included its small retrospective design. This was from a single-center study and therefore requires external validation. Comparisons to different treatment options were not randomized. Instead, clinical judgment was used to determine the best

possible treatment on a case-by-case scenario. The duration of the study was over a prolonged period, and the temporal relation of different immunosuppressive regimens on the incidence of ISR is unclear. Angiographic follow-up was not available in all patients. Quantitative coronary analysis was not performed by an angiographic core laboratory.

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Figure 1.
Flow diagram of study.

Figure 2. Freedom from composite of death, myocardial infarction, or repeat orthotopic heart transplantation.

Figure 3.
Freedom from death.

Figure 4.
Freedom from myocardial infarction.

Figure 5.
Freedom from repeat orthotopic heart transplantation.

Table 1

Baseline clinical characteristics

Variable	ISR		p Value
	Yes (n = 26)	No (n = 57)	
Age (years)	53.7 ± 14.9	56.9 ± 17.0	0.24
Men	65%	77%	0.26
Diabetes mellitus	31%	28%	0.44
Hypertension	69%	63%	0.59
Treatment with statin	73%	63%	0.38
Left ventricular ejection fraction (%)	48.8 ± 11.6	51.7 ± 11.3	0.98
Elective percutaneous coronary intervention	92%	93%	0.91
Age of allograft (years)	8.2 ± 4.2	8.9 ± 5.0	0.09
Symptom when in-stent restenosis detected			
Asymptomatic	69%	N/A	
Angina/dyspnea on exertion	19%	N/A	
Myocardial infarction	8%	N/A	
Cardiac arrest	4%	N/A	

Table 2

Baseline angiographic and procedural characteristics

Variable	ISR		p Value
	Yes (n = 26)	No (n = 57)	
Percent angiographic stenosis	85.2 ± 11.8	N/A	
Coronary artery treated			0.99
Left main	4%	5%	
Left anterior descending	46%	47%	
Left circumflex	19%	19%	
Right	31%	28%	
Intravascular ultrasound	35%	35%	0.97
Intra-aortic balloon pump	12%	5%	0.31
Glycoprotein IIb/IIIa inhibitor	31%	21%	0.34
Rotational atherectomy	4%	2%	0.56
Drug-eluting stent	46%	54%	0.15
Mean stent diameter (mm)	2.9 ± 0.4	3.0 ± 0.4	0.73
Mean stent length (mm)	22.9 ± 10.3	18.8 ± 10.1	0.28