Angioplasty versus stenting for cardiac allograft vasculopathy

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Background: Nearly all cardiac allografts develop a unique vasculopathy. Cardiac allograft vasculopathy (CAV), coupled with atherosclerotic coronary artery disease remains the primary cause for late allograft dysfunction. There is limited data comparing angioplasty to stenting for CAV. **Methods**: A qualitative analysis was performed to determine if further investigation of differences between angioplasty and stenting is required for CAV. A retrospective examination of patients with a cardiac transplant who developed CAV requiring percutaneous coronary interventions was performed. Baseline data were obtained on the patients. Annual coronary angiograms were performed for the diagnosis of CAV and to determine the patency after a percutaneous coronary intervention (quantitative coronary angiography was not performed). The primary end point was restenosis of the target lesion. Angioplastied lesions were compared with stented lesions for restenosis rate and time to first restenosis. **Results**: From 1984 to 2000, there were 452 cardiac transplants at our institution. A total of 11 patients received angioplasty and nine patients received a coronary artery stent. Overall, there were fifteen lesions angioplastied (73% restenosed) and thirteen lesions stented (15% restenosed). The time to restenosis was earlier in the stent group- 4 months vs. 25.9 months. **Conclusion**: The results suggest that if a CAV lesion is to be intervened upon, stenting provides a more durable treatment than angioplasty. This qualitative analysis confirms the necessity to quantitatively determine the difference between angioplasty and stenting for CAV.

The development of cardiac allograft vasculopathy (CAV) is a major determinant of survival in patients who have undergone orthotopic heart transplantation (OHT) and is the leading cause of death after the first year [1]. The estimated incidence of CAV is 11–14% at 1 year and 40–50% at 5 years [2,3]. CAV is thought to be in part an immune-mediated disease characterized by the development of diffuse, concentric intimal thickening affecting both epicardial and intramyocardial vessels as well as the development of discrete atherosclerotic plaques [4].

The heterogeneous nature of CAV presents a difficult therapeutic challenge. Prevention through pharmacological measures has had limited success. The most common interventional techniques for focal lesions are percutaneous transluminal coronary angiography (PTCA) and stent placement. Few studies have evaluated the long-term durability of PTCA or stent placement for CAV especially in a direct comparison of the two techniques. In this analysis, we compare the long-term outcome of PTCA versus stenting for the treatment of focal CAV stenosis.

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Methods

Patients

From 1984 to 2000, there were 452 OHTs performed at our institution. A total of 28 lesions were intervened upon. A total of 11 patients received angioplasty and nine patients received a coronary artery stent. Overall, there were 15 lesions angioplastied and 13 stented.

Procedural information

Percutaneous coronary intervention (PCI) was carried out in a standard fashion. All of the patients were referred for elective revascularization; none of the patients were referred for emergent revascularization. Procedural success was defined as a final lumen stenosis of 25% or less. All PCI were successful.

Angiographic follow-up

As part of the routine evaluation of OHT recipients at our institution, annual coronary angiography was performed on all the patients. The diagnosis of CAV focal stenosis was made by coronary angiography in all the patients. Target lesion restenosis was determined by angiography and was defined as greater than 75% diameter

Table 1. Baseline demographics.		
	PTCA	**Stent**
Mean age of HTX	52	58.5
Mean age of CVD	58	61.5
HTx to CAV (months)	54	36
Diabetes mellitus	7 (46.7%)	5 (38.5%)
Hypertension	15 (100%)	13 (100%)
Hyperlipidemia	12 (80%)	13 (100%)
Change in Cr	0.7	0.7
Statin therapy	8 (66.7%)	13 (100%)
Calcium blocker	8 (53.3%)	2 (15.4%)
ACE inhibitor	7 (46.6%)	3 (23.1%)
Aspirin	14 (93.3%)	13 (100%)
Cyclosporin A	15 (100%)	13 (100%)
Azathioprin	15 (100%)	8 (61.5%)
Prednisone	15 (100%)	13 (100%)
Mycofenolate	0 (0.0%)	5 (38.5%)
Tacrolimus	0 (0.0%)	2 (15.4%)
Sirolimus	0 (0.0%)	2 (15.4%)
FK506	0 (0.0%)	2 (15.4%)

ACE: Angiotensin-converting enzyme; CAV: Cardiac allograft vasculopathy;
Cr: Creatinine clearance; CVD: Cardiovascular disease; HTx: Heart transplant;
PTCA: Percutaneous transluminal coronary angiography.

lumen loss. Angiographic restenosis was determined qualitatively; quantitative coronary angiography was not performed.

Results

This is a pilot study with small numbers of patients in each arm. There did not appear to be any significant clinical or demographic differences between the patients who underwent PTCA versus those who underwent stenting. However, the stent group was more likely to be on a more complex immunosupression regimen. There were no patients in the PTCA group on mycofenolate, tacrolimas (FK506), or sirolimus; whereas, these drugs were part of the immunosupression regimen in some stent patients. This reflects the timing of the PCI and available drugs at that period.

Of the patients with CAV who underwent PTCA, 64% restenosed (73% of the lesions angioplastied) while 11% restenosed in the stent group (15% of the lesions stented). The patients in the stent group developed restenosis earlier than the PTCA group (mean time to restenosis: 4 vs 25.9 months).

Discussion

Select patients with end-stage cardiomyopathy are treated with OHT. In heart transplant recipients, the leading cause of death, after the first year, is CAV [1]. At 1 year, angiography demonstrates CAV in 11–14% of recipients and in 40–50% of recipients by 5 years [2,3]. However, intravascular ultrasound examination suggests a biphasic vasculopathy with coronary artery changes in up to 75% of patients at 1 year [5–7]. CAV is an incompletely understood process. Although immunosuppressive drugs limit acute allograft rejection, they do little to prevent the disease [8,9]. Inbred rat models have demonstrated the development of CAV in the absence of T-cell alloimmune response [10]. Humoral mechanisms may be important in the development of the disease [11]. The acute and chronic metabolic milieu of the transplanted heart has been implicated in the development of CAV. Increasing ischemic injury time coupled with immune mechanisms has increased CAV in models [12,13]. Insulin resistance and diabetes have been associated with the development and progression of CAV [14,15]. Cytomegalovirus infection is a risk factor for CAV which may be mediated through immunologic mechanisms [16]. There has been limited success with medical therapy for the prevention of cardiac allograft vasculopathy. Angiotensin-converting enzyme inhibitors, diltiazem, simvastatin and pravastatin, have demonstrated benefit in reducing intimal proliferation, smooth muscle cell proliferation, and the development of CAV [17–21]. Once established, however, focal CAV may be treated with a variety of mechanical interventions.[22] PTCA has been shown to have good initial angiographic results, however, restenosis at 6–8 months is between 55–67% [23,24]. Similar initial angiographic results have been obtained by using coronary artery tents, however, 6–8 month restenosis rates range from 25–64% [24,25]. Coronary artery bypass grafting was associated with a 33% perioperative mortality [23].

McKay and colleagues evaluated clinical and angiographic predictors of percutaneous revascularization in patients with CAV [26]. In an analysis of 62 lesions in 40 patients, they found that restenosis was higher in patients with IgG antibody to the MHC class I antigen. Additionally, vessel diameter and stenosis severity predicted restenosis [26].

However, the majority of these studies have limited long term follow-up. In this study, we demonstrate similar short-term restenosis rates as seen in other studies. Restenosis in the stent group occurred within six months after the intervention. Once past this window of restenosis, however, our data suggest the long term durability of stenting for CAV.

Highlights

- Cardiac allograft vasculopathy is a significant problem post cardiac transplantation.
- Stenting appears to be more durable than percutaneous transluminal coronary angiography alone.
- The role of drug eluting stents for cardiac allograft vasculopathy needs to be evaluated.

This study has several limitations. It was designed as a pilot study to determine if further investigation of differences between PTCA and stenting for CAV is warranted, and as such, the results should be interpreted with caution, since due to the small number of patients, accurate statistical analysis is not possible. The study was single institutional without randomization. The study period was large, during which time several technical and theoretical advancements were made with OHT transplantation, medical treatment of CAV, as well as interventional cardiology. A significant limitation was the fact that late restenosis may have been missed. Simpson and colleagues demonstrated a late restenosis after stenting, as well as the development of new lesions which necessitate repeat intervention [27]. This may also have occurred in our patients, but due to the timing of follow-up, it was not seen. Furthermore, the assessment of stenosis and restenosis was done qualitatively, not using quantitative measurements such as qualitative coronary angiography or intravascular ultrasound; qualitative visual estimation of restenosis may over or under estimate disease.

Conclusions

This study has demonstrated that PTCA is likely inferior to stenting for CAV. The results of this analysis justify further evaluation of these patients in order to quantitatively determine the difference between PTCA and stenting for CAV.

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