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Title:	JACC. Cardiovascular interventions
Title Abbrev:	JACC Cardiovasc Interv
Citation:	2010 Apr;3(4):367-77
Article:	Transplant coronary artery disease.
Author:	Zimmer R;Lee M
NLM Unique ID:	101467004 Verify: PubMed
PubMed UI:	20398862
ISSN:	1936-8798 (Print) 1876-7605 (Electronic)
Publisher:	Elsevier, New York :
Copyright:	Copyright Compliance Guidelines
Authorization:	Librarians
Need By:	N/A
Maximum Cost:	**$13.00**
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JACC: CARDIOVASCULAR INTERVENTIONS
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VOL. 3, NO. 4, 2010
ISSN 1936-8798/10/$36.00
DOI 10.1016/j.jcin.2010.02.007

STATE-OF-THE-ART PAPER

Transplant Coronary Artery Disease

Raymond J. Zimmer, MD, Michael S. Lee, MD

Los Angeles, California

Transplant coronary artery disease (TCAD) remains the most significant cause of morbidity and mortality after orthotopic heart transplantation. Transplant coronary artery disease is largely an immunologic phenomenon, driven by an inflammatory milieu consisting of multiple cell types that contribute to fibromuscular and smooth muscle cell proliferation with subsequent coronary obstruction. Multiple clinical factors contribute to the development of TCAD. Coronary angiography is the gold standard for the diagnosis of TCAD. Current treatments for TCAD include pharmacotherapy, percutaneous coronary intervention, and repeat transplantation, although other novel therapies are emerging. Although percutaneous coronary intervention has generally demonstrated high procedural success rates, it has been plagued by a high incidence of in-stent restenosis. Drug-eluting stents reduce in-stent restenosis compared with bare metal stents. Repeat transplantation is the only definitive treatment. Prospective randomized trials comparing different pharmacotherapies as well as revascularization strategies are needed to identify the optimal therapy for patients who develop TCAD. (J Am Coll Cardiol Intv 2010; 3:367–77) © 2010 by the American College of Cardiology Foundation

Orthotopic heart transplantation (OHT) has become a well-established therapeutic measure for patients with severe congestive heart failure. However, OHT brings various comorbidities, including rejection, infection, solid and hematologic malignancies, renal failure, and transplant coronary artery disease (TCAD) (1). Transplant coronary artery disease remains the most significant cause of morbidity and mortality after OHT, with angiographic evidence of TCAD in as many as 50% of patients at 5- to 15-year follow-up (1–4). There seems to be an exponential growth in incidence after the 5-year period, and some studies have shown an approximately 10% increase in disease incidence with every 2-year interval after OHT (5,6). Unsuspected severe disease has been found to be possibly responsible for up to 10% of early graft failures (6).

From the Division of Cardiology, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, California. Dr. Lee is on the Speakers' Bureau for Boston Scientific, BMS, Daiichi-Sankyo, and Schering-Plough.

Manuscript received December 22, 2009; revised manuscript received February 5, 2010, accepted February 17, 2010.

This review will highlight the pathogenesis, risk factors, and medical, interventional, and surgical treatment options for TCAD.

Pathogenesis of TCAD

Transplant coronary artery disease is largely an immunologic phenomenon that is influenced by nonimmunologic factors, with various components of humoral and cellular immunity associated with the development of TCAD. Examination of cellular infiltrates in the vessel walls of TCAD has shown a predominant T-cell population mainly localized in the neointima and adventitia (7). This particular cell population has been associated with a strong cytotoxic inflammatory response, and endotheliitis associated with a subendothelial accumulation of T lymphocytes is a common pathologic manifestation of chronic rejection (Fig. 1). Furthermore, allo- and tissue-specific immunity might contribute to the induction of TCAD, and a continued allo-immune response against graft tissue antigens might augment the progression of TCAD, as evidenced by increased levels of circulating allo- and cardiac myosin-specific antibodies after OHT (8). The presence of anti-human leu-

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kocyte antigen (HLA) class I and II antibodies has also been associated with an increased risk of developing TCAD at 5 years after OHT (9). Virtual histology intravascular ultrasound (IVUS) showed that the presence of "inflammatory" plaque at baseline evaluation several years after OHT, defined as necrotic core and dense calcium ≥30%, was associated with early recurrent rejection and more rapid and severe subsequent progression of TCAD compared to "non-inflammatory" plaque (10).

Although it has been difficult to isolate the precise sequence of events that initiates the immune dysfunction, it is believed that immune factors such as the ones described in the preceding text might result in endothelial injury and subsequent alterations in vascular permeability (Fig. 2). This then leads to vascular smooth muscle cell (SMC) activation and proliferation as well as migration from the vascular media into the intima (11). These SMCs proliferate and produce cytokines and extracellular matrix proteins, resulting in luminal narrowing and impaired vascular function (11). This is manifested in progressive fibromuscular intimal hyperplasia in both epicardial and intracardiac arteries (Fig. 3). One immunologic pathway that might be involved is apoptosis, because it is theorized that this might trigger a repair response that is characterized by vascular SMC proliferation with resulting lesions that are typical of TCAD (12). There are a number of other circulatory compounds that have been implicated as immunomodulatory factors in the initiation and progression of TCAD, including receptor activator for nuclear factor kappa B ligand—which might have a role in maintaining myocardial and/or endothelial integrity in OHT patients—as well as adhesion molecules such as P-selectin and intercellular adhesion molecule-1, which are part of the platelet-leukocyte adhesion cascade and might reflect a chronic inflammatory state that is associated with coronary vasomotor dysfunction and the subsequent beginnings of TCAD (13,14). Nitric oxide might play a role in preventing endothelial vasodilatory dysfunction, which might hinder the progression of structural changes characteristic of TCAD (15).

Endothelial injury at implantation of the transplanted heart has been shown to worsen endothelial dysfunction and exacerbate the intimal thickening that leads to TCAD (16). Ischemia-reperfusion injury to cardiac allografts results in oxidative stress that stimulates the production of pro-inflammatory cytokines and adhesion molecules that are associated with the development of TCAD, particularly superoxide anions and free radicals. Studies have shown that reductions in the amount of these compounds—via genetic alteration or increased activity of superoxide dismutase—result in the attenuation of inflammatory responses that are associated with ischemia-reperfusion injury and TCAD (17,18).

Although cellular infiltrates have been shown to be populated predominantly with T cells, multiple other immune cells have been shown to contribute to TCAD. Macrophage foam cells are a common component of the inflammatory cellular milieu in TCAD (Fig. 4). A central role has also been demonstrated for natural killer cells in the generation of TCAD via a pathway involving the recruitment of T cells not responsive to donor alloantigens (19). The humoral pathway has also been implicated in the form of Quilty lesions, which are nodular mononuclear endocardial infiltrates that contain significant numbers of B cells, plasma cells, and occasional CD21+ follicular dendritic reticulum cells (20). Heart transplant recipients who developed Quilty lesions within the first year were younger and more likely to have a biopsy diagnosis of acute rejection compared with those who did not, and among patients who did not form anti-HLA class II antibodies, those with Quilty lesions were more likely than patients without Quilty lesions to develop TCAD 5 years after OHT (20). This indicates that the presence of Quilty lesions might confer a slight risk of chronic rejection independent of the presence

Abbreviations and Acronyms

CMV = cytomegalovirus
CNI = calcineurin inhibitor
CT = computed tomography
HLA = human leukocyte antigen
IVUS = intravascular ultrasound
OHT = orthotopic heart transplantation
PCI = percutaneous coronary intervention
SMC = smooth muscle cell
TCAD = transplant coronary artery disease
TIMI = Thrombolysis In Myocardial Infarction

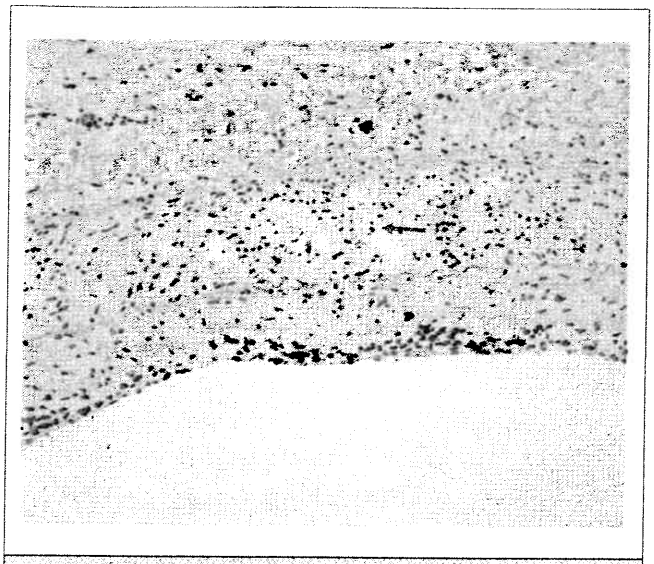

Figure 1. Immunohistochemical Stain for CD4 Cells in TCAD

Immunohistochemical stain for CD4 cells in an epicardial coronary artery of a patient with transplant coronary artery disease (TCAD) demonstrating subendothelial accumulation of T lymphocytes **(arrow)** characteristic of endotheliitis, which is a manifestation of chronic rejection. Image courtesy of Michael Fishbein, MD, UCLA Department of Pathology and Laboratory Medicine.

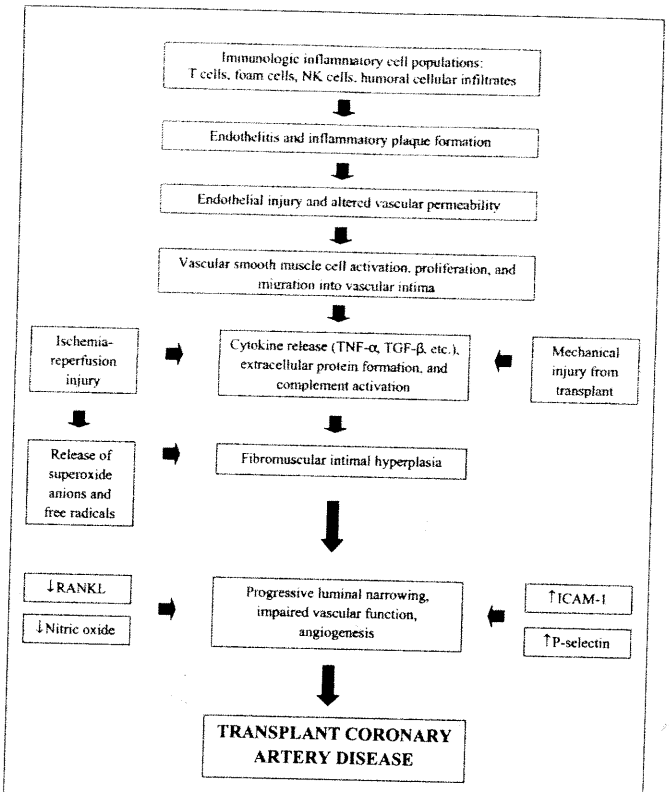

Figure 2. Schematic Representation of the Development of TCAD

ICAM = intercellular adhesion molecule; NK = natural killer; RANKL = receptor activator for nuclear factor kappa B ligand; TCAD = transplant coronary artery disease; TGF = transforming growth factor; TNF = tumor necrosis factor.

of anti-HLA class II antibodies, which is a significant inciting factor for the development of TCAD.

Genetic factors that are associated with the expression or absence of certain proteins might also predispose to the development of TCAD. A study analyzing a polymorphism associated with high tumor necrosis factor (TNF)-alpha production showed that homozygosity for this polymorphism (and subsequently higher level of TNF-alpha production) was associated with the development of TCAD and a trend toward increased mortality (21). This might not be surprising because TNF-alpha is a pro-inflammatory cytokine that is released at sites of inflammation and upregulates adhesion molecules and major histocompatibility complex expression, activates endothelial cells, induces vasodilation, and increases vascular permeability (22). The expression of heat shock protein 27 was absent in biopsied vessels of patients with TCAD, demonstrating that this protein—which is present in normal blood vessels—might have a protective effect on the development of TCAD by an unknown mechanism (23). A polymorphism that is associated with decreased transforming growth factor beta-1 production was also shown to be associated with lower rates of TCAD when the polymorphism is present in the recipient genome, but there is no difference in the rate of TCAD when the polymorphism is present in the donor genome (24). Decreased transforming growth factor beta-1 production impairs recruitment of a variety of cells, including endothelial cells, SMCs, leukocytes, and fibroblasts, which are all cell populations that are prevalent in biopsied lesions of TCAD.

Many of these factors create an inflammatory milieu that is typified by responses such as angiogenesis, endothelial activation, and complement activation, all of which increase the degree and severity of vascular changes that typify TCAD, including constrictive remodeling—which is a decrease in the external elastic membrane area of the affected vessel that occurs primarily in the first 2 years after OHT—and intimal hyperplasia (25). The presence of angiogenesis within the intima of TCAD lesions, which is associated with strong expression of endothelial activation markers by the endothelial cells lining these new vessels, suggests that the inhibition of endothelial damage might reduce the recruitment of inflammatory cells to transplanted vessels via reduced circulation of endothelial activation markers (26). There is evidence, however, that some of these responses might be adaptive measures that help mitigate the tissue injury and inflammation occurring in this environment. Animal and clinical studies have shown that heme-oxygenase 1, a protein produced by macrophages in response to inflammatory factors, might be beneficial to the development of TCAD as determined by an association with increased pro-apoptotic markers that likely curtail some of the inflammatory changes described in the preceding text (27).

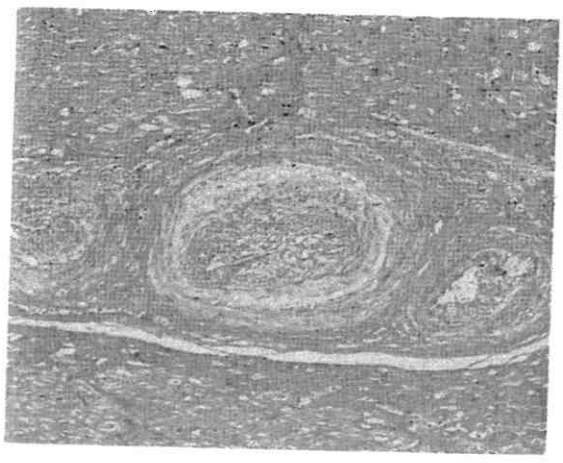

Figure 3. Fibromuscular Intimal Hyperplasia in TCAD

Trichrome stain of an intracardiac coronary artery demonstrating fibromuscular intimal hyperplasia in a patient with transplant coronary artery disease (TCAD). Image courtesy of Michael Fishbein, MD, UCLA Department of Pathology and Laboratory Medicine.

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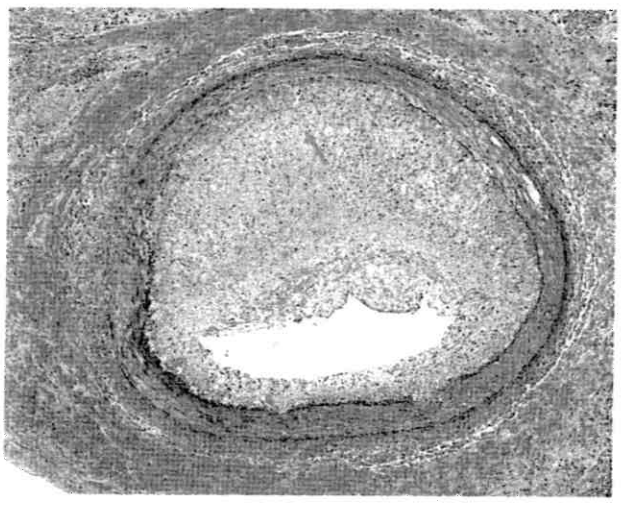

Figure 4. Lipid-Laden Foam Cell Macrophages in TCAD

Trichrome elastic stain of a coronary artery demonstrating progressive arterial occlusion with lipid-laden foam cell macrophages (**arrow**) in a patient with transplant coronary artery disease (TCAD). Image courtesy of Michael Fishbein, MD, UCLA Department of Pathology and Laboratory Medicine.

Factors Influencing Progression of TCAD

Donor risk factors that have shown some association with TCAD include older age, male sex, and hypertension, whereas recipient risk factors include male sex, older age, early severe rejection (International Society of Heart and Lung Transplantation grade 3 or greater), as well as increased number of rejection episodes—particularly within the first year after OHT—cytomegalovirus (CMV) infection, insulin resistance, hypertension, hyperlipidemia, and higher body mass index (6,24,28–31). Increasing age might lead to endothelial changes that might predispose to TCAD (32). Recipient smoking has also been shown to accelerate the progression of TCAD (33).

The association between early and increased number of episodes of rejection and the presence of TCAD further supports the underlying immunologic pathology that characterizes TCAD. Studies have noted an incidence of TCAD as high as 40% in OHT patients who had 2 or more episodes of rejection in their lifetimes (34). Patients who were noncompliant with their immunosuppressive medication regimen late after OHT (>1 year after OHT) were found to have an increase in the incidence of TCAD, confirming the role of immunomodulation in controlling the immunologic milieu that contributes to TCAD (35). The total and any rejection score at 6-month follow-up (based on the 2004 International Society of Heart and Lung Transplantation R grading system), evaluated by 3-dimensional IVUS and virtual histology IVUS, were significantly associated with increased risk of TCAD onset and also demonstrated that 6-month total rejection score of >0.3 was associated with shorter time to onset of TCAD, effects that are likely mediated by increased inflammation resulting in increased plaque burden (36).

Glucose intolerance has been associated with the development of TCAD, as measured by hemoglobin A1c levels in post-OHT patients, and a higher degree of glucose intolerance was a powerful predictor of increased severity of TCAD (37).

Hyperlipidemia has also been implicated as a risk factor for TCAD, as evidenced primarily by studies demonstrating increased lipid levels in patients after OHT as well as therapeutic trials examining the effect of statins on patients with TCAD. Lipid levels, primarily total cholesterol and low-density lipoprotein cholesterol levels, increase after OHT (38). Statins seem to have a direct immunomodulatory effect, likely secondary to attenuation of inflammatory infiltrates (39). Control of hyperlipidemia has been conversely associated with regression of plaques characteristic of TCAD (29).

Although donor coronary artery disease might not affect the progression of TCAD, the incidence of TCAD up to 3 years after OHT was higher in recipients with discrete donor lesions compared with recipients without donor lesions (25% vs. 4%, $p < 0.001$), although the 3-year mortality rate was similar between recipients with and those without donor lesions (4.5% vs. 5.2%, $p = 1.0$) (40). Pre-OHT vascular disease might have a negative effect on outcomes but does not seem to affect the development of TCAD (41).

Although the precise mechanism is unclear, there is evidence that CMV causes impaired endothelial function, modulates the inflammatory response in traditional atherosclerotic plaques, and accelerates TCAD by upregulating wound repair and angiogenesis genes (42). Positive recipient CMV status was the only independent predictor of all 3 outcomes measures: coronary artery disease (hazard ratio: 3.6), all-cause mortality (partial hazard ratio: 4.1), and coronary death (hazard ratio: 4.6) (43).

Components of standard therapy after OHT might also influence the development of TCAD. Long-term survivors of OHT (>10 years) who were receiving maintenance steroid therapy had a higher incidence of TCAD compared with those who were not (32.0% vs. 10.3%, $p = 0.03$) (44).

Diagnosis of TCAD

Clinical history is generally unreliable in the diagnosis of TCAD, because of the denervation of the allograft, although pediatric patients have indicated that symptoms such as abdominal, chest, and/or arm pain are strongly associated with the presence of TCAD (45). Because of the inherent variability in clinical diagnosis and possible lack of symptoms, multiple methods of evaluating TCAD have been employed.

The gold standard for diagnosing and monitoring TCAD is coronary angiography. Although angiography is particularly useful for discerning focal lesions, which are commonly seen in native coronary artery disease, TCAD often presents as diffuse concentric disease without discrete stenoses, making angiography a less sensitive modality for diagnosis in these cases (46). The Thrombolysis In Myocardial Infarction (TIMI) frame count and myocardial perfusion grade have provided an objective method of assessing coronary artery blood flow and reperfusion in native coronary atherosclerosis (47). The TIMI frame counts of coronary arteries increase, and TIMI myocardial perfusion grade gradually deteriorates during the first year after OHT, and the mortality rate was significantly higher among patients whose global TIMI frame count increased from baseline (48).

Intravascular ultrasound can evaluate all layers of the vessel wall as well as the lumen, and an intimal thickness of >0.5 mm in a single transplant coronary artery has generally been used to define the presence of TCAD as suggested by the American College of Cardiology Clinical Expert Consensus Document on the standards for acquisition, measurement, and reporting of IVUS studies (49). Lesions can often resemble those of native coronary atherosclerosis, with eccentric plaque formation that tends to occur at branching points. Plaque composition has generally been classified into fibrous, fibrofatty, dense calcium, and necrotic core; and via virtual histology IVUS, data have emerged indicating that inflammatory plaque (increased necrotic core and dense calcium) is associated with early recurrent rejection and higher progression of TCAD (10). IVUS can subsequently confer prognostic information for cardiovascular complications associated with TCAD, as evidenced by findings that severe and rapid increases in intimal thickness, particularly an increase of 0.5 mm or greater within the first year after OHT, are strongly correlated with the future development of angiographic disease up to 5 years after OHT and are also associated with increased mortality, myocardial infarction, and the need for repeat revascularization (50,51) (Fig. 5). Limitations of IVUS include higher cost compared with angiography, lack of general expertise in its use, requirement for concurrent invasive angiography, decreased ability to examine secondary and tertiary vessels because of the larger size of the catheter, and higher risk of complications compared with routine angiography (46). IVUS-derived radiofrequency plaque composition analysis has been shown to give more detailed information about plaque morphology and composition in different stages of TCAD (52).

Cardiac computed tomography (CT) can evaluate wall thickening as well as intimal hyperplasia and might therefore be a useful mode of TCAD evaluation, grading, and monitoring (53). Studies directly comparing CT angiography with invasive coronary angiography with respect to detecting significant stenoses have demonstrated sensitivities of 70% to 86%, specificities of 92% to 99%, positive predictive values of 81% to 89%, and negative predictive values of 77% to 99%, with good to excellent image quality and moderate to excellent test characteristics for detecting TCAD (54,55). In a study that analyzed the ability of dual source CT to detect TCAD compared with IVUS as a standard, the sensitivity, specificity, and positive and negative predictive values for the detection of TCAD by dual source CT were 85%, 84%, 76%, and 91%, respectively (56). CT angiography requires the use of contrast and thus has limited utility in patients with renal insufficiency, which is a common comorbidity among OHT patients (57).

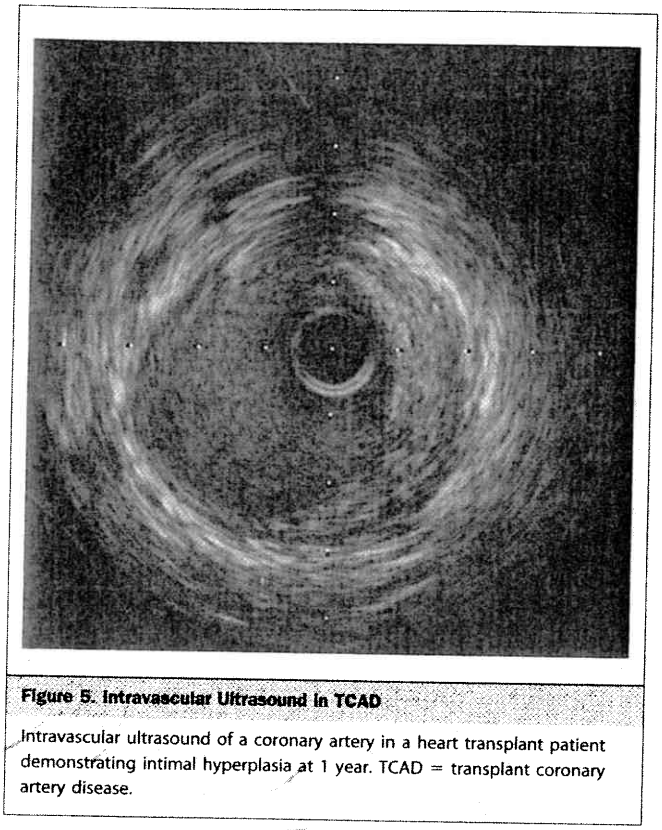

Figure 5. Intravascular Ultrasound in TCAD

Intravascular ultrasound of a coronary artery in a heart transplant patient demonstrating intimal hyperplasia at 1 year. TCAD = transplant coronary artery disease.

Nuclear imaging, particularly when coupled with exercise testing, provides a high specificity for diagnosing TCAD and increased sensitivity as the burden of TCAD increases (58). Myocardial contrast echocardiography can adequately detect the presence of TCAD but was unable to identify the extent of disease compared with angiography (59).

Various serum markers and acute phase reactants, which include high-sensitivity C-reactive protein and serum amyloid A protein (61,62), have been evaluated as indicators of the presence and progression of TCAD. The levels of soluble intercellular adhesion molecule-1 were significantly higher in pediatric OHT patients who had TCAD compared with those without evidence of TCAD on angiography ($p < 0.005$), and plasma soluble intercellular adhesion molecule-1 levels above 1,500 ng/ml were indicative of the

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presence of TCAD (odds ratio: 2.7; 95% confidence interval: 1.34 to 5.56, p = 0.022) (62). Higher brain natriuretic peptide levels, particularly above 250 pg/ml, in patients who are farther out from OHT have also been associated with allograft dysfunction and TCAD and independently predict cardiovascular death (63).

Treatment of TCAD

Conventional coronary artery disease risk-factor modification. Angiotensin-converting enzyme inhibitors after OHT have been associated with regression of TCAD plaques (29). This effect might be mediated by angiotensin-converting enzyme inhibition of the upregulation of angiogenic mediators such as vascular endothelial growth factor and platelet-activating factor in the post-OHT period, both of which directly stimulate angiogenesis and thus indirectly promote TCAD (64). Angiotensin receptor blockers have shown similar results in murine models, with reduction in the numbers of peripheral mononuclear cells that differentiate into smooth muscle-like cells, which are critical components of the cellular environment that promotes TCAD (65). Angiotensin II promotes cellular growth, apoptosis, fibrosis, inflammation, and extracellular matrix remodeling and therefore might play an important direct and immunomodulatory role in TCAD, evidenced by the fact that increased synthesis of angiotensin II receptors correlates with increased risk of TCAD in OHT patients (66).

Statins improved outcomes after OHT as well as reduced incidence and progression of plaques observed in TCAD (67). Statins have immunomodulatory effects that are independent of their cholesterol-lowering properties, which might partly explain their effectiveness in inhibiting the development of TCAD (68).

Immunosuppressive therapies. The traditional immunosuppressive regimen in the post-OHT period has consisted of calcineurin inhibitors (CNIs) like cyclosporine or tacrolimus combined with mycophenolate mofetil (MMF) or azathioprine and glucocorticoids. Higher doses and longer duration of cyclosporine treatment correlated with markedly reduced macrophage and helper T-cell infiltration, preventing the formation of TCAD in a dose-dependent manner (69,70). However, cyclosporine leads to endothelial dysfunction by decreasing nitric oxide levels, inhibiting nitric oxide synthase activity, inhibiting local prostacyclin synthesis, increasing production of thromboxane A2, increasing the release of endothelin-1 from endothelial cells, and increasing the expression of endothelin-1 receptors (71–76). The CNIs are nephrotoxic, which often limits their use after OHT. Further evaluation is needed to better delineate the risks and benefits of CNIs in TCAD and the optimal doses.

Mycophenolate mofetil inhibits inositol monophosphate dehydrogenase, reduces antibody production, inhibits proliferation of SMCs and fibroblasts, and reduces Epstein-Barr virus stimulation, which might reduce development of lymphoma after OHT (77). Compared with azathioprine, MMF significantly improves long-term mortality in OHT patients from all causes, including TCAD, and reduces the need for repeat OHT, the number and severity of rejection episodes, and the development and progression of TCAD (78,79). Mycophenolate mofetil remains an important component of the immunosuppressive regimen, given its beneficial effects and lack of significant nephrotoxicity.

Proliferation signal inhibitors, namely sirolimus and its derivative everolimus, are increasingly playing an important role in the treatment and prevention of TCAD. Sirolimus has been used as a substitute for CNIs as a way of averting nephrotoxicity. It inhibits activated T-cell proliferation and migration in response to alloantigens, regulates the proliferation and migration of vascular SMCs, increases production of nitric oxide, and inhibits the accumulation of extracellular matrix and fibrotic tissue (80–82). A randomized trial comparing sirolimus with azathioprine in combination with cyclosporine and steroids reported a lower incidence of rejection and less luminal narrowing in patients treated with sirolimus, without a concomitant increase in the rate of diabetes or malignancy (83). Potential side effects include hyperlipidemia, abdominal pain, neutropenia, anemia, oral ulcers, pericardial effusion, and interstitial lung disease (84). Sirolimus inhibits coronary artery SMC proliferation as measured by a decrease in deoxyribonucleic acid synthesis as well as improved coronary artery physiology involving both the epicardial and microvasculature (85). Although proliferation signal inhibitors have previously been used as secondary immunosuppressive agents in place of azathioprine or MMF, sirolimus might be used as a primary immunosuppressant in lieu of CNIs, because sirolimus attenuated the progression of TCAD with no exacerbation in renal dysfunction (86). Furthermore, baseline renal function improved significantly after 1-year follow-up in patients in the sirolimus group. Sirolimus is associated with less coronary epicardial endothelial dysfunction compared with cyclosporine, an effect that is likely mediated by increased prostacyclin production, increased vasomotor relaxation, and decreased oxidative injury compared with cyclosporine (87). The use of sirolimus in the early post-OHT period might be limited, due to the negative impact of sirolimus on wound healing (88).

Revascularization. Percutaneous coronary intervention (PCI) has been increasingly used as a therapeutic option for TCAD with high initial success rates (Table 1, Figs. 6A and 6B). Although the pattern of TCAD is generally typified by diffuse concentric intimal thickening, lesions that are proximal and discrete might be appropriate targets for PCI (89). Balloon angioplasty is associated with poor clinical results (89–91). Stenting reduced early and mid-term restenosis compared with balloon angioplasty but did not impact graft survival (92). Factors that have been shown to diminish

Table 1. Selection of Studies on the Use of PCI for TCAD in Cardiac Transplant Recipients

First Author (Ref. #)	No. of Patients/ No. of Stented Lesions	Procedural Success Rate (<50% residual stenosis)	Mean, Median, or Stated Follow-Up Time	Patients With Adverse Clinical Outcome During Follow-Up	Restenosis Rates of BMS and DES or Freedom From Restenosis Rates	Notes
Bader et al. (28)	40/78 (65 BMS, 13 DES)	91%	40.8 ± 34.5 months	8 (20%): 6 deaths, 2 repeat OHT	31% vs. 15% (p = 0.27)	
Simpson et al. (90)	33/34 (97 PCI, 63 balloon angioplasty alone)	99%	6 months, 12 months, and 5 yrs	39.3% died or retransplanted after mean 1.9 ± 2.3 yrs after first PCI	BMS vs. balloon angioplasty: 6 months: 31% vs. 41%, 12 months: 46% vs. 53%, 5 yrs: 69% vs. 68%	
Benza et al. (91)	62/219 lesions	97%	Angiographic follow-up at 3–6 months, then annually	Repeat PCI rate 34%, PCI related death rate 2.6%	Freedom from restenosis: 95% at 1 month, 81% at 3 months, 57% at 6 months	2-yr freedom from TCAD or graft loss was 74% with 1-vessel disease at time of first PCI, 75% for 2-vessel, and 27% for 3-vessel
Wellnhofer et al. (92)	160 patients (227 BMS, 66 DES, 209 balloon angioplasty alone)	97%	Clinical: 9.9 ± 4.4 yrs Angiographic: 28 ± 30 months	—	38% restenosis rate	
Lee et al. (96)	82 patients, 158 PCI (98 BMS, 80 DES)	100%	Angiographic only: 70% of BMS lesions at 9.5 ± 5.5 months, 76% of DES lesions at 12.6 ± 8.2 months	20% with adverse outcome	Binary restenosis rate: 30% BMS vs. 12% DES (p = 0.02)	No angiographic stent thrombosis observed with DES
Zakliczynski et al. (97)	13 patients with 24 BMS, 17 patients with 28 DES, 7 patients with both BMS and DES	—	20 months for BMS, 14 months for DES	3 deaths (18%) among DES, 4 (31%) with BMS, and 1 (14%) with DES and BMS (p = NS)	DES: 7%, BMS: 58%	Longer time of freedom from ISR after PCI with DES (p = 0.022). No angiographic stent thrombosis observed with DES

BMS = bare metal stents; DES = drug-eluting stents; ISR = in-stent restenosis; PCI = percutaneous coronary intervention; TCAD = transplant coronary artery disease.

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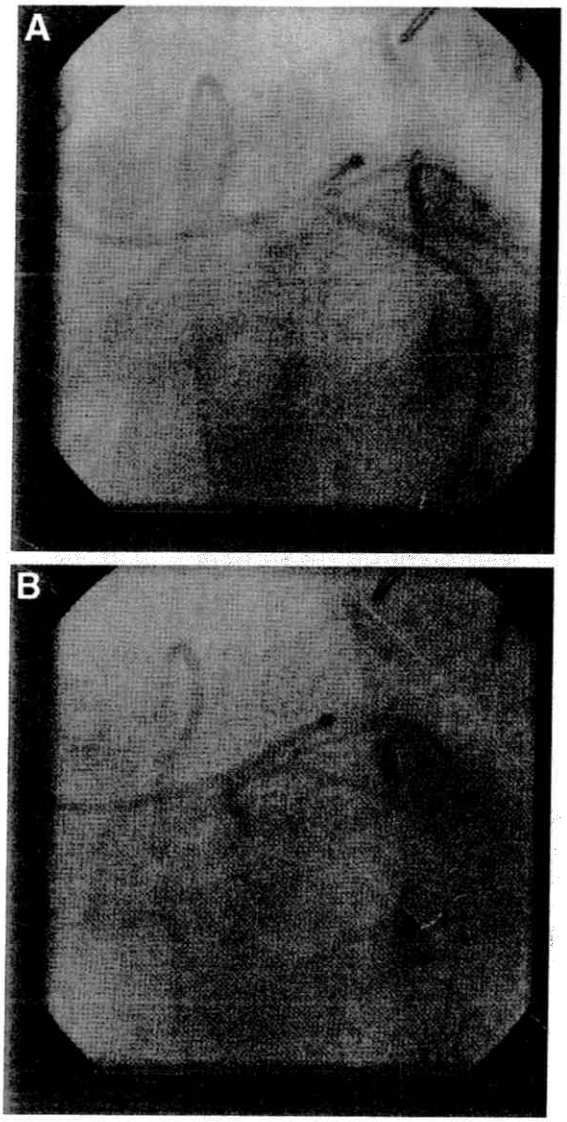

Figure 6. Severe Left Main Disease and Stenting in TCAD

(A) Severe left main disease in transplant coronary artery disease (TCAD). Coronary angiography of a heart transplant recipient with TCAD with a significant stenosis **(arrow)** at the distal bifurcation of the left main coronary artery. **(B)** Left main stenting in TCAD. Coronary angiography after percutaneous coronary intervention with 2 drug-eluting stents deployed in the distal bifurcation of the left main coronary artery showing excellent angiographic results. Repeat angiography in this patient at 1 year demonstrated severe in-stent restenosis at the ostium of the left circumflex artery that was treated with repeat percutaneous coronary intervention with drug-eluting stent placement, with good angiographic results and no evidence of significant restenosis at 2-year angiographic follow-up.

recurrent stenosis and improve graft survival in OHT patients requiring PCI include the use of stents, higher antiproliferative immunosuppressant dosing, early reduction of steroid dosing, the use of MMF, and the use of statins (91,92). Nevertheless, stenting in TCAD patients is associated with a higher rate of in-stent restenosis compared with stenting in native coronary arteries. This is due to the unique lymphoproliferative inflammatory response that characterizes TCAD, which contrasts with the typical atherosclerotic process of plaque formation in native coronary vessels and predisposes to restenosis (93). This is evidenced by the finding that lumen loss and histological staining of biopsies in stented TCAD lesions correlates closely with lumen loss and staining findings in nonstented lesions, whereas in native atherosclerosis, in-stent restenosis and remote disease progression are generally not correlated (93). Furthermore, TCAD is a diffuse process with a tendency toward progression of disease in nonstented areas of the artery, and the presentation of a focal lesion is generally a marker of diffuse disease. Stenting significantly reduced early and mid-term restenosis but did not affect late restenosis, emphasizing the diffuse and progressive nature of TCAD (90). The inflammatory environment and the degree of endothelial cell activation before PCI also influence the response to stenting, because high baseline levels of inflammatory markers such as monocyte chemoattractant protein-1 and von Willebrand factor have been associated with restenosis in TCAD patients (94). The rate of restenosis after PCI was also associated with the frequency of major histocompatibility complex class 1 immunoglobulin antibody (95). Drug-eluting stents decrease the rate of in-stent restenosis and target vessel revascularization compared with bare-metal stents (96,97).

Surgical revascularization might be a viable treatment option in appropriate patients. Although coronary artery bypass grafting is uncommonly performed for the treatment of TCAD because of its diffuse nature, OHT patients who underwent bypass surgery had a 92% and 83% survival at 1 and 7 years, respectively (98).

Although the only definitive therapy for TCAD is repeat OHT, it is associated with increased mortality compared with primary OHT patients at long-term follow-up (99).

Conclusions and Recommendations

Transplant coronary artery disease is a complex disorder and remains a significant cause of morbidity and mortality in OHT patients. We recommend annual angiography for 5 years after OHT—after which time, if there are no significant abnormalities, angiograms can be performed biannually. Findings consistent with TCAD should prompt reversion to annual catheterization or more frequent angiography depending on severity of disease. Intravascular ultrasound is an important adjunct in the diagnosis of TCAD in the more immediate post-transplant period and is routinely performed 4 to 6 weeks after OHT at our institution and subsequently at 1 year but is not employed thereafter, largely because the findings on IVUS have generally not affected the timing of coronary angiography. Treatment options range from pharmacotherapy to percutaneous and surgical

revascularization to repeat OHT. Progression of TCAD should prompt reconsideration of the patient's immunosuppressive regimen, with addition or titration of agents, including cyclosporine, tacrolimus, sirolimus, or steroids as able in light of the patient's existing comorbidities. The presence of diffuse, severe disease that has been unresponsive to pharmacotherapy and that is not amenable to PCI merits evaluation for possible repeat OHT. Prospective randomized trials comparing different pharmacotherapies as well as revascularization strategies are needed to identify the optimal therapy for patients who develop TCAD.

Reprint requests and correspondence: Dr. Michael S. Lee, UCLA Medical Center, Adult Cardiac Catheterization Laboratory, 10833 Le Conte Avenue, Room A2-237 CHS, Los Angeles, California 90095-171715. E-mail: mslee@mednet.ucla.edu.

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Key Words: drug-eluting stent ■ heart transplantation.