

Accelerated Coronary Vascular Disease in the Heart Transplant Patient: Coronary Arteriographic Findings

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Annual coronary arteriograms have been obtained from all heart transplant recipients at Stanford University Medical Center since 1969. Angiographic lesions in 81 transplant patients exhibiting coronary vascular disease were classified into three categories: type A, discrete or tubular stenoses; type B, diffuse concentric narrowing; and type C, narrowed irregular vessels with occluded branches. The 81 arteriograms showing transplant coronary vascular disease were contrasted with 32 from nontransplant patients with coronary artery disease analyzed in a similar fashion.

The nontransplant angiograms showed 178 lesions, all of type A (discrete or tubular) morphology, 75% of which were located in primary epicardial coronary vessels and 25% in secondary branch vessels. In the patients with transplant coronary vascular disease, 349 (76%) of 461 lesions were type A: 57% in primary vessels, 42% in secondary branches and 1.4% in tertiary branches. Of the

112 type B and C lesions (diffuse narrowing, tapering and obliteration), 25% were in primary vessels, 44% in secondary vessels and 31% in tertiary branches ($p < 0.05$ for patients with transplant coronary vascular disease versus patients with nontransplant coronary artery disease). Total vessel occlusion was found in proximal or middle vessel segments in 96% and distally in 4% of patients with "ordinary" coronary artery disease versus 49% distally in patients with transplant coronary disease ($p < 0.002$). In the presence of total vessel occlusion, collateral vessels were poor or absent in 92% of transplant versus 7% of nontransplant patients with coronary disease ($p < 0.002$).

Therefore, coronary artery disease in transplant patients represents a mixture of typical atheromatous lesions and unique transplant-related progressive distal obliterative disease that occurs without collateral vessel development.

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Four hundred heart transplant procedures and 30 heart and lung transplant procedures were performed in 368 and 29 patients, respectively, at Stanford University Medical Center from January 6, 1968 to December 31, 1985. One year survival rates for heart transplant recipients increased from 22% in 1969 (1) to 83.4% in 1985. Early mortality, which generally results from acute rejection, acute donor heart failure or infectious complications, has decreased substantially. Later stage complications, particularly accelerated coronary vascular disease, have become major causes of late morbidity and mortality (2-4). Because lack of afferent

cardiac innervation makes transplant recipients unable to experience angina pectoris, the first sign of transplant coronary disease can be the appearance of silent myocardial infarction on the electrocardiogram, development of congestive heart failure or ventricular arrhythmia leading to sudden death. Because the disease can be clinically silent and can progress rapidly in many cases, annual coronary arteriograms have been performed as a matter of policy in all heart transplant patients at Stanford. A total of 634 of these sequential coronary arteriograms were available for analysis.

The purposes of this study are 1) to evaluate the prevalence of accelerated coronary vascular disease in the cardiac allograft, and 2) to study the characteristic angiographic features of this process and delineate its differences from "ordinary" (nontransplant) coronary angiographic lesions.

Methods

Study patients. The patient data base for this study consisted of 221 heart transplant patients (including 13 heart and

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lung transplant patients) and 32 nontransplant patients with coronary artery disease diagnosed by standard clinical and angiographic criteria.

The transplant recipients were classified into two groups: The first group consisted of 132 patients (including 13 heart and lung transplant recipients) who underwent heart transplantation after 1979, survived at least 1 year and had annual follow-up arteriography for 1 to 5 years (mean 2.4). The second group consisted of 37 patients who had transplant procedures before 1979, survived at least 1 year and had annual coronary angiography for a mean of 5.3 years during which development of coronary vascular disease was documented. An additional 52 heart transplant patients operated on before 1979 who survived at least 1 year without known development of coronary disease were excluded because many of their early arteriograms were not available for comparison with later studies.

A third group consisted of 32 nontransplant patients with clinically stable, medically treated coronary artery disease who were participating in a separate research protocol and who had both baseline arteriograms and repeat studies performed 5 years later.

Cardiac catheterization. All patients were evaluated with left and right heart catheterization and selective coronary arteriography using the percutaneous femoral approach. Left ventricular cineangiography was performed in all patients. Cardiac output was determined by the Fick method. The procedures for cardiac catheterization were explained to all patients and informed consent was obtained under Stanford Institutional Review Board guidelines.

Coronary arteriography. On the basis of a pilot project reviewing serial arteriograms in 15 transplant hearts with coronary disease, a list of descriptors for various coronary morphologic abnormalities and collateral vessel qualities was developed. These descriptors were used in interpreting the arteriograms of both transplant and nontransplant patients with coronary diseases. The angiographic findings were reviewed by two angiographers independently, and a consensus on interpretation was reached. All arteriographic interpretations were based on side by side comparisons of serial films.

The following anatomic abnormalities were coded (Fig. 1): Type A, discrete stenosis, tubular stenosis and multiple stenoses in the proximal, middle or distal segment branches; type B, diffuse concentric narrowing with onset in mid to distal artery; type B₁, proximal vessel maintaining normal diameter with abrupt onset of distal concentric narrowing and obliteration; type B₂, gradual transition from normal proximal vessel with tapering concentric narrowing gradually increasing in severity distally; and type C, diseased vessels, diffusely irregular, that have lost small branches; they do not taper normally but exhibit terminations that are often nontapered, squared off and end abruptly.

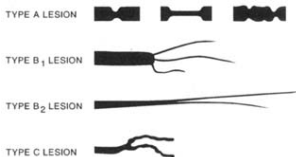


Figure 1. Anatomic abnormalities in transplant coronary vascular disease. Type A lesion: discrete, tubular or multiple stenoses. Type B₁ lesion: abrupt onset with distal diffuse concentric narrowing and obliterated vessels. Type B₂ lesion: gradual, concentric tapering with distal portion having some residual lumen. Type C lesion: narrowed irregular distal branches with terminations that are often nontapered and squared off, ending abruptly.

Definition of arterial vessels. These anatomic abnormalities were identified as being in primary, secondary or tertiary vessels.

Primary vessels. These are the large epicardial vessels, including the left main, left anterior descending, left circumflex and right coronary arteries.

Secondary vessels. These are the major branch vessels of the primary epicardial coronary vessels. The major diagonal, marginal, posterior descending and posterolateral branches constitute the secondary branches.

Tertiary vessels. These are angiographically visible small branches of both primary and secondary vessels. They are larger in diameter than the fine arteriolar or capillary network, but are short in length and subtend relatively small areas of myocardium.

Both primary and secondary vessels are of sufficient length to divide into proximal, middle and distal segments. Segmentation for primary vessels was based on nomenclature used in the Coronary Artery Surgery Study (5); that for secondary vessels was based on equal subdivisions.

Criteria for collateral vessel quality. *Good:* The collateral channels are discrete and visible. Collateralized vessels are visualized so that walls and lesions can be identified. *Fair:* The proximal or distal segments of collateralized vessels are filled, but not enough to visual anatomic detail. *Poor:* The collateralized vessels are faintly filled. *None:* There is no visualization of the main trunk of occluded vessel other than scattered tiny disconnected faint twigs.

Statistical Analysis. All data are presented as mean \pm 1 SD. Comparisons among groups were analyzed with the two-sample Student's *t* test for differences in proportion and means, respectively. The chi-square test was used to assess intergroup differences in distribution of lesions, quality of collateral supply and incidence of transplant coronary disease. A difference of $p < 0.05$ was considered statistically significant.

Table 1. Incidence of Coronary Vascular Disease in 221 Heart Transplant Recipients

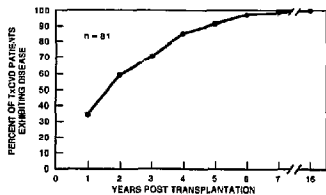
Year of Transplant Procedure	No. of Patients	Angiographic Follow-up (mean years)	Incidence
1968 to 1978			
TxCVD	37		37 of 89
No TxCVD	52		
Total	89	5.3	(41.5%)
1979 to 1984			
TxCVD	44		44 of 132
No TxCVD	88		
Total	132	2.4	(33%)

TxCVD = transplant coronary vascular disease.

Results

Prevalence of transplant coronary vascular disease (Table 1). Forty-four (33%) of 132 heart transplant patients operated on after 1979 showed angiographic evidence of transplant coronary disease. In patients operated on before 1979, 37 (41.5%) of 89 had documented coronary artery lesions. The prevalence of coronary disease was higher in the available patients in the pre-1979 group than in patients in the post-1979 group ($p > 0.05$); this difference is at least in part explained by the longer follow-up period for the early group.

Arteriographic findings of transplant coronary vascular disease. For morphologic analysis, the 37 pre-1979 transplant patients with angiographic coronary vascular disease were included with the 44 post-1979 transplant patients who also exhibited coronary disease. To demonstrate time of initial detection of coronary disease in these 81 transplant recipients, cumulative occurrence rates for transplant coronary disease in relation to time after surgery are shown in Figure 2. Definite angiographic coronary disease was de-

**Figure 2.** Timing of initial detection of cardiac transplant-accelerated coronary vascular disease (TxCVD) in 81 transplant patients.

ected in 34.5% of these 81 patients in the first year, 59% the second year and 91% 5 years after transplantation. Examples of these typical morphologic features and their progression are shown in Figures 3 through 7.

Analysis of the distribution of lesions revealed a significant difference between transplant and nontransplant patients (Table 2). In patients with transplant coronary vascular disease, most of the concentric and distal obliterative lesions of types B₁, B₂ and C appeared in the secondary vessels (type B₁, 27 [24%]; type B₂, 10 [9%]; type C, 12 [11%]) and tertiary vessels (type B₁, 1 [0.8%]; type B₂, 2 [2%]; type C, 32 [28.5%]). In contrast, no type B₁, B₂ or C lesions were seen in the nontransplant coronary artery disease group. Sixty patients (74%) with transplant coronary disease showed some type A lesions in primary branch vessels. In comparison, type A lesions appeared in primary branch vessels of all nontransplant patients with coronary artery disease. Table 3 summarizes the distribution of the concentric tapering and obliterative type B₁, B₂ and C lesions that have a clear association with transplant coronary disease.

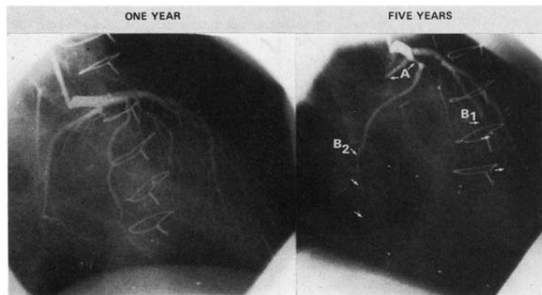
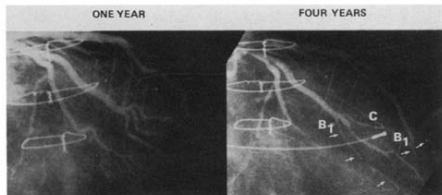
**Figure 3.** Right anterior oblique view of left coronary artery injection showing essentially normal left coronary anatomy 1 year after cardiac transplantation (left). Five years after transplantation (right), the arteriogram shows a totally occluded left circumflex artery and a discrete lesion in the obtuse marginal artery (type A lesions), a type B₁ lesion in the diagonal branch and a type B₂ lesion in the obtuse marginal branch.

Figure 4. Left coronary artery arteriogram shows essentially normal anatomy 1 year after cardiac transplantation (left). Four years after transplantation (right), the arteriogram shows a B₁ lesion in the distal left anterior descending coronary artery and both B₁ and C lesions in the distal branches of the obtuse marginal artery (arrows).



Comparison of the site of total occlusion of vessels and the quality of collateral vessel formation also revealed striking differences between the two groups (Table 4). In transplant patients, 16 (43%) of 37 vessels were occluded proximally and 18 (49%) of 37 vessels were occluded in their distal segments. In the nontransplant patients with coronary artery disease, 21 (72%) of 29 vessels had occluded in the proximal segment and only 1 (3.5%) of 29 vessels had occluded distally.

Collateral vessel formation was very poor in transplant patients (Table 5). Collateral vessels to occluded vessels could not be seen at all in 29 (78%) of the 37 arteries, and 5 (14%) of the 37 occluded vessels had only faintly filled collateralized vessels. In contrast, in the nontransplant group with coronary artery disease, 22 (76%) of 29 occluded vessels had good collateral vessels and 5 (17%) of 29 occluded vessels had fair collateral vessels. In no instance were collateral vessels absent.

Discussion

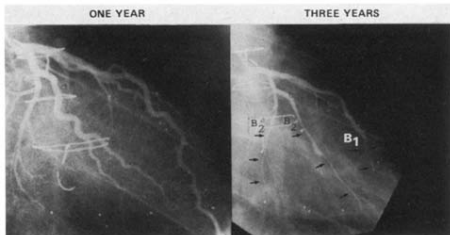
Prevalence of coronary vascular disease. A very diffuse and often rapidly progressive type of occlusive coronary vascular disease has been found to affect a substantial number of cardiac allograft recipients in the late postoperative period. As survival after cardiac transplantation improves because of increasingly successful management of

allograft rejection and infectious complications, accelerated coronary vascular disease or allograft atherosclerosis may constitute the major limitation to long-term survival for heart transplant recipients (6).

The incidence of angiographic coronary vascular disease in heart transplant recipients was first reported by the Stanford group in 1981 (2) to be approximately 40% (21 of 85 patients) at 5 years after transplantation. More recent data from our group (7) suggest that this incidence has not changed since the introduction of cyclosporine-based immunosuppression in 1980. The more exhaustive review reported here confirms the previously described high incidence of the disease. It is worthwhile to note here that these prevalence figures denote only the angiographic documentation of some disease but not its severity or the existence of clinical sequelae. Many of these patients have apparently mild disease with as yet no detectable clinical sequelae.

Arteriographic findings. Analysis of coronary arteriograms of affected cardiac allografts presented here reveals unique morphologic features of this disease consisting of diffuse concentric narrowing, prominent in middle to distal vessels, with distal vessel obliteration. The vessels narrow distally in one of three ways: 1) gradual transition from normal proximal vessel with smooth concentric tapering, the distal vessel having some residual lumen (type B₂); 2) abrupt narrowing with concentrically narrowed and obliterated distal vessel (termed "pruning"), with only faintly visualized

Figure 5. Left coronary artery arteriogram shows essentially normal anatomy 1 year after cardiac transplantation (left). Three years after transplantation (right), the arteriogram shows type B₂ lesions in the left circumflex and marginal coronary arteries and a type B₁ lesion in the distal anterior descending coronary artery.



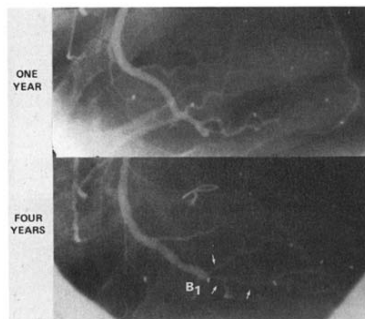


Figure 6. The left coronary artery arteriogram shows essentially normal anatomy 1 year after cardiac transplantation (top). Four years after transplantation (bottom), the arteriogram shows type B₁ lesions in the obtuse marginal branch.

channels remaining (type B₁); and 3) narrowed irregular distal branches with loss of small branches (type C). These type C vessels often contain some ectatic areas following areas of narrowing; their terminations are often nontapered and squared off and end abruptly. In terminal branch coronary vessel segments, type C lesions predominate, whereas in conduit coronary segments, type A lesions predominate. There is a striking lack of development of collateral blood supply to affected vessels, with supply graded as poor or absent in 92% of the totally occluded vessels in 20 transplant patients with coronary diseases.

These unique morphologic findings in arteriograms of transplant coronary disease differ greatly from arteriogram-

Table 2. Comparison of Different Types of Lesions in Primary, Secondary and Tertiary Branch Vessels of Coronary Arteries in 81 Transplant Patients Versus 32 Nontransplant Patients With Coronary Disease

Lesion Type	No. of Lesions		p Value
	TxCVD (81 patients)	CAD (32 patients)	
Primary Vessels			
A	198	133	<0.001
B ₁	17	0	<0.05
B ₂	11	0	NS
C	0	0	NS
Secondary Vessels			
A	146	44	NS
B ₁	27	0	<0.05
B ₂	10	0	NS
C	12	0	NS
Tertiary Vessels			
A	5	1	NS
B ₁	1	0	NS
B ₂	2	0	NS
C	32	0	<0.05

Lesion type: A = discrete stenosis; B₁ = concentric-sharp taper, B₂ = concentric-gradual taper, C = distal obliteration. CAD = nontransplant coronary artery disease; NS = not significant; TxCVD = transplant coronary vascular disease.

mic features in typical nontransplant patients with coronary artery disease. However, a number of typical proximal discrete stenoses similar to those in nontransplant patients were also noted. Thus, angiographic findings in transplant coronary vascular disease are a mixture of both typical atherosclerotic lesions and unusual, presumably transplantation-related, progressive diffuse distal obliterative disease without collateral vessel development.

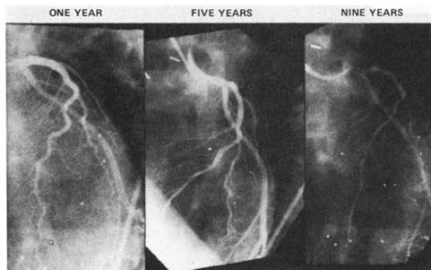


Figure 7. The left coronary artery arteriogram shows essentially normal anatomy 1 year after cardiac transplantation (left). Five years after transplantation (middle), the arteriogram shows smooth concentric narrowing in the mid to distal left anterior descending coronary artery and a tubular stenosis after takeoff of the second diagonal branch. Nine years after transplantation (right), the arteriogram shows a diffusely diseased left anterior descending coronary artery.

Table 3. Comparison of Type A Lesions and Other Types of Lesions in 81 Transplant Patients Versus 32 Nontransplant Patients With Coronary Disease

Group	No. of Patients	Total Lesions	p Value
Type A lesion			
TxCVD	81	349	NS
CAD	32	178	
Type B ₁ + B ₂ + C lesions			
TxCVD	81	112	<0.001
CAD	32	0	

Abbreviations as in Table 2.

Morphologic changes. The angiographic features of transplant coronary disease described here can be related to histopathologic changes described in explanted allografts or allografts examined at autopsy (8-10). The histopathologic changes of atherosclerosis in human cardiac allograft recipients were first described in autopsy findings from 12 patients. These changes consisted of a circumferential and longitudinal increase in intimal fibrous tissue and myointimal cells limited to coronary arteries with muscular media and not present in arterioles and veins. The thickness of the intima was roughly proportional to the age of the graft, with some thickening developing as early as 9 days; thickening was present in six of seven allografts from patients surviving >1 month. Of note, purely proliferative intimal lesions were seen in grafts studied early after implantation, and large numbers of lipophages and lipid droplets appeared in grafts studied later (9,11). Atherosclerotic lesions in major coronary arteries of patients who die from transplant coronary vascular disease are histopathologically similar in composition to those occurring in nontransplant coronary artery disease (8) but differ in their diffuse distribution, correlating well with the arteriographic features of transplant coronary disease we have described.

Follow-up and therapy. Because of the longitudinal and concentric distribution of transplant coronary vascular disease, it is important to compare serial angiograms to detect a general decrease in caliber of vessels, "dropout" of

Table 4. Comparison of Site of Occlusive Coronary Disease in 20 Transplant Patients Versus 16 Nontransplant Patients in Serial Angiographic Studies

Group	No. of Patients	No. of Occluded Vessels	Site of Vessel Occlusion			p Value
			Proximal	Middle	Distal	
TxCVD	20	37	16 (43%)	3 (8%)	18 (48%)	0.0002
CAD	16	29	21 (72%)	7 (24%)	1 (3.5%)	

Abbreviations as in Table 2.

Table 5. Comparison of the Quality of Collateral Supply in Serial Angiographic Studies of 20 Transplant Patients Versus 16 Nontransplant Patients With Coronary Disease

	No. of Patients	No. of Occluded Vessels	Quality of Collateral Supply				p Value
			Good	Fair	Poor	None	
TxCVD	20	37	1 (3%)	2 (5%)	5 (14%)	29 (78%)	0.0002
CAD	16	29	22 (76%)	5 (17%)	2 (7%)	0 (0%)	

Abbreviations as in Table 2.

branches or distal "pruning" of vessels. Precise quantitation of progressive concentric narrowing may be done by serial quantitative arteriography, and prospective studies with this technique are underway at our institution. The Stanford group initially decided to perform angiograms in this patient group at 1 year intervals. Because of the abrupt occurrence of severe coronary disease within a single year in a number of these patients, this interval has never been increased. The diffuse distribution and rapid progression of transplant coronary disease makes these patients poor candidates for conventional therapy with angioplasty or coronary artery bypass graft surgery. Elective retransplantation, currently the only recognized treatment for severe stages of transplant coronary disease, is offered to patients believed to be at high risk of death from this disease.

Pathogenesis of transplant coronary vascular disease. Despite many investigations (12,13), the pathogenesis of transplant coronary disease remains undetermined, although some type of vascular immunologic injury is presumed by most to be involved. The lesions of experimental cardiac allograft atherosclerosis were first described at the microscopic level (14) in material from canine cardiac allografts; that study also noted a time-related occurrence of coronary intimal thickening, not correlated with acute allograft rejection, which was present in almost all the large coronary arteries in dogs surviving >1 year. Other investigators have demonstrated the induction of occlusive allograft coronary vascular disease in rat (13,15) and rabbit (16) models. Relating these observations to the histopathologic change in human allograft atherosclerosis has led to the assumption that initial proliferative intimal lesions eventually become infiltrated with lipid and, subsequently, fibrous scoring additionally leads to the nonspecific appearance of ordinary atherosclerotic disease. Accelerated vascular disease has been observed in other organ grafts (17,18). Histopathologic changes described in the arteries of renal grafts include fibroproliferative lesions in the intima, necrosis of the media and degeneration of smooth muscle cells. The arterial intima is thickened by myofibroblast proliferation, which can lead to severe narrowing or even occlusion of the arterial lumen and can result in renal infarctions (19,20). These arterial

changes are similar to the intimal proliferative lesions noted in transplant patients with coronary disease (8).

The extent to which immunologic injury or steroid use contributes to transplant coronary vascular disease is uncertain. Coronary atherosclerosis and myocardial infarction associated with systemic lupus erythematosus in young adults have been reported (21,22). Thirty-six patients with systemic lupus erythematosus who had received long-term corticosteroid treatment and 20 patients who did not were compared in one study. Twenty (56%) of the 36 corticosteroid-treated patients showed intramural coronary artery narrowing. These vessels were narrowed by fibrous intimal proliferation and sometimes the endothelial cells were degenerated. The walls of these vessels were occasionally necrotic. Extramural coronary artery narrowing by >50% was noted in 9 (25%) of 36 patients. Atherosclerotic plaques blocked these vessels (23).

High levels of serum lipids are known to correlate with increased incidence of ordinary coronary artery disease and could be contributing factors in the pathogenesis of transplant coronary vascular disease. Elevated levels of serum triglyceride have been noted in patients with transplant coronary disease (1,6,24), but elevated cholesterol levels have not, and the incidence of coronary disease has shown surprisingly little correlation with lipid levels in transplant recipients.

It seems likely that immunologic injury is the primary mechanism of this disease, although proof or correlation with incidence of rejection episodes is lacking. Immunologically induced injury to the coronary artery intima theoretically could lead to platelet aggregation and intimal thickening and eventually to obliterative arterial disease. Thus the development of new immunosuppressive modalities that more effectively and selectively control the immune response may be necessary to decrease the incidence of this disease.

Conclusions. 1) Coronary vascular disease is a frequent late postoperative complication in heart transplant recipients. 2) Cardiac transplant accelerated coronary vascular disease is a mixture of typical proximal atherosclerotic lesions and unusual diffuse obliterative disease, characterized by concentric and longitudinal narrowing with distal pruning, vessel obliteration and absence of collateral vessels. 3) Accurate detection of progressive concentric narrowing and distal vessel obliteration necessitates side by side comparison of serial angiograms.

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