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Early Development of Accelerated Graft Coronary Artery Disease: Risk Factors and Course

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Objectives. **This study assessed the time of first appearance of angiographic graft coronary artery disease in relation to clinical and laboratory variables and clinical events in heart transplant recipients.**

Background. **Graft coronary artery disease is the main factor limiting long-term survival after heart transplantation, and it is important to understand its natural history.**

Methods. **One hundred thirty-nine consecutive patients who developed angiographic coronary artery disease after heart transplantation were classified according to early (≤2 years) versus late (>2 years) posttransplantation initial detection of coronary artery disease. These subgroups were analyzed for differences in clinical and laboratory demographics, incidence of progression to ischemic events and incidence of antecedent cytomegalovirus infection.**

Results. **The early-onset group (64 patients) had more rapid progression to ischemic events than the late-onset group (75 patients), with 59% of the late group and only 35% of the early group free from ischemic events by 5 years after initial detection ($p = 0.02$), but there were no significantly correlated clinical or laboratory predictors of ischemic events. The early group had a significantly higher incidence of antecedent cytomegalovirus infection.**

Conclusions. **We conclude that 1) accelerated graft coronary artery disease develops at variable times after heart transplantation; 2) the early appearance of graft coronary artery disease may be a marker of intrinsically more aggressive disease; 3) cytomegalovirus infection is associated with earlier onset of graft coronary artery disease. Patients with early development of graft coronary artery disease should potentially be given priority for interventional strategies as they are developed.**

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The occurrence of a diffuse form of coronary intimal thickening in many patients with cardiac allografts has come to be a well recognized phenomenon. It is generally agreed that the ischemic sequelae of this process are the main complications limiting long-term survival in cardiac allograft recipients. The diffuseness of the disease makes standard revascularization techniques such as angioplasty and bypass surgery palliative at best, and retransplantation is currently the only definitive form of therapy for accelerated allograft coronary artery disease. Because donor resources are limited and results after retransplantation are less satisfactory than after a first transplant procedure (1,2), it is important to understand the natural history of accelerated graft coronary artery disease to select subsets of patients with the disease who are at highest risk of dying of it and who will thus have the greatest benefit from retransplantation or from newer interventional therapies.

We postulated that early (versus late) onset of accelerated graft coronary artery disease might portend a worse prognosis and, along with other clinical or laboratory predictors of accelerated graft coronary artery disease, might identify patients at higher risk for ischemic events. We therefore sought to 1) evaluate the natural course of the disease, including its progression and sequelae; 2) compare the prognosis of early versus late appearance of accelerated graft coronary artery disease; and 3) document the incidence of antecedent cytomegalovirus infection associated with early versus late disease and the clinical course of patients with coronary artery disease with and without cytomegalovirus infection.

Methods

Study patients. The patient data base included 569 consecutive heart transplant recipients undergoing transplant surgery at Stanford between January 1968 and February 1990. A total of 402 of these patients survived at least 1 year after transplantation and had at least one annual coronary arteriogram available for review. Two patients, both children, died suddenly during the first postoperative year and were found to have had accelerated graft coronary artery disease at autopsy. These patients are not included in this analysis. One hundred thirty-nine patients developed angiographically apparent accelerated graft coronary artery disease during follow-up and constitute the study group. This group was then analyzed

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according to the time of first detection of accelerated graft coronary artery disease, the time to detection of 50% stenosis in one or more coronary arteries after initial appearance of coronary artery disease, as well as the timing of ischemic events after initial detection of accelerated graft coronary artery disease. These 139 patients were classified into two groups on the basis of arbitrarily defined criteria of early versus late appearance of accelerated graft coronary artery disease. The *early group* was defined as those patients who developed accelerated graft coronary artery disease ≤2 years postoperatively, and those who developed accelerated graft coronary artery disease >2 years postoperatively were defined as the *late group*. There were 64 patients in the early group (mean time of detection of graft coronary artery disease 1.5 years after transplantation, range 0.7 to 2.0) and 75 in the late group (mean time of detection 4.9 years after transplantation, range 2.3 to 17). These groups were compared for differences in clinical outcome as well as possible risk factors for the occurrence or progression of accelerated graft coronary artery disease.

Three patients had preexisting angiographic coronary disease on their predischarge (baseline) angiogram, one with 20% stenosis in the early group, and two with 20% and 40% stenosis in the late group. These three patient had the appearance of new lesions as well as progression of preexisting disease on their follow-up angiograms.

The incidence of cytomegalovirus infection in these patients was reviewed. Ninety-two of 139 patients were treated during the cyclosporine era of immunosuppression and had complete cytomegalovirus infection information for analysis. These 92 patients were also classified into groups according to the presence or absence of evidence of postoperative cytomegalovirus infection, and these groups were compared for differences in clinical outcome. Cytomegalovirus data were not available for patients operated on before 1980; therefore, 47 of the original 139 could not be included in this analysis.

Cardiac catheterization. All patients were evaluated annually near the anniversary of their transplant procedure with right and left heart catheterization and selective coronary arteriography using the percutaneous femoral approach and standard angiographic techniques. Written informed consent was obtained from all patients under Stanford Institutional Review Board guidelines.

Criteria for diagnosis of transplant coronary artery disease. A diagnosis of *accelerated graft coronary artery disease* was made if any angiographic evidence of coronary artery narrowing was seen, whether in proximal or distal branches. Serial cine films were compared using two projectors for side by side comparisons, and arterial lesions were classified as ≥50% or <50% diameter stenosis. The presence or absence of disease and the classification of lesions were determined by a consensus of two angiographers (S.Z.G., E.L.A.). The side by side serial comparisons made possible not only the recognition of focal atherosclerotic-type lesions, but also the recognition of the diffuse concentric narrowing in the mid to distal artery and distal "pruning" of vessels characteristic of accelerated graft coronary artery disease; changes that otherwise could be easily missed. Since 1986, baseline coronary angiograms have been obtained routinely in patients with implanted hearts within a few weeks after transplantation. If any evidence of coronary artery disease existed on the baseline studies, accelerated graft coronary artery disease was defined as evidence of new abnormalities in different locations or progression of a previously existing stenosis. Quantitative angiography was not used for this study.

Criteria for diagnosis of cytomegalovirus infection. *Cytomegalovirus infection* was defined for purposes of this study as either seroconversion of a previously cytomegalovirus-seronegative patient, a fourfold increase in a previously positive cytomegalovirus immunoglobulin G titer, positive cultures for cytomegalovirus, demonstration of cytomegalovirus inclusion in tissue specimens or a clinical illness documented to be due to cytomegalovirus. As previously stated, such data were not routinely collected before 1980 and thus were not available for 47 of the 139 patients.

Clinical events. Clinical findings that were considered ischemic events included clinical evidence of myocardial infarction, clear-cut electrocardiographic evidence of new myocardial infarction with or without a clinical event, pathologic findings of infarction in explanted hearts or postmortem specimens, the development of congestive heart failure unrelated to cellular or vascular rejection, retransplantation for accelerated graft coronary artery disease and sudden death.

Immunosuppressive protocols. Different immunosuppressive protocols were used sequentially throughout the evolution of the Stanford program. Protocols used azathioprine and prednisone between 1968 and 1979, cyclosporine and prednisone between 1980 and 1983 and triple immunosuppression with cyclosporine, azathioprine and prednisone between 1983 and 1990. In addition, anti-T cell (induction) therapy protocols used antilymphocyte globulin between 1968 and 1974, horse or rabbit antithymocyte globulin between 1974 and 1976, rabbit antithymocyte globulin between 1980 and 1984, horse antithymocyte globulin between 1985 and 1987 and OKT3 between 1987 and 1990. All patients received aspirin and dipyridamole. From 1986 to February 1990, patients who consented were randomized to receive diltiazem or no calcium channel blocking agent shortly after operation. Preliminary results of the effects of calcium channel blockers have been reported separately (3). In the current analysis, four patients (5.3%) in the late group and three (4.7%) in the early group were taking calcium channel blockers.

Other clinical risk factors. Comparisons between the two groups were made with regard to a number of possible clinical risk factors. These included recipient and donor age and gender, number of human leukocyte antigen (HLA) mismatches, number of treated rejection episodes during the first year after transplantation and graft ischemic time. They also included time-related systemic blood pressure, daily doses of the various immunosuppressive agents and lipid values. Data for donor/recipient race and HLA-DR matching and use of lipid-lowering therapy are not available for the majority of these patients.

Statistical analysis. All results are presented as mean value ± SD. The Kaplan-Meier method was used to calculate probability of freedom from the first appearance of graft coronary artery disease on angiography after transplantation, 50% diameter stenosis of one or more coronary arteries and clinical ischemic event after initial detection of graft coronary artery disease. The Mantel-Hænzel log-rank test was used to compare the equality of survival curves between early and late groups. Differences between the group characteristics were assessed with the chi-square test for categoric variables and two-tailed *t* tests for continuous variables. Multivariate logistic regression analysis was used to identify predictors for ischemic events. A p value <0.05 was considered statistically significant.

Results

The clinical characteristics of patients with early versus late appearance of transplant coronary artery disease are compared in Table 1. Patients with early appearance tended to be older, had received hearts from older donors and had lower high density lipoprotein (HDL) cholesterol blood levels.

Initial appearance. Time-related freedom from any angiographic appearance of accelerated graft coronary artery disease for the whole group of 139 patients who had documented graft coronary artery disease was analyzed. Initial detection of graft coronary artery disease occurred in 21%, 56% and 83% of this group at 1, 3 and 5 years after transplantation, respectively. This result shows that 50% of all patients who by definition eventually develop accelerated graft coronary artery disease by 3 years after operation.

Ischemic events after initial appearance of accelerated graft coronary artery disease. At initial detection of accelerated graft coronary artery disease, 45 (32%) of 139 patients already had at least one lesion judged to be ≥50% obstructive. By 2 years after initial detection, an additional 17% of patients had developed ≥50% stenosed lesions (Fig. 1). Figure 1 also shows the incidence of ischemic events after initial detection of any accelerated graft coronary artery disease, displayed as an actuarial curve of freedom from ischemic events. Several patients underwent arteriography because of the occurrence of an ischemic event. For this reason, freedom from ischemic events at "time zero," in time of detection of disease, is <100%. At 1, 3, and 5 years after initial appearance of accelerated graft coronary artery disease, 23%, 43% and 53% of patients had sustained ischemic events, respectively, and 50% of all patients had an ischemic event within 4 years of disease detection.

Ninety-five ischemic complications occurred in 66 patients and included 16 patients with congestive heart failure, 27 with myocardial infarction, 34 with retransplantation for severe coronary artery disease and 18 with sudden death. Eighty-two of the 139 patients have died (graft coronary artery disease in 60 [73.2%], infection in 14 [17.1%], lymphoproliferative disease in 1 [1.2%], nonspecific graft failure in 2 [2.4%], pulmonary embolism in 1 [1.2%], other causes in 4 [4.9%]).

Freedom from ischemic events: early versus late groups. Figure 2 presents data on freedom from ischemic events after initial detection of accelerated graft coronary artery disease for the early- and late-appearance groups. The two groups appear to be parallel in their rate of developing ischemic events for the first 2 years after detection, but diverge markedly after 2 years, with 59% of the late group and only 34% of the early group free of ischemic events by 5 years after initial detection. These curves were significantly different at the $p = 0.02$ level.

Relation to cytomegalovirus infection. Because there is a well recognized association between the occurrence of cytomegalovirus infection and the incidence of accelerated graft coronary artery disease, we analyzed this group of patients to determine whether cytomegalovirus infection was associated with early versus late development of disease. There was no difference in the prevalence of preoperative donor or recipient seropositivity for cytomegalovirus infection between the early and late groups. Table 2 shows the early and late groups of patients classified into subsets according to the presence or absence of postoperative cytomegalovirus infection.

Our data show that 66% (21 of 32) of the early and only 34% (11 of 32) of the late graft coronary artery disease-onset group had evidence of antecedent cytomegalovirus infection ($p = 0.02$). If one considers only symptomatic cytomegalovirus infections, the percentages are 93% (13 of 14) for the early group and 7% (1 of 14) for the late group ($p = 0.0007$).

The post-1980 patient group was classified into 32 patients who had evidence of cytomegalovirus infection and 60 who did not. Comparison of freedom from ischemic events for these two overall groups did not reach statistical significance.

Multivariate regression analysis for predictors of ischemic events. Clinical variables, including recipient and donor age; ischemic time; systolic and diastolic blood pressures; incidence of serologic and symptomatic cytomegalovirus infection after transplantation; number of rejection episodes; prednisone, azathioprine and cyclosporine dosage; plasma concentrations of triglycerides, total serum cholesterol, low density lipoprotein cholesterol, HDL cholesterol and very low density lipoprotein cholesterol, were analyzed by multivariate logistic regression analysis. Only a somewhat lower cyclosporine dosage ($p = 0.02$) was a statistically significant predictor of ischemic events.

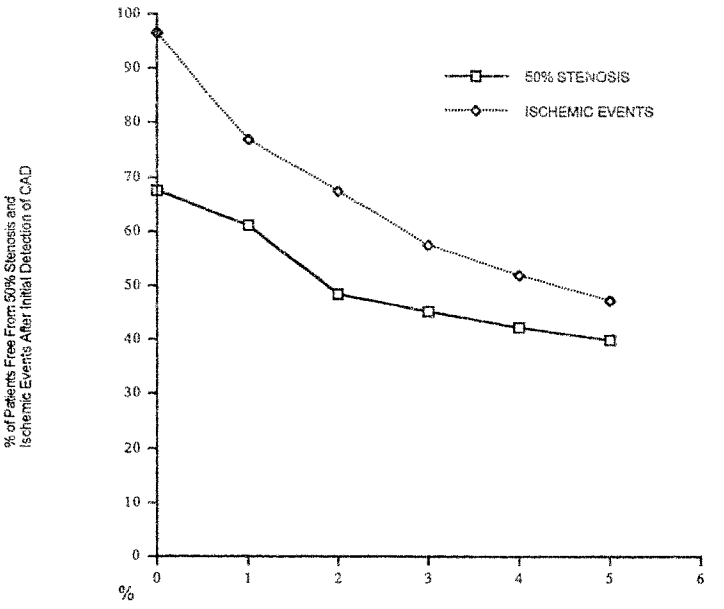
Discussion

Angiographically apparent accelerated graft coronary artery disease is generally agreed to have a prevalence of ~50% by 5 years after transplantation (4–6), and the prevalence is expected to approach 100% in truly long-term survivors. Standard angiographic techniques clearly underestimate the occurrence and extent of the disease (7–9). In one study (10), 60 patients evaluated by intracoronary ultrasound ≥1 years after transplantation all had at least minimal intimal thickening. Studies of autopsy specimens suggest that the incidence of histologically evident coronary intimal thickening is 100% by 1 year after transplantation (11). Given the universal occurrence of this process and the eventually lethal sequelae of its

Table 1. Comparison of Risk Factors in Early and Late Graft Coronary Artery Disease Groups

	Early Group (n = 64)	Late Group (n = 75)	p Value
Recipient age (yr)	41.1 ± 9.2	37.4 ± 12.2	0.05
Donor age (yr)	26.7 ± 8.4	22.8 ± 7.1	0.003
Donor CAD	1	2	0.88
Male/female	56/8	62/12	0.79
Original cardiac disease			
CAD	29	34	
Cardiomyopathy	29	34	
Other	5	7	0.92
HLA mismatch (no. of loci)			
A	1.4 ± 0.7	1.3 ± 0.6	0.28
B	1.6 ± 0.0	1.7 ± 0.5	0.32
A+B	3.0 ± 1.1	2.9 ± 0.8	0.24
Ischemic time (min)	118.7 ± 60.7	100.9 ± 54.3	0.08
No. of rejection episodes (1st yr post-op)	2.6 ± 1.2	2.3 ± 1.6	0.25
Blood pressure (mm Hg)			
Systolic			
1 yr	129.2 ± 16	132 ± 18	0.40
2 yr	133 ± 19	133 ± 18	0.99
Average	129 ± 14	132 ± 14	0.21
Diastolic			
1 yr	90 ± 12	90 ± 12	0.83
2 yr	91 ± 14	91 ± 16	0.83
Average	89 ± 10	89 ± 9	0.66
Prednisone dose (mg/kg per day)			
1 yr	0.27 ± 0.17	0.27 ± 0.18	0.90
2 yr	0.24 ± 0.13	0.22 ± 0.10	0.21
Average	0.26 ± 0.16	0.26 ± 0.30	0.97
Cyclosporine dose (mg/kg per day)			
1 yr	3.2 ± 2.8	3.6 ± 3.5	0.43
2 yr	2.6 ± 2.5	3.1 ± 3.0	0.37
Average	2.7 ± 2.3	3.2 ± 3.9	0.38
Azathioprine dose (mg/kg per day)			
1 yr	1.3 ± 1.0	1.3 ± 1.0	0.99
2 yr	1.4 ± 1.0	1.4 ± 1.0	0.64
Average	1.4 ± 1.4	1.4 ± 1.1	0.76
Plasma TG (mg/dl)			
1 yr	253 ± 264	194 ± 130	0.15
2 yr	215 ± 117	218 ± 129	0.92
Average	246 ± 243	200 ± 117	0.17
TC (mg/dl)			
1 yr	246 ± 84	255 ± 86	0.60
2 yr	257 ± 93	259 ± 89	0.92
Average	249 ± 80	255 ± 75	0.63
HDLC (mg/dl)			
1 yr	43 ± 15	48 ± 17	0.09
2 yr	44 ± 13	48 ± 17	0.23
Average	43 ± 14	49 ± 15	0.04
LDLC (mg/dl)			
1 yr	149 ± 61	161 ± 85	0.42
2 yr	211 ± 353	167 ± 79	0.43
Average	153 ± 77	171 ± 73	0.18
VLDLC (mg/dl)			
1 yr	36 ± 29	33 ± 17	0.52
2 yr	37 ± 19	41 ± 28	0.48
Average	36 ± 24	37 ± 20	0.83

Data presented are mean value ± SD or number of patients. CAD = coronary artery disease; HDLC = high density lipoprotein cholesterol; HLA = human leukocyte antigen; LDL = low density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; VLDLC = very low density lipoprotein cholesterol.



No. at risk:						
50% Stenosis	139	68	65	54	43	31
Ischemic events	139	102	68	46	35	26

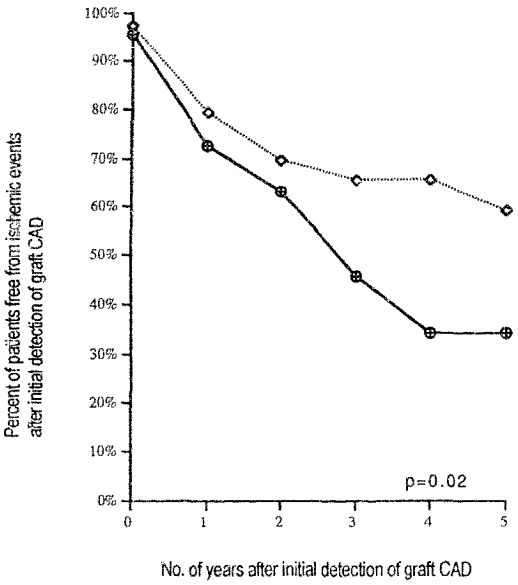
Figure 1. Time-related percent of freedom from 50% diameter stenosis and ischemic events after initial detection of accelerated graft coronary artery disease (CAD): 33% of patients (45 of 139) had >50% diameter stenosis at initial detection, and 4% (5 of 139) experienced ischemic events simultaneously with first detection.

progression, it is important to understand its natural history and identify subsets of patients most in need of retransplantation or (eventually) other types of interventional therapy.

Graft coronary artery disease—high risk subgroups. In the current analysis we take a different approach by concentrating on the subgroup of our patients known to have angiographic evidence of some graft coronary artery disease and determine which features are associated with the worst prognosis. In an earlier analysis of the same group (12), we found that the rapidity of angiographic progression of accelerated graft coronary artery disease did portend the development of an ischemic event. The current study suggests that an earlier appearance of accelerated graft coronary artery disease and an association with cytomegalovirus infection may also be markers of intrinsically more aggressive disease.

Graft coronary artery disease—risk factors for early appearance. It has been difficult to identify clinical or laboratory correlates to predict very accurately which patients will develop accelerated graft coronary artery disease (13–15). Neither the type of original heart disease (atherosclerotic vs. other), nor any of the standard risk factors are helpful prospectively to identify patients at high risk for the disease. Several centers have reported a much higher incidence of accelerated graft coronary artery disease in patients with cytomegalovirus infection (16–19), but whether cytomegalovirus-related coronary artery disease occurs earlier (or has a worse prognosis) has not been previously assessed. In the present analysis, cytomegalovirus infection is significantly correlated with early angiographic appearance of graft coronary artery disease. There is a suggestion that more advanced age of both the donor and recipient is also associated with the early appearance of coronary artery disease. There is evidence that hearts from older donors, particularly those with risk factors, may have preexisting, angiographically inapparent, coronary artery disease (10). Whether these preexisting lesions become the substrate for more rapid later progression remains to be evaluated. In the present study, new-onset and progression of coronary artery disease on follow-up angiograms were required to be incremental to preexisting donor disease, which was angiographically detectable in only 3 of the 139 patients.

The association between earlier onset of angiographic coronary artery disease and subsequent earlier development of lesions and ischemic events seems predictable and serves the goal of identifying those patients for whom more aggressive and earlier treatments might be initiated to mitigate this process. These high risk patients (with early appearance and rapid progression of accelerated graft coronary artery disease)



No. at risk:						
Early Group	64	45	30	18	12	10
Late Group	75	57	38	28	23	16

Figure 2. Comparison of time-related percent of freedom from ischemic events in the early (**circles**) and late (**diamonds**) groups: 5% (3 of 64) of the early and 3% (2 of 75) of the late group experienced an ischemic event simultaneously with first detection of coronary artery disease (CAD).

would also be prime targets for future clinical trials of any proposed therapeutic modalities.

Surveillance angiography. The need to continue annual coronary angiography if the results of first angiogram are normal has been questioned by some (20). The present study suggests that even though ischemic sequelae are less frequent in late-onset graft coronary artery disease, such sequelae do occur frequently, and prospective awareness of a patient's risk for sustaining them may be valuable knowledge.

Conclusions. Accelerated graft coronary artery disease seems to develop at variable times after transplantation, and about one-third of patients show severe stenosis when coronary artery disease is initially detected. The early appearance of accelerated graft coronary artery disease may be a marker of intrinsically more aggressive disease. Cytomegalovirus infection is associated with early onset of graft coronary artery disease. Patients with early development of coronary artery disease are potential priority candidates for interventional strategies as they are developed.

Table 2. Comparison of Posttransplant Cytomegalovirus Infection in Early Versus Late Graft Coronary Artery Disease Groups

Cytomegalovirus Infection*	Early Group	Late Group	p Value
No (n = 60)	23/60 (38%)	37/60 (62%)	0.02
Yes (n = 32)	21/32 (66%)	11/32 (34%)	

*Fourfold immunoglobulin G anti-cytomegalovirus antibody titer increase, positive culture for cytomegalovirus, cytomegalovirus inclusion body in tissue.

Table 3. Comparison of Pretransplant Seropositivity in Early Versus Late Graft Coronary Artery Disease Groups

Cytomegalovirus Infection	Early Group	Late Group	p Value
Donor			
No (n = 40)	18/40 (45%)	22/40 (55%)	NS
Yes (n = 40)	21/40 (53%)	19/40 (47%)	
Recipient			
No (n = 37)	15/37 (41%)	22/37 (59%)	NS
Yes (n = 53)	28/53 (53%)	25/53 (47%)	

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