CARDIAC TRANSPLANT CORONARY ARTERY DISEASE

A multivariable analysis of pretransplantation risk factors for disease development and morbid events

Coronary artery disease after cardiac transplantation is a major obstacle to long-term survival. The development and progression of coronary artery disease after cardiac transplantation was analyzed in 217 consecutive patients undergoing transplantation. The actuarial freedom from any coronary artery disease (by angiography or autopsy) was 81% at 2 years and 20% at 8 years after transplantation. Coronary artery disease was more prevalent in male than female patients (30% versus 50% free of coronary artery disease at 5 years, $p = 0.01$). By multivariable analysis, pretransplantation risk factors identified for coronary artery disease included pretransplantation positive cytomegalovirus serologic status of the recipient ($p = 0.002$) and older donor age ($p = 0.07$). Progression of coronary artery disease was variable in both time of onset and rate. Earlier detection did not result in more rapid progression. Coronary events severe enough for retransplantation ($n = 8$) and/or death from coronary artery disease ($n = 9$) occurred in 15 patients, of whom four underwent retransplantation. The actuarial freedom from coronary events was 88% at 5 years and 79% at 8 years. By multivariable analysis, only male recipient ($p = 0.05$) was a risk factor for coronary events. Seven of the 15 patients (47%) with coronary events died suddenly of coronary artery disease without prior angiographic evidence of severe coronary disease. Coronary artery disease is progressive. Improved surveillance methods are required to detect the disease and institute timely intervention to prevent the occurrence of unanticipated death. (J THORAC CARDIOVASC SURG 1995;109:1081-9)

David C. McGiffin, MD[a] (by invitation), Timo Savunen, MD[a] (by invitation), James K. Kirklin, MD,[a] David C. Naftel, PhD[a] (by invitation), Robert C. Bourge, MD[b] (by invitation), Thomas D. Paine, MD[b] (by invitation), Connie White-Williams, RN[a] (by invitation), Tero Sisto, MD[a] (by invitation), and Lesley Early, RN[a] (by invitation), *Birmingham, Ala.*

Posttransplantation coronary artery disease (CAD) is one of the major obstacles to long-term survival after cardiac transplantation. Available information suggests that the process is initiated by immune-mediated injury to the endothelium of the coronary vessels,[1-4] but the final expression of the injury as CAD is undoubtedly a complex interplay between atherogenic factors and the immunologic milieu created by donor and recipient interaction.

From the Division of Cardiothoracic Surgery, Department of Surgery,[a] and the Division of Cardiology, Department of Medicine,[b] University of Alabama at Birmingham, Birmingham, Ala.

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Address for reprints: David C. McGiffin, MD, Associate Professor of Surgery, University of Alabama at Birmingham, Birmingham, AL 35294.

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To better understand the incidence of, risk factors for, and progression of CAD after cardiac transplantation in the current era, we undertook the following study. The study aims included the determination of the prevalence and pretransplantation risk factors for CAD after cardiac transplantation, analysis of the progression of CAD, and identification of risk factors for serious CAD events such as death and retransplantation.

Patients and methods

Patient population. Between November 1981 and January 1, 1991, 217 patients underwent cardiac transplantation at The University of Alabama at Birmingham. Seventeen patients (nine of whom died early) did not have information regarding the presence of CAD in their initial transplanted heart and were excluded from the analysis. Consequently, the analysis includes 200 patients. Follow-up for this study was complete through June 30, 1992.

Immunosuppression therapy. From 1981 through 1987, immunosuppression included azathioprine and prednisone. Between 1984 and 1987, cyclosporine and

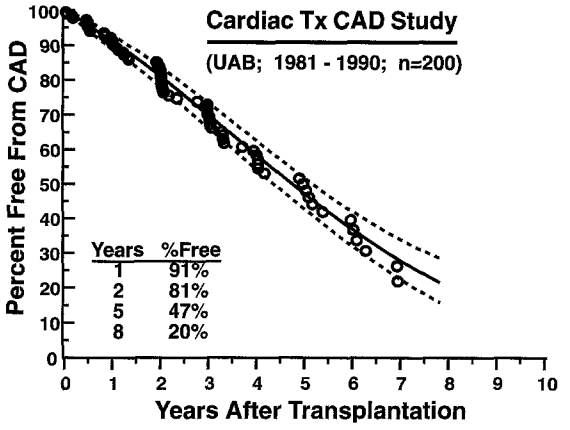

Fig. 1. Actuarial (Kaplan-Meier) freedom from the angiographic (or autopsy) appearance of any cardiac transplant CAD (angiographic score greater than 0). *Open circles* represent actuarial appearance of CAD. The *solid line* represents the parametric estimate surrounded by the 70% confidence limits *(dashed lines). UAB,* University of Alabama at Birmingham.

prednisone were used, and from 1987 to 1991, triple-drug immunosuppression consisting of cyclosporine, azathioprine, and prednisone was used. Induction therapy was used throughout the time frame with either rabbit antithymocyte globulin or OKT3. Acute cardiac rejection was managed initially with intravenous methylprednisolone sodium succinate (Solu-Medrol) for 3 days. Refractory or recurrent episodes of rejection were managed with steroids and cytolytic therapy (rabbit antithymocyte globulin or OKT3), and in the latter part of the experience methotrexate and total lymphoid irradiation were also used.

Data collection. A number of pretransplantation demographic, clinical, donor, and donor/recipient matching variables were collected (see Appendix A).

The presence and extent of CAD was assessed by posttransplantation coronary arteriograms (n = 633), autopsy reports (n = 69), and explanted hearts (n = 12). All available angiograms on all patients were examined by two of the investigators and each was scored according to the extent of CAD (see *CAD scoring system*). Throughout this experience, a general protocol of yearly coronary angiography was conducted for surveillance of CAD development. From approximately 1987 through 1991, additional surveillance angiograms were obtained at 6 weeks and 6 months after transplantation.

Each patient was assessed for the development of morbid or fatal events related to CAD. These "CAD events" included death resulting from CAD, retransplantation resulting from CAD, and consideration of retransplantation because of CAD (but not actually performed because of extenuating medical circumstances).

CAD scoring system. A scoring system was developed to grade the angiographic severity of CAD in the epicardial arteries and also take into account the impact of specific disease on overall myocardial perfusion. The severity of angiographic disease was graded (0 to 5) in 17 segments of the major coronary arteries and their epicardial branches. A weighting factor (maximum of 4) was assigned to each coronary artery segment on the basis of the relative importance of the lesion with respect to myocardium supplied. The segment score and the weighting factor were multiplied and then all were summed to generate a total angiographic score (see Appendix B). In general, a score exceeding 15 indicated severe three-vessel CAD. The angiograms were also categorized according to the presence or absence important disease in each of the three major coronary artery systems. A score of 4 or more in the left anterior descending or circumflex territory and a score of 3 in the right coronary system were considered indicative of important disease in that territory (see Appendix B).

Data analysis. The data were examined by means of standard contingency tables and Kaplan-Meier actuarial analysis. Multivariable analyses were then performed in the hazard function domain[5] to identify potential pretransplantation risk factors associated with the angiographic appearance of any disease and CAD events. The rate of progression of disease was analyzed by linear and nonlinear regression.

Results

Incidence of cardiac transplant CAD. Sixty-eight patients had angiographic or autopsy evidence of cardiac transplant CAD (angiographic score greater than 0) over the 10-year study period. At 1 year and 8 years after transplantation, 91% and 20%, respectively, of patients were free of angiographic CAD (Fig. 1). The hazard function indicates a progressively rising risk of developing CAD (Fig. 2).

Risk factors for CAD. By univariate analysis, female patients had greater freedom from CAD than did male recipients (Fig. 3). However, by multivariable analysis, the only pretransplantation risk factors identified for the development of CAD were a positive pretransplantation cytomegalovirus (CMV) serologic status in the recipient and older donor age (Table I). A non-risk-adjusted comparison of freedom from CAD stratified by pretransplantation CMV serologic status suggests that the effect of pretransplantation CMV serology is apparent after about 4 years (Fig. 4). The effect of donor age on the subsequent development of CAD was most pronounced for donors older than 35 years (Fig. 5). Among donors older than 35 years, 16 were 35 to 40 years and 4 were 40 to 45 years. No relationship was identified between recipient age and development of CAD.

Severity and progression of CAD. Considering all sources of CAD information (angiogram, autopsy, explanted heart), more than 70% of studies showed no CAD, 15% showed a score of 1 to 5, and less than 6% had a score exceeding 10 (Table II). Among the

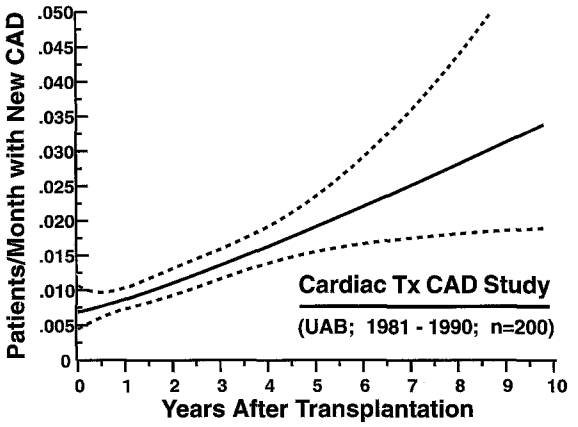

Fig. 2. Hazard function for the angiographic appearance of any cardiac transplant CAD, represented on the *vertical axis* as the number of patients per month in whom any CAD develops. It consists of a constant and a late phase. The hazard function (instantaneous risk) is represented by the *solid line* and is surrounded by the 70% confidence limits *(dashed lines). UAB,* University of Alabama at Birmingham.

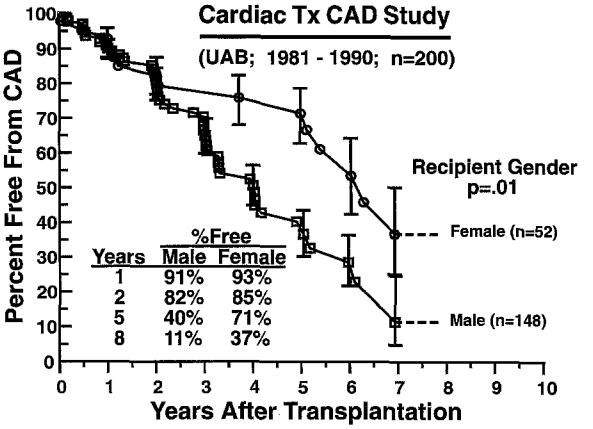

Fig. 3. Actuarial (Kaplan-Meier) freedom from the angiographic (or autopsy) appearance of any cardiac transplant CAD stratified by recipient gender. *Circles,* Female; *squares,* male. The *error bars* indicate 70% confidence limits. *UAB,* University of Alabama at Birmingham.

Table I. *Risk factors for cardiac transplant CAD*

Risk factors	*p Value*	
	Constant	*Late*
Recipient pretransplantation positive CMV status	—	0.0007
Donor age (older)	—	0.03

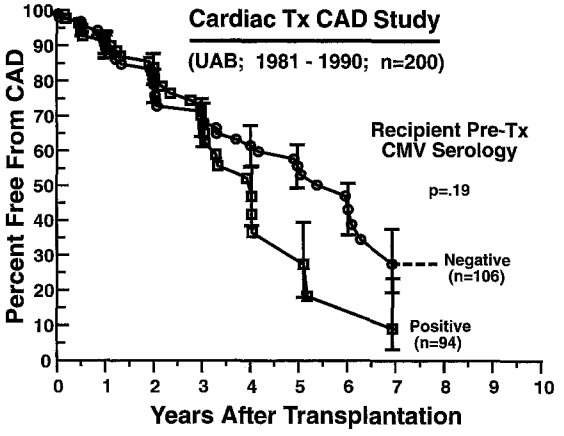

Fig. 4. Actuarial (Kaplan-Meier) freedom from the angiographic (or autopsy) appearance of any cardiac transplant CAD (angiographic score greater than 0) stratified by recipient pretransplantation CMV serologic status. *Circles,* negative; *squares,* positive. *Error bars* indicate 70% confidence limits. *UAB,* University of Alabama at Birmingham.

studies revealing CAD, 37% of these had important single-vessel disease, 5% two-vessel disease, and 13% three-vessel disease. In 45%, the CAD was considered trivial (Table III). Of the 69 autopsied hearts, 51 (74%) had no evidence of CAD (score 0), 4 had mild CAD (score 1 to 10), 3 had a score of 10 to 15, and 11 (16%) had severe CAD (score ≥15). Analyzed according to number of vessels involved, 4% of the autopsied hearts had single-vessel disease, 3% two-vessel disease, and 17% three-vessel disease. For the overall group, the mean CAD score increased over time, but even at 8 years the mean CAD score remained less than 10. Throughout the study period, the mean CAD score for male patients was consistently greater than that for female patients (Fig. 6). To examine the rate of progression of CAD relative to the first appearance of disease, we examined the rate of increase in angiographic CAD score for each patient with CAD as a function of the year after transplantation in which CAD first appeared (Fig. 7). Although there is considerable variability, it is noteworthy that earlier appearance of CAD (for example, within the first 2 years) was not associated with more rapid disease progression. Particularly after the second year, the rate of progression among groups was similar.

Invasive therapy for CAD. Seven patients underwent percutaneous transluminal angioplasty (PTCA) as palliative therapy for posttransplantation vasculopathy. Initial PTCA occurred 2.5 to 7.0 years (median 4.1 years) after cardiac transplantation. Three patients (38%) required multiple PTCAs (two, two, and three). Two patients underwent coronary bypass grafting after PTCA; one patient in

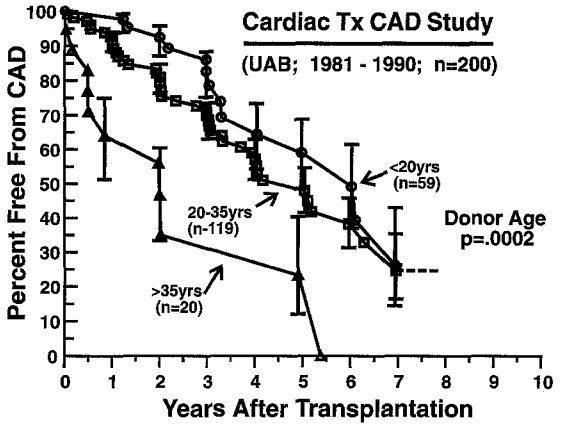

Fig. 5. Actuarial (Kaplan-Meier) freedom from angiographic (or autopsy) appearance of any cardiac transplant CAD stratified by donor age. *Circles,* less than 20 years; *squares,* 20 to 35 years; *triangles,* greater than 35 years. The *error bars* indicate 70% confidence limits. *UAB,* University of Alabama at Birmingham.

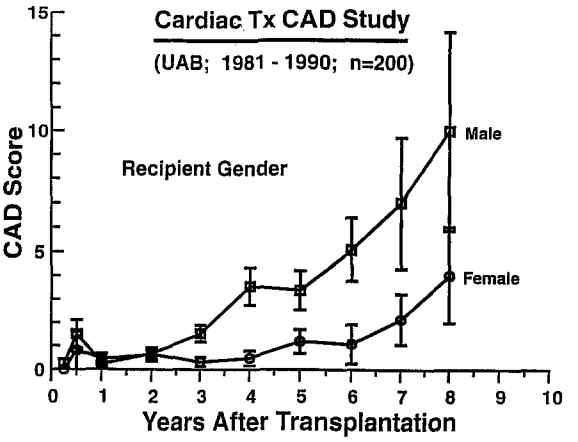

Fig. 6. Relationship between mean CAD score and increasing time from transplantation stratified by recipient gender. *Circles,* Male; *squares,* female. The *error bars* indicate 70% confidence limits. *UAB,* University of Alabama at Birmingham.

Table II. *CAD scores*

*CAD index**	*n*	*% of 714*
0	521	73
1–5	107	15
6–10	46	6
11–20	23	3
21–30	10	1.4
31–40	6	0.8
41–50	1	0.1
Total	714†	100

*Maximum possible score = 105.

†Includes coronary arteriograms (n = 633), autopsy reports (n = 69), and explanted hearts (n = 12).

Table III. *Number of arteries affected by CAD*

	*Number of major coronary artery systems with disease**				
CAD index	*0*	*1*	*2*	*3*	*Total*
0	521	0	0	0	521
1–5	83	24	0	0	107
6–10	3	42	1	0	46
11–15	0	6	7	2	15
16–20	0	0	1	7	8
>20	0	0	1	16	17
Total	607	72	10	25	714

*See *Patients and methods* (CAD scoring system).

shock on an emergency basis on the same day after attempted PTCA and the other 1 year after PTCA. Both patients died.

CAD events after cardiac transplantation. Among the 200 patients, 15 CAD events occurred (see again

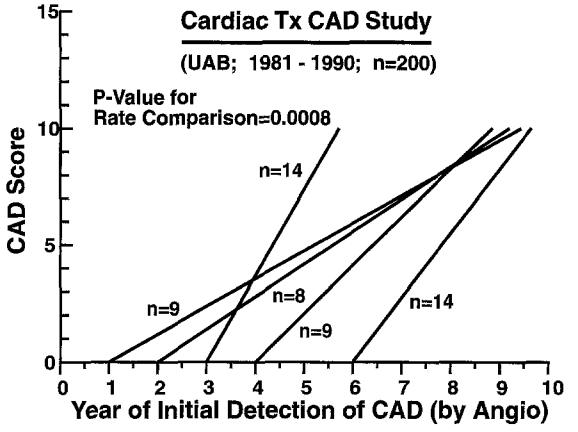

Fig. 7. Regression lines for rate of increase in mean CAD score according to the year of first angiographic detection of CAD. *UAB,* University of Alabama at Birmingham.

Patients and methods). Four patients underwent retransplantation for CAD, four additional patients were considered for retransplantation because of extensive CAD but were denied the operation because of coexisting medical problems (two of these subsequently died of CAD), and seven patients died unexpectedly of CAD (identified at autopsy) who did not have extensive CAD identified by previous angiography. Thus 47% of serious CAD events were unanticipated on the basis of routine surveillance angiography.

Of the total of 95 deaths from all causes in the 217 transplant recipients, only nine could be attributed

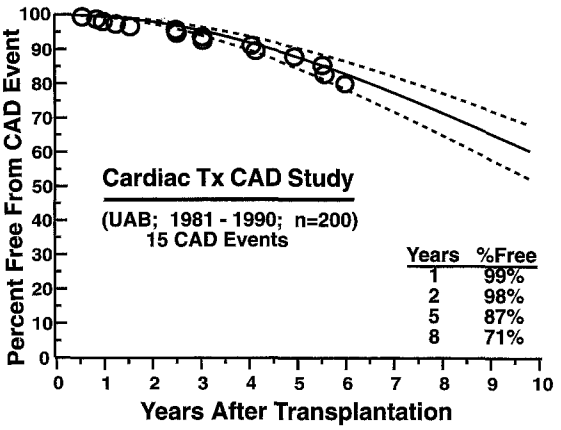

Fig. 8. Actuarial (Kaplan-Meier) and parametric freedom from a CAD event. *Open circles* indicate individual CAD events depicted actuarially. The *solid line* represents the parametric depiction with its 70% confidence limits. *UAB,* University of Alabama at Birmingham.

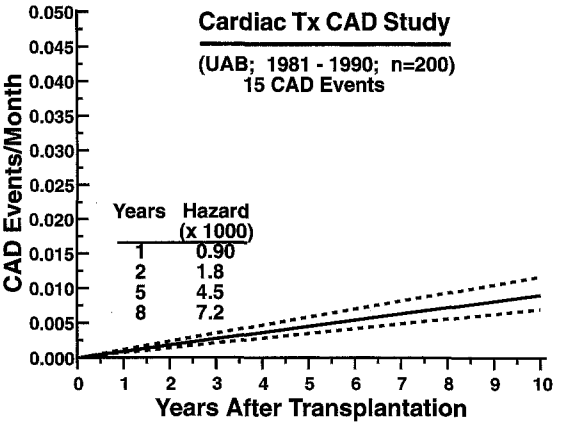

Fig. 9. Hazard function for a CAD event. It consists of a late phase only. The hazard function (instantaneous risk) is represented by the *solid line* and is surrounded by the 70% confidence limits *(dashed lines). UAB,* University of Alabama at Birmingham.

to CAD. Of the 19 deaths occurring between the third and eighth years after transplantation, only four (21%) were due to CAD. The remaining causes of death more than 3 years after transplantation were malignancy ($n = 3$), rejection ($n = 4$), pulmonary embolism ($n = 1$), suicide ($n = 1$), cirrhosis ($n = 1$), renal failure ($n = 1$), cerebral hemorrhage ($n = 1$), multisystem failure ($n = 1$), multifocal leukoencephalopathy ($n = 1$), and unknown ($n = 1$).

The actuarial and parametric freedom from a serious CAD event was 71% at 8 years (Fig. 8). The linear slope of the hazard function indicates a gradually increasing risk of such an event over time (Fig. 9). By multivariable analysis, the only pretransplantation risk factor identified for a subsequent CAD event was recipient male gender ($p = 0.05$). At 6 years, nearly 30% of male recipients had a CAD event compared with about 2% among female recipients (Fig. 10).

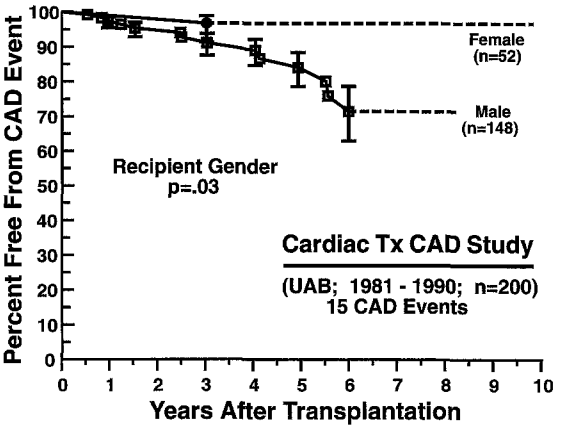

Fig. 10. Actuarial (Kaplan-Meier) freedom from a CAD event stratified by recipient gender. *Circles,* Female; *squares,* male. The *error bars* indicate 70% confidence limits. *UAB,* University of Alabama at Birmingham.

Discussion

Limitations of the study. In this study, coronary arteriography formed the basis of detection of posttransplantation CAD. Although recognized as the standard diagnostic technique for coronary arteriopathy, angiography is known to be a less sensitive method of coronary disease detection than autopsy studies[6-8] and the more recent technique of intracoronary ultrasonic imaging.[9, 10] The relative insensitivity of coronary arteriography may relate in part to the pathologic basis of posttransplantation vasculopathy, in that the primary lesion is a proliferative response of the vascular wall smooth muscle cells, which is distributed throughout the length of the coronary arteries.[11, 12] Angiographically, this proliferation may appear as concentric luminal narrowing in small intramyocardial coronary arteries with abrupt ending of distal branches.[13, 14] The diffuse nature of the process with resultant narrowing of luminal caliber throughout the length of coronary vessels contributes to the difficulty of angiographic detection of abnormalities. In addition to this proliferative response, there is a superimposed atherosclerotic component that results in the eccentric lesions more typical of native CAD.[6] Thus the findings in this study relative to the incidence of CAD are likely a minimum estimate.

Regarding the risk factor analysis, this study examined only *pretransplantation variables* as predictors of posttransplantation CAD. The aim of this analysis was to identify patient subsets before transplantation who may be more vulnerable to posttransplantation CAD and events. Further studies of this type will be necessary to incorporate detailed multivariable analyses of posttransplantation phenomena, including such variables as rejection history, CMV disease, complex lipid alterations, tobacco habits, and development of obesity. Previous studies have alluded to some of these factors in the development of posttransplantation vasculopathy.[11, 15-19]

This study is also limited by a relatively small number of patients at a single institution. There would be obvious advantages to a multiinstitutional study of posttransplantation vasculopathy, which might more accurately reflect the variability of this disease. On the other hand, however, this study has the advantage of complete review of all angiograms in the experience. Other reports in the literature have often relied totally on angiographic reports from the patient records rather than a separate individual review of all angiograms.

Incidence and pretransplantation risk factors for cardiac transplant CAD. The incidence of angiographically apparent CAD in this study of 80% at 8 years is consistent with the findings of other reports.[17, 20, 21] However, the true incidence of at least the proliferative component is much greater. In a study of autopsy and explanted heart material, essentially all patients had important coronary artery lesions by 12 months after transplantation.[22]

The finding of older donor age as a risk factor for CAD development was previously noted by Gao and colleagues[23] in a univariate analysis, but the effect was weak. In the present study, the effect of older donor age was most prominent for donors older than 35 years, although the number of older donors in this experience was limited. Presumably, this donor age effect relates to an increased propensity for atherosclerotic changes in the older donor.

The association between recipient pretransplantation CMV-positive serology and the development of CAD is provocative. It is particularly interesting that the apparent effect of CMV serology was manifest only after about 4 years (see again Fig. 4). Perhaps this delay relates in some way to the long dormant interval typically observed before the activation of CMV disease. Although this study did not address the possible impact of posttransplantation CMV disease or seroconversion, Loebe and colleagues[15] noted a higher incidence of positive CMV serology among patients with coronary vasculopathy. A number of clinical studies have reported an association between CMV infection and the subsequent development of CAD.[15, 24-26] It has been postulated that CMV may promote graft intimal disruption by modulating major histocompatibility antigens, endothelial monocyte antigens, endothelial cell antigenicity, or adhesion molecules, thus producing an enhanced immunologic target.[11, 27] CMV nucleic acids have been detected in the endothelial cells and smooth muscle cells of the coronary arteries in a significant proportion of hearts with transplant vasculopathy.[28]

CAD progression. Little published data is available regarding the details of CAD progression after cardiac transplantation. In this study, both the time of angiographic appearance and the rate of progression after disease-free intervals were variable. It is of interest, however, that earlier detected CAD was not associated with a more accelerated rate of CAD progression (see again Fig. 7). These findings are consistent with a hypothesis that incorporates immunologic events (manifesting at a variable period after transplantation) initiating intimal damage with superimposed development of accelerated atherosclerosis as an independent phenomenon. Support or rejection of this hypothesis will require further complex analyses.

Morbid and fatal CAD events. The important mortality associated with the development of posttransplantation CAD has been reported by Uretsky,[29] Keogh,[30] and others. Keogh and colleagues[30] reported an actuarial survival of 44% at 2 years after angiographic appearance of greater than 40% stenosis in one or more major epicardial vessels. Survival was particularly poor in patients with extensive three-vessel disease. The CAD event–free survival in the present study was 71% at 8 years. This rate is surprisingly high given the mere 20% freedom from angiographically detectable CAD by 8 years and may partially reflect an aggressive use of PTCA for posttransplantation CAD. In a multiinstitutional study, Halle and colleagues[31] reported favorable intermediate-term results of PTCA therapy in this setting. Despite the serious implications of CAD development, coronary vasculopathy accounted for a small proportion of late mortality (20% of deaths occurring 3 to 8 years after transplantation). This mortality is somewhat lower than

might be expected given the disease incidence and its progressive nature, and it underscores the importance of also focusing diagnostic and therapeutic efforts at other causes of late mortality, such as rejection, infection, and malignancy.

The inadequacy of yearly surveillance coronary arteriography as a method for preventing CAD mortality is supported by the important incidence of CAD-related deaths that were unanticipated by previous angiographic studies. Thus there clearly is a need for more sensitive invasive and noninvasive techniques for detection of the posttransplantation CAD process.

From this study we draw the following inferences:

- CAD by angiography is detected by 8 years in more than 80% of long-term survivors of cardiac transplantation, and it is more prevalent among recipients with positive CMV serology and older donor hearts.
- The rate of progression of CAD is variable, and earlier detection does not predict more rapid progression of disease.
- Despite the frequency of CAD, serious coronary events (relisting for retransplantation or CAD-related death) occur in only about 25% of patients by 8 years and are more likely among male recipients.
- Cardiac transplant CAD accounts for approximately 20% of deaths occurring 3 to 8 years after transplantation.
- Despite a protocol of routine yearly surveillance angiograms, more than 40% of coronary events present as sudden or unexpected death without previously detected CAD.

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Discussion

Dr. Severi P. Mattila *(Helsinki, Finland).* Vasculopathy is one of the most important factors influencing the late outcome of patients after cardiac transplantation. Our experience is limited to 150 patients, with 78% survival at 8 years. In one patient with CMV who died we found extreme vasculopathy with enormous intimal thickening of the coronary arteries. Therefore, we decided to review all of the cases of symptomatic CMV infection, as well as doing endomyocardial biopsy and coronary angiography, and we compared these two groups of patients.

Table I summarizes the occurrence of the occlusive changes in coronary arteries of the patients with CMV infection and in the other group of patients. At 2 years there was a statistically significant difference between the two groups. Thus in our experience CMV infection seems to accelerate the vasculopathy in the coronary arteries.

Table II shows the histologic part of our study, and it confirms the coronary arteriographic study. The intimal thickening developed earlier in those patients with CMV infection, but at 4 years there was no statistically significant difference in our series.

We can conclude that CMV infection accelerates the appearance of coronary vasculopathy after heart transplantation, and it can be seen in both coronary arteriograms and endomyocardial biopsy specimens of the small arteries.

Dr. McGiffin. The association between CAD after cardiac transplantation and CMV infection has been demonstrated before, and you have provided more confirmatory information. Obviously some complex interplays are involved, with immunologic risk factors and also probably the more traditional atherosclerotic risk factors. It is interesting to speculate on why CMV should be associated with CAD. Perhaps it is in part the result of endothelial damage of the coronary arteries producing an inflammatory response with the production of cytokines, resulting in the proliferative process that we see in the coronary arteries.

Table I. *The number of angiograms analyzed and the frequency of cardiac allograft vasculopathy (CAV) detected during the 4 posttransplant years*

	Year after cardiac transplantation			
	1	*2*	*3*	*4*
Angiograms	50	31	25	9
CMV patients	28	19	16	5
CAV total (%)	16	39	52	56
CAV, CMV (%)	25*	53*	56†	60†
CAV, CMV-free (%)	5*	17*	44†	50†

*$p < 0.05$.
†Not significant.

Table II. *The number of endomyocardial biopsy (EMB) specimens analyzed and the frequency of vascular changes (VC) observed during the 4 posttransplantation years*

	Year after cardiac transplantation			
	1	*2*	*3*	*4*
EMB specimens	43	28	25	8
CMV patients	26	19	16	4
VC total (%)	74	79	88	100
VC, CMV (%)	77*	84*	81	100
VC, CMV-free (%)	71*	67*	100	100

*$p < 0.05$.

Dr. Norman E. Shumway *(Stanford, Calif.).* In any instance did you detect angina in the patients? We have wondered about that for many years.

Dr. McGiffin. Yes, some of these patients did have classic angina, and others had angina-equivalent symptoms. I guess this response may suggest some reinnervation of the heart. That I the only evidence of reinnervation that we have observed.

Dr. Shumway. We thought that these symptoms might be due more to left atrial distention in patients who are having moderate cardiac failure with their CAD rather than an indication of true reinnervation.

Dr. Robert M. Mentzer, Jr. *(Madison, Wis.).* One of the problems with this disease is that it can be difficult to differentiate typical atherosclerosis from cardiac allograft vasculopathy. This problem is going to become more complex as we use organs from older donors. Currently, we use angiography to differentiate the two diseases. This technique, however, may not be the best way of assessing progression of disease despite the fact that transplant vasculopathy differs pathologically from typical atherosclerosis. One diagnostic alternative that may give us more insight into differentiation and progression is intravascular ultrasography. We and others are beginning to realize that this may be a much better technique for diagnosing transplant vasculopathy as well as monitoring progression.

What has been your experience in the use of intravascular ultrasonography? Can you shed any light on new techniques for differentiating and following the course of the two diseases?

Dr. McGiffin. You are absolutely correct. Intracoronary ultrasonography is almost certainly more sensitive than angiography, which is very insensitive. We have not yet used intracoronary ultrasonography, but we will be starting that very soon. It will be interesting to see in a few years' time with the increased sensitivity of this test whether the same risk factors that we have demonstrated will also be operative when we are using a more sensitive method.

Dr. Davis C. Drinkwater *(Los Angeles, Calif.).* We have noted another risk factor for transplant CAD. We recently reported at the International Society for Heart and Lung Transplantation Meeting that the preservation solution may be related as a cofactor with this process. We have better results with our University of Wisconsin solution in terms of length of preservation and functional outcomes, but we also saw a significant increase in the prevalence of coronary arterial vasculopathy at a 36-month mean follow-up in our first 100 patients in whom this solution was used.

Do you have any information on the preservation solution, and did you vary it in your own patient population?

Dr. McGiffin. I am familiar with the information that you presented in Italy, and it is very interesting. We did not include preservation solution as a risk factor in this multivariable analysis.

Appendix A

Variables for analysis

Demographic: Age, gender, number of pregnancies, race, weight, height, body surface area.

Clinical: Diagnosis, blood type, CMV serology, panel reactive antibody, immunosuppression protocol, cholesterol, triglyceride, tobacco use.

Donor: Age, gender, race, weight, height, body surface area, blood type, pressors.

Donor/recipient matching: Age, gender, race, body surface area, weight, blood type, crossmatch, human leukocyte antigen mismatches.

Multivariate equation for CAD

Constant phase: intercept − 0.00859

Late phase: donor age (years) 0.0897 ± 0.0412, recipient pretransplantation positive CMV serology 2.22 ± 0.65, $\tau = 1$, $\alpha = 1$, $\eta = 1$, $\gamma = 4.48$, intercept = 1.013×10^{-10}

Multivariate equation for CAD event

Late phase: male recipient 2.06 ± 1.04, $\tau = 1$, $\gamma = 1$, $\alpha = 1$, $\eta = 2.01$, intercept = 6.98×10^{-6}.

Appendix B. CAD score

Each of the 17 portions of the coronary arteries is graded as follows:

0 Normal
1 Minor wall irregularities
2 Stenosis <50%
3 Stenosis ≥50% and <70%
4 Stenosis ≥70%
5 Occluded

Diffuse narrowing is given a score of 2 unless there is a discrete stenosis that warrants a higher score. Numbers in parentheses in the table are for left dominant systems.

Appendix B table

Vessel	*Multiplication factor*	*Maximum possible score*
Left main	4	20
LAD		
Proximal	2	10
Mid	1	5
Distal	1	5
First diagonal	2/3	
Second diagonal	2/3	
Third diagonal	2/3	
Left circumflex		
Proximal	2 (3)	10 (15)
Mid	1	5
First marginal	2/3	
Second marginal	2/3	10
Third marginal	2/3	
RCA		
Proximal	2 (1)	10 (5)
Mid	1	5
Distal	1	5
PDA	1	5
LV branch	1	5
Total		105

LAD, Left anterior descending; *RCA,* right coronary artery; *PDA,* posterior descending artery; *LV,* left ventricular.