

ASSOCIATION BETWEEN PRIOR CYTOMEGALOVIRUS INFECTION AND THE RISK OF RESTENOSIS AFTER CORONARY ATHERECTOMY

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ABSTRACT

Background Restenosis occurs commonly after coronary angioplasty and atherectomy, but the causes of restenosis are poorly understood. Recently, it has been found that cytomegalovirus (CMV) DNA is present in restenotic lesions from atherectomy specimens. This and other evidence suggest that CMV may have a role in the process of restenosis.

Methods We prospectively studied 75 consecutive patients undergoing directional coronary atherectomy for symptomatic coronary artery disease. Before atherectomy was performed, we measured blood levels of anti-CMV IgG antibodies to determine whether previous exposure to CMV increased the risk of restenosis, as determined by coronary angiography performed six months after atherectomy.

Results After atherectomy, the mean (\pm SD) minimal luminal diameter of the target vessel was greater in the 49 patients who were seropositive for CMV than in the 26 patients who were seronegative (3.18 ± 0.51 mm vs. 2.89 ± 0.45 mm, $P = 0.01$). After six months, however, the seropositive patients had a greater reduction in the luminal diameter (1.24 ± 0.83 mm vs. 0.68 ± 0.69 mm, $P = 0.003$), resulting in a significantly higher rate of restenosis in the seropositive patients (43 percent vs. 8 percent, $P = 0.002$). In a multivariable logistic-regression model, CMV seropositivity and the CMV titer were independently predictive of restenosis (odds ratios, 12.9 and 8.1, respectively). There was no evidence of acute infection, since the titer of anti-CMV IgG antibodies did not increase over time and tests for anti-CMV IgM antibodies were negative in all patients.

Conclusions Prior infection with CMV is a strong independent risk factor for restenosis after coronary atherectomy. If confirmed, these findings may help identify patients at risk for restenosis. (N Engl J Med 1996;335:624-30.)

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NEOINTIMAL hyperplasia and arterial remodeling cause restenosis in 20 to 50 percent of patients who have undergone coronary angioplasty.^{1,2} Although the mechanisms are unknown, previous findings have raised the possibility that cytomegalovirus (CMV) contributes to the development of restenosis in some patients.³ In approximately one third of patients with restenosis, the lesions contain CMV DNA sequences. Smooth-muscle cells grown from such lesions express IE84, one of the virus's immediate early proteins, and

IE84 binds to and inhibits the p53 tumor-suppressor gene product. These effects may enhance the proliferation of smooth-muscle cells or inhibit apoptosis, either of which may contribute to restenosis.³

CMV infection in immunocompetent adults is common⁴ and usually asymptomatic.^{5,6} Like other herpesviruses, CMV persists indefinitely in certain host cells.^{7,8} Under certain circumstances (such as immunosuppression due to the acquired immunodeficiency syndrome⁹ or treatment after organ transplantation¹⁰), the virus can be reactivated and cause serious disease. In these situations, viral replication contributes to the disease process. However, there is evidence that CMV can also contribute to the disease process during an abortive infection,¹¹ which is characterized by viral-gene expression limited to immediate early gene products without viral replication. CMV immediate early gene products, for example, are known to affect the expression of many human cellular genes involved in inflammation and immunologic responses,¹² and as previously documented, CMV is present in smooth-muscle cells from restenotic lesions and can express immediate early gene products, which inhibit the p53 function.³ We therefore hypothesized that latent CMV may be reactivated locally in response to vascular injury in a subgroup of patients undergoing coronary angioplasty. By inhibiting the capacity of p53 either to block the progression of the cell cycle or to initiate apoptosis, as well as by other mechanisms, the virus may enhance the accumulation of smooth-muscle cells and thereby facilitate the development of restenosis. We conducted a prospective investigation to test this hypothesis.

METHODS

The patients in our study were part of the Optimal Atherectomy Restenosis Study (OARS), which was designed to determine the frequency of restenosis after directional coronary atherectomy. A follow-up angiographic evaluation was performed approximately six months after the surgery. Our patients were from Washington Hospital Center, Washington, D.C., which was one of four centers participating in OARS and which recruited 100 of its 211 patients. Of these 100 patients, 75 were enrolled in our

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study; 7 patients were not enrolled because of an initial procedural complication or a protocol violation, and 18 patients did not undergo follow-up angiography.

Before and six months after surgery, blood samples were collected for assays of anti-CMV IgG and IgM antibodies. The assays were performed without knowledge of the angiographic findings.

A patient was considered to have diabetes if he or she was taking insulin or oral hypoglycemic agents or had previously received such treatment and was currently using dietary modification to control the condition. A patient was considered to have hypertension if he or she had received the diagnosis or was being treated with antihypertensive medications or dietary modification. A patient was considered to have hypercholesterolemia if he or she had a serum cholesterol value higher than 240 mg per deciliter (6.2 mmol per liter) at the time of angioplasty or was receiving cholesterol-lowering treatment.

Directional Atherectomy

Optimal directional coronary atherectomy consists of local plaque resection followed by circumferential plaque resection with the use of larger devices or higher balloon pressures and usually concludes with adjunctive low-pressure balloon dilation. Ultrasonographic guidance is used to optimize the results. Of the 75 patients in the study, 65 (87 percent) had adjunctive percutaneous transluminal coronary angioplasty, resulting in a mean additional 10 percent reduction in the degree of stenosis. Stents were placed in two patients (3 percent) after the atherectomy, because of severe lumen-compromising dissections.

Angiographic Analysis

Cineangiograms were forwarded to the central angiographic laboratory and were evaluated without knowledge of whether the patients were seropositive or seronegative for anti-CMV antibodies. Base-line, postsurgical, and follow-up (six-month) cineangiograms were analyzed with an automated edge-detection algorithm (Cardiovascular Measurement System, Medis Medical Imaging Systems, Nuenen, the Netherlands). The minimal luminal diameter, interpolated reference diameter, and percentage of stenosis before and after atherectomy and at six months were measured from two projections; the average of these two values is reported. An early gain in the diameter of the target vessel was defined as the minimal luminal diameter immediately after surgery minus the minimal luminal diameter before surgery. A late loss in the luminal diameter was defined as the minimal luminal diameter immediately after surgery minus the minimal luminal diameter at six months. The loss index was defined as the late loss divided by the early gain, expressed as a percentage. Restenosis was defined as more than 50 percent stenosis at follow-up in a vessel with less than 50 percent stenosis immediately after atherectomy.

Assays for CMV Antibodies

Tests for anti-CMV IgG antibodies were performed with an enzyme-linked immunosorbent assay (ELISA) kit (Cytomegelisa II, BioWhittaker, Walkersville, Md.), according to the manufacturer's directions. Antibody titers were determined on the basis of a standard curve. The threshold value was determined prospectively: an ELISA value of less than 0.25 unit was considered a negative result, and a value of 0.25 unit or higher was considered a positive result, indicating prior exposure to CMV.

Tests for anti-CMV IgM antibodies were performed with an enzyme-linked antibody-capture assay kit (CMV CAP-M, BioWhittaker), according to the manufacturer's directions. An index value of less than 0.9 was interpreted as a negative result, and a value of more than 1.1 was interpreted as a positive result; values between 0.9 and 1.1 were considered equivocal results.

Statistical Analysis

Statistical analyses of frequency counts were performed with the use of the chi-square test or Fisher's exact test for small sam-

ples, and means were compared with the two-sample t-test. All tests were two-sided. The odds ratio was used as a measure of the risk of restenosis in patients with a given risk factor as compared with those without the risk factor. Modeling of the dichotomous variable of restenosis at six months was performed with the logistic-regression model. Factors affecting the loss index were identified by linear regression. The covariates considered were seropositive CMV status, higher CMV titer, diabetes, hypercholesterolemia, hypertension, location of the stenosis in the left anterior descending coronary artery, small reference vessel (<3 mm in diameter), a recent history of smoking, male sex, older age, and unstable angina as the indication for atherectomy. All covariates were examined as predictors of restenosis and the loss index in univariate analyses, as a group in one multivariate model, and in a stepwise multivariable model. Values are reported as means ±SD.

RESULTS

Characteristics of the Patients

The 75 patients ranged in age from 35 to 78 years (mean, 58); there were 58 men and 17 women (Table 1). Our patients were similar to the total OARS cohort with respect to age, sex, and the proportion of patients with single- or double-vessel disease (Table 1), suggesting that the subgroup was representative of the patients undergoing directional coronary atherectomy in the larger study.

Forty-nine of the 75 patients (65 percent) had positive tests for anti-CMV IgG antibodies at the time of enrollment in the study, indicating prior exposure to CMV — a prevalence of seropositivity similar to that reported in several epidemiologic studies involving subjects of a similar age.¹² Of the 18 patients excluded from the study because an angiogram was not obtained at six months, 11 (61 percent) were seropositive for CMV, which is similar to the prevalence among the 75 patients included in the study. Restenosis developed in 23 of the 75 patients (31 percent).

The prevalence of several potential risk factors for

TABLE 1. CHARACTERISTICS OF THE TOTAL COHORT IN THE OPTIMAL ATHERECTOMY RESTENOSIS STUDY (OARS) AND THE SUBGROUP OF PATIENTS IN THE PRESENT STUDY.

CHARACTERISTIC	OARS COHORT (N=199)*	SUBGROUP STUDIED (N=75)	P VALUE
Age — yr			
Mean ±SD	58±11	58±10	1.00†
Range	36–80	35–78	
Male sex — no. of patients (%)	152 (76)	58 (77)	0.868‡
Single- or double-vessel disease — no. of patients (%)	187 (94)	73 (97)	0.525§

*Twelve patients did not return for follow-up studies.

†By a two-sample t-test (two-tailed).

‡By the chi-square test.

§By Fisher's exact test (two-tailed).

restenosis did not differ according to the CMV status of the patients. The one exception was hypertension, which was present in 59 percent of the seropositive patients but in only 31 percent of the seronegative patients ($P=0.02$). Additional analyses showed, however, that the presence of hypertension was unrelated to restenosis ($P=0.18$).

Correlation between CMV Seropositivity and Restenosis

Of the 49 patients with prior exposure to CMV, 21 (43 percent) had restenosis at six months, as compared with only 2 of the 26 patients (8 percent) without prior exposure to the virus ($P=0.002$) (Fig. 1). When the percentage of stenosis of the target vessel at follow-up was analyzed as a continuous variable, CMV infection was associated with more severe stenosis ($P=0.01$) (Table 2 and Fig. 1). The minimal

luminal diameter and percentage of stenosis at base line, immediately after directional coronary atherectomy, and at six months are shown in Table 2. Figure 2 shows the distribution of stenotic target vessels according to the minimal luminal diameter at each of the three points in time. At base line, the reference diameter of the vessel and the minimal luminal diameter of the stenotic segment tended to be larger in the seropositive patients than in the seronegative patients, but there was no significant difference in the percentage of stenosis. Immediately after the procedure, the seropositive group had a slightly larger minimal luminal diameter ($P=0.01$), but the mean gain was similar. At six months, however, the seropositive group had a much greater loss of luminal diameter ($P=0.003$) and, most important, an 89 percent higher loss index than the seronegative group ($P<0.001$) (Table 2 and Fig. 3).

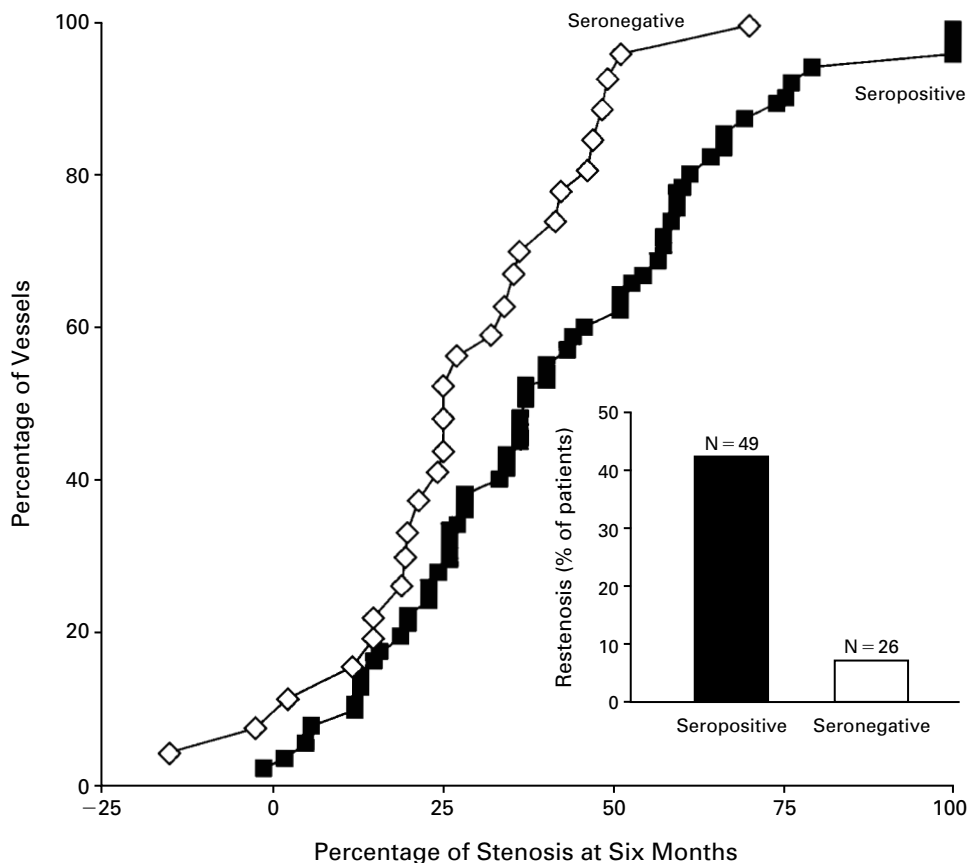


Figure 1. Influence of Prior Cytomegalovirus (CMV) Infection on the Distribution of Stenosis in 85 Target Vessels in 75 Patients, as Determined by Angiography Six Months after Directional Coronary Atherectomy.

The patients were divided into two groups on the basis of whether they were seropositive or seronegative for anti-CMV IgG antibodies at base line. A seropositive status was defined prospectively as an assay value of 0.25 unit or higher. At six months, vessels in the seropositive patients had a higher percentage of stenosis than vessels in the seronegative patients ($P=0.01$). The inset shows the incidence of restenosis (>50 percent narrowing of the vessel diameter), which was also higher in the seropositive patients ($P=0.002$).

TABLE 2. ASSOCIATION BETWEEN CMV STATUS AND ANGIOGRAPHIC FINDINGS IN 85 TARGET VESSELS BEFORE AND AFTER ATHERECTOMY.

ANGIOGRAPHIC FINDINGS*	SEROPOSITIVE VESSELS (N=58)	SERONEGATIVE VESSELS (N=27)	P VALUE†
	mean ±SD		
Before atherectomy			
Reference diameter (mm)	3.23±0.42	3.05±0.48	0.07
MLD (mm)	1.29±0.44	1.09±0.33	0.045
Stenosis (%)	60±12	64±11	0.21
Immediately after atherectomy			
Reference diameter (mm)	3.37±0.44	3.21±0.47	0.13
MLD (mm)	3.18±0.51	2.89±0.45	0.01
Stenosis (%)	5±13	10±10	0.11
At six months			
Reference diameter (mm)	3.27±0.49	3.08±0.40	0.08
MLD (mm)	1.93±0.94	2.20±0.6	0.12
Stenosis (%)	42±25	28±18	0.01
Gain or loss			
Early gain (mm)	1.90±0.56	1.80±0.55	0.44
Late loss (mm)	1.24±0.83	0.68±0.69	0.003
Loss index (%)	68±47	36±33	<0.001

*Reference diameter denotes the diameter of the normal segment of the vessel adjacent to the stenotic segment, and MLD the minimal luminal diameter of the stenotic segment. Early gain, late loss, and the loss index are defined in the Methods section.

†P values were calculated with a two-sample t-test (two-sided).

Influence of CMV Seropositivity and Other Risk Factors on Restenosis

Univariate analyses (Table 3) showed that CMV seropositivity was the only statistically significant predictor of restenosis (odds ratio, 9.0; P=0.002). An analysis of the association between the mean IgG antibody titer and restenosis confirmed the finding (mean titer, 0.66±0.30 unit among the patients with restenosis and 0.44±0.35 unit among those without restenosis; P=0.01). There were no other statistically significant predictors of restenosis. The relation of CMV seropositivity and the CMV titer with the risk of restenosis did not change in the multivariate logistic-regression models (odds ratio for restenosis associated with a positive CMV status as compared with a negative status, 12.9; 95 percent confidence interval, 2.3 to 71.1; P=0.003; odds ratio associated with a higher CMV titer as compared with a lower titer, 8.1; 95 percent confidence interval, 1.5 to 43.2; P=0.01).

Influence of CMV Seropositivity and Other Risk Factors on the Loss Index

Simple linear regression models showed that both the continuous variable for the CMV status (the CMV titer) and the dichotomous variable for the CMV status (an ELISA value ≥0.25 unit indicating seropositivity and a lower value indicating seronegativity) were strong predictors of the loss index (P=0.01 and P=0.002, respectively).

The full multiple regression model for the loss index showed that the CMV status, analyzed as either a continuous or a dichotomous variable, was a persistent and independent predictor of restenosis, over and above the effects of all other covariates in the model (P=0.03 and P=0.01, respectively). Table 4 shows the results of the full model with the CMV titer. The results of multivariate analyses of the other risk factors did not differ appreciably from the results of the univariate analyses. A stepwise approach to model selection also identified the continuous and dichotomous variables for the CMV status as the only significant predictors of the loss index. Although the relation between the CMV titer and restenosis was significant (P=0.01), the CMV titer accounted for only 7 percent of the variation in the loss index at six months (r²=0.07). To put this in perspective, taken as a whole, all the risk factors we analyzed explained only 11.5 percent of the total variation in the loss index.

To determine whether the effect of exposure to CMV differed in subgroups of patients defined according to the other variables analyzed in the study, we tested a two-factor interaction of each variable with CMV exposure. None of the interactions were significant.

Evidence against the Presence of Acute Infection and Systemic Viremia

Anti-CMV IgM antibodies, which are usually present only early after the acute infection, were not detected in any of the patients at base line. At approximately six months (when follow-up angioplasty was performed), a second assay of anti-CMV IgG anti-

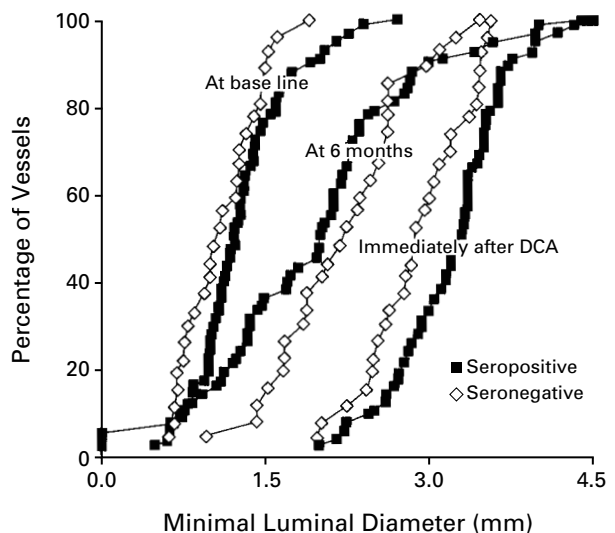


Figure 2. Distribution of Minimal Luminal Diameters at Base Line, Immediately after Directional Coronary Atherectomy (DCA), and at Six Months.

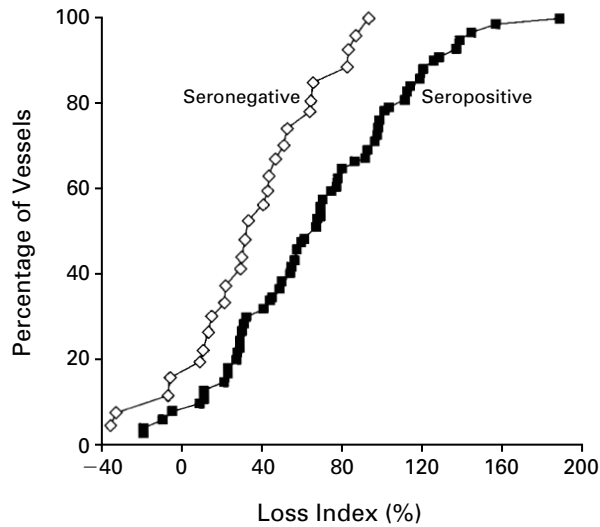


Figure 3. Distribution of the Loss Index at Six Months. The loss index was calculated as the late loss (the minimal luminal diameter immediately after atherectomy minus the minimal luminal diameter at six months) divided by the early gain (the minimal luminal diameter immediately after atherectomy minus the minimal luminal diameter before atherectomy), expressed as a percentage. The seropositive patients had a higher loss index than the seronegative patients ($P < 0.001$).

bodies showed no significant change in the titer (Fig. 4). Most important, no patient who was initially seropositive for anti-CMV IgG antibodies had a significant increase in the titer (to more than two times the initial value), and titers fell to the seronegative range in only four initially seropositive patients (all of whom had restenosis). In addition, none of the initially seronegative patients became seropositive.

Seropositivity for Hepatitis A Virus

To determine whether the correlation between CMV seropositivity and restenosis merely reflected a generalized susceptibility to viral infection or an increased but nonspecific immune response, we determined whether there was a correlation between pre-existing antibodies to hepatitis A virus and restenosis (the frequency of seropositivity for hepatitis A virus is approximately the same as that for CMV). Forty-one percent of the 75 patients were seropositive for hepatitis A virus. However, no significant association was found between seropositivity and restenosis. The rate of restenosis was 35.7 percent among the patients who were seropositive for hepatitis A virus and 37.5 percent among those who were seronegative.

DISCUSSION

The present study provides prospective evidence that prior exposure to CMV, as indicated by the presence of anti-CMV IgG antibodies at the time of coronary atherectomy, is a strong independent risk factor for restenosis. The importance of this risk factor is reflected by the odds ratio for restenosis, which was nine times higher among the patients who had previously been exposed to CMV than among those who had not been exposed to the virus. None of the other variables tested were associated with a significantly increased risk of restenosis — findings that are generally consistent with the results of other studies.¹³⁻¹⁸

In our primary analysis, we considered the end point of restenosis as a dichotomous variable (i.e., restenosis vs. no restenosis). However, when the degree of stenosis was considered as a continuous variable, the patients who were seropositive for CMV had a higher percentage of stenosis than the sero-

TABLE 3. UNIVARIATE ASSOCIATION BETWEEN RESTENOSIS AND POTENTIAL RISK FACTORS.*

RISK FACTOR	RESTENOSIS (N=23)	NO RESTENOSIS (N=52)	ODDS RATIO (95% CI)	P VALUE†
	no. of patients (%)			
CMV seropositivity	21 (91)	28 (54)	9.00 (1.91-42.38)	0.002
Diabetes	4 (17)	8 (15)	1.16 (0.31-4.31)	1.00
Lesion in left anterior descending artery	11 (48)	25 (48)	0.99 (0.37-2.64)	0.98
Small vessel (<3 mm in diameter)	8 (35)	21 (40)	0.79 (0.28-2.19)	0.65
Hypertension	14 (61)	23 (44)	1.96 (0.72-5.33)	0.18
Hypercholesterolemia	7 (30)	21 (40)	0.65 (0.23-1.84)	0.41
Smoking	5 (22)	17 (33)	0.57 (0.18-1.8)	0.34
Male sex	20 (87)	38 (73)	2.44 (0.63-9.09)	0.19
Unstable angina	17 (74)	40 (77)	0.85 (0.27-2.64)	0.78

*Restenosis was defined as more than 50 percent narrowing of the luminal diameter. CI denotes confidence interval.

†All P values were calculated with the chi-square test, except for the P value for diabetes, which was calculated with Fisher's exact test (two-tailed).

TABLE 4. ASSOCIATION BETWEEN POTENTIAL RISK FACTORS AND THE LOSS INDEX.*

RISK FACTOR	ASSOCIATION WITH LOSS INDEX	
	SLOPE	P VALUE
CMV titer†	0.36	0.025
Diabetes	-0.03	0.83
Lesion in left anterior descending artery	0.09	0.42
Small vessel (<3 mm in diameter)	-0.03	0.78
Hypertension	-0.06	0.62
Hypercholesterolemia	0.06	0.58
Unstable angina	-0.06	0.64
Smoking	-0.03	0.81
Male sex	-0.13	0.35
Age	0.01	0.30

*Data are from the full multiple linear regression model.

†When CMV status was defined as a dichotomous variable (seropositive vs. seronegative), the association with the loss index was even stronger (P=0.007).

negative patients. Considered as a continuous variable, the minimal luminal diameter immediately after directional coronary atherectomy was larger in the seropositive patients than in the seronegative patients. However, the seropositive patients had a markedly greater loss of luminal diameter and a higher loss index at six months, resulting in a tendency toward a smaller minimal luminal diameter and a higher incidence of restenosis.

Given that the processes leading to restenosis are complex and undoubtedly multifactorial, it is all the more compelling that one factor — exposure to CMV — conveyed such a high risk. The diagnosis of restenosis in this study was based on angiographic evaluation rather than clinical assessment, which is known to be highly inaccurate in predicting restenosis. Confidence in the results also derives from the fact that this study was prospective in design, that the angiograms were evaluated without knowledge of the patients' CMV status, and that the tests for anti-CMV antibodies were performed without knowledge of the angiographic results.

The association between the development of restenosis and prior exposure to CMV was based on assays of anti-CMV IgG antibodies performed at the time of the atherectomy. Antibody levels did not increase during the ensuing six months. This finding, in conjunction with the fact that anti-CMV IgM antibodies were not detected, suggests that acute CMV infection with systemic viremia did not occur. We cannot rule out the possibility that acute viremia developed shortly after the atherectomy, with antibody levels returning to base-line values by six months. Our results, however, are most compatible with the idea that either the virus produced an abortive infection

(i.e., the expression of viral genes was limited to immediate early gene products) or viral replication occurred locally in the absence of systemic viremia.

CMV is a complex virus — it has a large genome with over 200 open reading frames. Thus, it undoubtedly possesses many viral proteins that may influence neointimal accumulation. In addition to the effects of IE84, which binds to and inactivates p53, the infection of smooth-muscle cells with CMV leads to the expression and secretion of growth factors,^{19,20} and CMV infection has been shown to activate NF-κB, a transcription factor involved in stimulating a broad range of genes, including those that have roles in inflammatory and immune responses.²¹ The virus also increases the adhesion of leukocytes and platelets to endothelial cells by inducing cellular expression of adhesion molecules²²⁻²⁵ and causes changes that are procoagulant.²⁶⁻²⁸ Furthermore, CMV increases the activity of the scavenger receptor, and IE72, another immediate early gene product, increases the expression of the scavenger-receptor gene.²⁹ The increased accumulation of oxidized low-density lipoprotein cholesterol in lesional smooth-muscle cells may contribute to an atherogenic process such as restenosis. Finally, it has recently been shown that IE72 and IE84 inhibit apoptosis, which may increase neointimal accumulation.³⁰

Unexpectedly, we also found a strong association between exposure to CMV and hypertension. Because this association was not a prospectively defined end point, additional studies are needed to val-

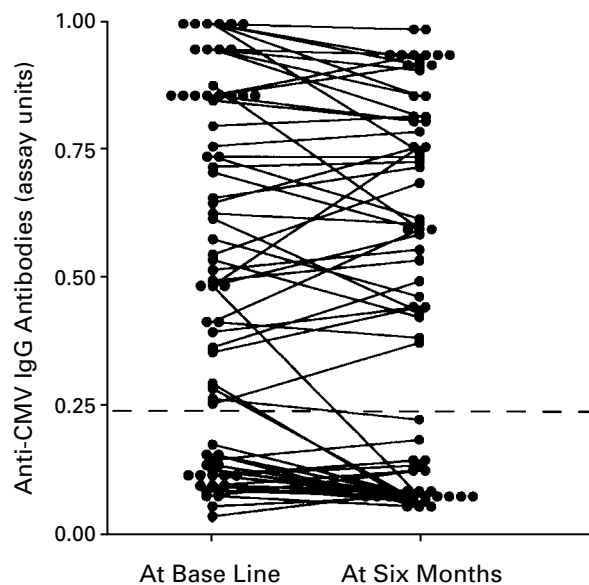


Figure 4. Titer of Anti-CMV IgG Antibodies at Base Line and at Six Months.

A titer of 0.25 unit or higher (i.e., a value above the broken line) was considered to indicate seropositivity.

idate the potentially important link between CMV infection and hypertension. It is possible that the relation between CMV infection and restenosis observed in the present investigation is due to the particular type of angioplasty used — atherectomy — and that different results would have been observed with other types, such as balloon angioplasty. Separate studies of other types of angioplasty will be needed to settle this issue.

It is possible that CMV seropositivity, instead of reflecting a causal role of CMV infection in the development of restenosis, is just a marker of another process that causes restenosis. Although a causal relation has not yet been definitively demonstrated, our previous studies showed that CMV DNA is present in restenotic lesions in humans,³ a CMV gene product inhibits the transcriptional activity of p53 in human coronary-artery smooth-muscle cells,³ and acute CMV infection increases neointimal formation in rats with balloon injuries.³¹ Taken together with the results presented here, these findings support the idea that CMV infection plays a part in restenosis.

The results of the present investigation, if confirmed by additional large studies, demonstrate that CMV provides a means of stratifying patients according to the risk of restenosis. Thus, the knowledge (based on the results of a simple, standard blood test) that a given patient has less than a 10 percent chance of restenosis (i.e., is seronegative for CMV) or more than a 40 percent chance (i.e., is seropositive for CMV), when considered together with the patient's specific clinical profile, may influence the clinician's judgment of whether that patient will benefit from atherectomy or should instead undergo coronary-artery bypass surgery. And if future studies establish a causal role of CMV infection in the development of restenosis, it may be possible to prevent restenosis by using specific antiviral strategies.

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