Cytomegalovirus Infection in Heart Transplant Recipients Is Associated With Impaired Endothelial Function

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Background—Cardiac allograft vasculopathy (CAV) is initiated by allograft endothelial injury. We hypothesized that a major mechanism by which cytomegalovirus (CMV) could contribute to CAV is by dysregulation of the endothelial vasomotor response.

Methods—Coronary endothelial vasomotor function was determined in 183 consecutive patients (24±33 months after transplantation), and was correlated with recipient and donor CMV serological status before transplantation and with documented CMV infection episodes (CMVpp65Ag+). Serial endothelial function measurements were performed in a subgroup of 53 transplant recipients (1 month and 12 months after transplantation). The composite endpoint of cardiovascular related events and death during a follow-up of 66±41 months was analyzed based on the CMV serological status before transplantation.

Results—The medium event-free time for CMV-negative recipients of CMV-positive hearts was 8.1 years compared with 13.3 years for the other groups (P<0.05). Distal epicardial but not microvascular endothelial function was significantly impaired in CMV seronegative recipients of seropositive donor hearts (n=48) compared with all other groups (P<0.01 versus seronegative recipient/seronegative donor; P<0.05 versus seropositive recipient/seronegative donor; P<0.05 versus seropositive recipient/seropositive donor). Distal epicardial endothelial dysfunction was more pronounced in heart transplant recipients with a history of documented CMV infection compared with patients without any documented CMV infection (P<0.01). In a longitudinal subgroup analysis, distal epicardial and microcirculatory endothelial vasomotor response deteriorated significantly in recipients with documented CMV infection (P<0.05 versus baseline) but not in patients without previous CMV infection.

Conclusion—Documented CMV infection episodes in heart transplant recipients are associated with impaired coronary endothelial function. CMV-negative recipients of CMV-positive donor hearts have an impaired distal epicardial endothelial function and an increased incidence of cardiovascular-related events and death during follow-up. CMV infection may contribute to allograft failure by accelerating coronary endothelial dysfunction. (Circulation. 2004;110[suppl II]:II-207–II-212.)

Key Words: inflammation ■ endothelium ■ nitric oxide ■ coronary vasomotor function

Cardiac allograft vasculopathy (CAV) limits the long-term success of cardiac transplantation and is characterized by diffuse functional and structural coronary alterations in concert with systemic inflammatory activation.1

The evidence supporting a role for cytomegalovirus (CMV) infection is based on epidemiologic and observational data, experimental models, and therapeutic trials.2–8 Most strikingly, prophylactic treatment of cardiac transplant recipients with ganciclovir and/or CMV hyperimmune globulin has been shown to reduce the incidence of CAV.4,5

However, the mechanisms by which CMV may trigger atherogenesis are incompletely defined. Here we hypothesized that CMV contributes to coronary endothelial dysfunction, an early marker and mediator of structural coronary alterations and graft dysfunction. It was the aim of this post-hoc analysis to determine the prognostic impact of CMV serostatus before heart transplantation and CMV infection episodes after transplantation on coronary vasomotor function and cardiovascular-related events and death.

Methods

This investigation was performed with approval by the institutional ethics committee. Informed consent was obtained from all subjects. The study group consisted of 183 consecutive patients (24±33 months after orthotopic heart transplantation) undergoing routine diagnostic coronary angiography after transplantation. Patients were selected according to predefined exclusion criteria (acute rejection or...
infection episode at time of the study, and significant endocrine, hepatic, or renal disorders). The patients were in the fasting state and all cardiovascular medications had been discontinued for at least 24 hours. All patients studied were maintained on a tacrolimus or cyclosporine and mycophenolate mofetil-based immunosuppression protocol. Steroids were withdrawn in 48% of the patients 12 months after transplantation. CMV serostatus (IgG-positive or IgG-negative) of all transplant donors and recipients was analyzed before transplant. Patients were followed-up for 66 ± 41 months (1 to 8 years). Detailed patient characteristics are listed in the Table.

### Cardiac Catheterization

Measurements of coronary vasomotor response (quantitative coronary angiography and intracoronary Doppler flow measurement) and determination of intimal thickening (intravascular ultrasound) have been described in detail elsewhere. In brief, after the diagnostic procedure including left ventriculography and coronary angiography, a Doppler Flow-wire (Endosonics Corporation) was placed in the proximal left anterior descending artery, permitting measurement of coronary blood flow velocities; 5000 IU of heparin was given intravenously. Blood flow velocity was recorded continuously during administration of the study agents. First, adenosine (160 μg/min over 5 minutes; Adrek, Sanofi-Winthrop, Munich, Germany) was infused into the left coronary system to achieve maximal (endothelium-independent) coronary flow. Second, intracoronary acetylcholine (Ach) (1 and 30 μg/min over 5 minutes each; Miochol, CIBA Visions Vetrieb GmbH, Großostheim Germany) was infused to investigate epicardial and microvascular endothelial vasomotor function (estimated final blood concentrations in the coronary bed of 10^{-7} and 3×10^{-6} mol/L). Finally, intracoronary nifedipine (Adalat; Bayer AG) was administered as a bolus (0.2 mg/30 seconds) to obtain maximal (endothelium-independent) epicardial vasodilation. Baseline status was achieved after each new intervention. At the end of each infusion, coronary arteriography was performed and analyzed off-line using quantitative coronary angiography.

### Coronary Flow Reserve

The coronary flow velocity reserve, as a marker of the microvascular reactivity, was determined by the ratio of the maximal coronary flow velocity (cm/sec) after pharmacological stimulation to the basal flow velocity. Coronary flow is critically controlled at the level of the resistance vessels, provided no severe stenosis is present in the epicardial arteries. In the present study, no epicardial constriction >50% in response to Ach was observed. Therefore, diameter changes were not included in the calculation of coronary flow velocity reserve.

### Quantitative Coronary Angiography

Quantitative coronary angiography was performed to investigate epicardial vasomotor response using a computerized automated analysis system (HICOR, Siemens). Nonstenotic proximal and distal coronary arterial segments identified between easily visualized branch points were selected for analysis in the left anterior descending artery. Responses of the proximal and distal coronary segments to the different stimuli were measured in a blinded fashion and were expressed as percent change versus control value. Intraobserver and interobserver variability showed high reproducibility (r>0.89, P<0.001).

### Intravascular Ultrasound

Intravascular ultrasound (IVUS) was performed in a subgroup of 89 patients 12 ± 6 months after transplantation. Immediately after the Doppler flow measurement, IVUS was performed to detect atherosclerotic plaques not visible with angiography in a subgroup of 83 patients (14 ± 8 months after transplantation). The imaging system consisted of a 30-MHz ultrasound transducer enclosed within an acoustic housing on the tip of a 2.9-French flexible, rapid exchange catheter (CVIS Inc). The catheter was advanced to the distal left anterior descending and/or circumflex artery, carefully observing a standardized pullback maneuver, images were documented on videotape for further off-line analysis. The 3 sites with the most severe intimal proliferation were evaluated and the averaged maximal intimal thickness was calculated.10 Maximal intimal thickness was measured as the greatest distance from the intimal leading edge to the media adventitia border.

Functional and morphological measurements were performed by investigators without knowledge of the CMV status of the patients.

### CMV pp65 Antigen Detection

The CMV pp65 antigenemia immunofluorescence assay was used for the qualitative detection and identification of the lower matrix protein pp65 of CMV in isolated peripheral blood leukocytes. The immediate early CMV antigen pp65 was investigated in all patients on a regular basis 1, 6, and 12 months after transplantation. In the case of any clinical signs of CMV infection, antigen detection was performed between the regular intervals. CMV pp65 positivity has been shown to be a reliable early marker of relevant CMV infection.11

### CMV Serostatus

We tested for IgG CMV antibodies in serum with a commercially available enzyme-linked immunosorbent assay according to the
suggestions of the manufacturer (Enzygnost anti-CMV IgG, H9251-testing; Dade Behring). Results were interpreted to be positive if the corrected absorbance values (\(A_{\text{ant} \times \text{control antigen}}\)) were greater than the cutoff of 0.2 optical density (OD), and were interpreted to be negative if the absorbance values were less than the cutoff of 0.2 OD.

Survival Analysis
The composite endpoint of cardiovascular-related events (progressive heart failure, acute myocardial infarction, coronary revascularization, retransplantation) and death during the follow-up period of 66±41 months was compared between CMV-negative recipients of CMV-positive hearts and all other groups (CMV-negative recipients of CMV-negative hearts; CMV-positive recipients of CMV-positive hearts, CMV-positive recipients of CMV-negative hearts, CMV-negative recipients of CMV-positive hearts) using a Kaplan–Meier analysis.

Statistical Analysis
Continuous variables are presented as mean±SD. When comparing several groups, 1-way ANOVA was followed by the Student-Newman-Keuls post hoc test for statistical significance. For comparisons within the same individuals over time (prospective study groups), the paired-samples \(t\) test was used. Discrete variables are presented as percentages. The Pearson χ² test was used to determine significant differences. Cumulative event-free survival rates were estimated by Kaplan–Meier survival curves (life test procedure of SPSS). Probability values for survival curve comparisons were calculated with the log-rank statistic. Cox proportional hazards multivariate stepwise regression analysis (SPSS) was used to determine the univariate and multivariate relationship between CMV, clinical variables, and cardiovascular events/death during the follow-up period.

Statistical significance was assumed if the null hypothesis could be rejected at \(P=0.05\).

Results
Coronary Vasomotor Function and CMV Serostatus: Epicardial Function and Microvascular Function
Proximal epicardial endothelium-dependent (Ach) and endothelium-independent (Nifedipine) vasomotor responses were comparable between the groups (data not shown).

Distal epicardial vasomotor response to Ach but not nifedipine was significantly impaired in CMV-negative recipients of CMV-positive hearts compared with all groups (Figure 1). In CMV-negative recipients of CMV-negative hearts, distal epicardial endothelial function was significantly better compared with CMV-positive recipients of CMV-negative hearts (\(P<0.05\)), significantly better compared with CMV-negative recipients of CMV-positive hearts (\(P<0.05\)), and tended to be better compared with CMV-positive recipients of CMV-positive hearts (\(P=0.07\)) (Figure 1).

Microvascular endothelium-dependent and endothelium-independent vasomotor function was comparable between the groups (Figure 2).

Coronary Intimal Thickening and CMV Serostatus
Averaged maximal intimal thickness was similar in all groups. Intimal thickness was 0.8±0.3 mm in CMV-negative recipients of CMV-negative hearts, 1.0±0.5 mm in CMV-
negative recipients of CMV-positive hearts, 0.7±0.4 in CMV-positive recipients of CMV-positive hearts, and 0.9±0.4 in CMV-positive recipients of CMV-negative hearts ($P=\text{NS}$).

**Coronary Vasomotor Function and Previous CMV Infection**

To further analyze the impact of documented CMV infection episodes on endothelial function, patients were grouped according to the results of the CMV pp65 antigen analysis in CMV-positive (at least 1 positive CMV pp65 detection; n=15) and CMV-negative patients (n=168). Despite CMV prophylaxis with ganciclovir over 6 weeks in recipients of CMV-positive donor hearts, CMV antigen positivity still tended to occur more often in recipients of CMV-positive compared with CMV-negative donor hearts ($\chi^2=3.2; P=0.076$).

Coronary distal epicardial endothelial function was significantly impaired in CMV-positive compared with CMV-negative patients ($P<0.05$; Figure 3). Microcirculatory endothelial function tended to be reduced in CMV-positive versus CMV-negative patients ($P=0.12$; Figure 3). No further impairment of epicardial endothelial function was detectable in patients with CMV disease (diagnosed by 2 physicians after the established clinical criteria). However, in patients with a history of CMV disease (n=9), microvascular endothelial function was significantly impaired compared with patients without CMV disease (coronary flow increase to ACh 1.9±0.3 versus 2.5±0.6; $P<0.01$).

Endothelium-independent vasomotor responses were comparable between patients with and without documented CMV infection (data not shown). CMV infection remained an independent predictor of distal epicardial endothelial dysfunction after adjustment for the indication of transplantation (ischemic heart disease, cardiomyopathy, and others), statin therapy, and after adjustment for the risk factors of donor ischemic time, acute rejection episodes, hyperlipidemia (cholesterol $>200$ mg/dL), hypertension, smoking, and diabetes ($P=0.046$ using multivariate regression analysis).

In a further subgroup analysis of 7 CMV-positive patients in whom vasomotor function was assessed before and after the documented CMV infection, coronary endothelial function significantly deteriorated during follow-up compared with 46 CMV-negative patients. Distal epicardial vasoconstriction in response to ACh was $-8\pm7\%$ at baseline and $-12\pm3\%$ during follow-up in CMV-positive patients, compared with $-6\pm5\%$ at baseline and $-5\pm4\%$ during follow-up in CMV-negative patients ($P<0.05$). Microvascular endothelium-dependent function significantly decreased during follow-up in CMV-positive patients (coronary flow increase to ACh was 2.4±0.6 versus 2.0±0.4 during follow-up; $P<0.05$), whereas it was unchanged in CMV-negative patients (coronary flow increase to ACh was 2.5±0.5 at baseline versus 2.3±0.7 during follow-up; $P=0.32$).

**Cardiovascular-Related Events and Death and CMV Serostatus Before Transplantation**

The incidence of cardiovascular-related events and death during the follow-up period of 66±41 months was significantly elevated in CMV-negative recipients of CMV-positive donor hearts (Figure 4). The event-free survival 18 months (5 years) after transplantation was 90±4% (73±7%) in CMV-negative recipients of CMV-positive hearts, compared with 98±1% (86±3%) in the other groups ($P<0.05$). The median event-free time for CMV-negative recipients of CMV-positive hearts was 8.1 years compared with 13.3 years for the other groups ($P<0.05$).

Accordingly, cardiovascular-related events and death were significantly reduced in CMV-negative recipients of CMV-negative donor hearts (Figure 5). Event-free survival after 5 years was 92±4% in CMV-negative recipients of CMV-negative hearts compared with 81±4% in the other combined groups ($P<0.05$).

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**Figure 3.** Patients with documented CMV infection have impaired distal epicardial endothelium-dependent vasomotor function ($P<0.05$ versus CMV antigen-negative-negative transplant patients). Microvascular endothelial function tended to be impaired in CMV-positive compared with CMV-negative patients without reaching statistical significance ($P=0.12$).

**Figure 4.** CMV-seronegative (−) transplant recipients of CMV-seropositive (+) donor hearts have an increased risk for cardiovascular related events and death during the follow-up period of 66±41 months (1 to 8 years).
endothelial dysfunction and intimal hyperplasia.13 barrier result in response to injury mechanisms leading to may include pathogens like CMV.15 contributing to endothelial injury after heart transplantation and other studies.1,16,17 epicardial and microvascular endothelial dysfunction in this might help explain the partially absent association between proximal, distal, and resistance vessels of the cardiac allograft tion in patients with symptomatic infections. CMV infection have an impaired distal epicardial vasomotor function and an in- creased cardiovascular related event rate during follow-up. CMV-seronegative (−) donor hearts have a reduced risk for cardio-vascular-related events and death during the follow-up period of 66±41 months (1 to 8 years).

**Cardiovascular-Related Events and Death and CMV Infection**

Patients with documented CMV infections tended to have an increased cardiovascular related event rate during follow-up. Event-free survival at 5 years after transplantation was 72±9% in CMV pp65 antigen-positive patients compared with 85±8% in CMV pp65 antigen-negative patients (P=0.14).

**Discussion**

The salient findings of the present study are: (1) CMV seronegative recipients of seropositive donor hearts have an impaired distal epicardial vasomotor function and an increased cardiovascular related event and death rate during follow-up; (2) heart transplant recipients with documented CMV infection have an impaired distal epicardial endothelial function; and (3) epicardial and microvascular endothelial function deteriorates over time in recipients with documented CMV infection.

Activation of the arterial endothelium predicts development of cardiac allograft vasculopathy and increases risk of graft failure.12,13 Repetitive alterations of the endothelial barrier result in response to injury mechanisms leading to endothelial dysfunction and intimal hyperplasia.13–15 Insults contributing to endothelial injury after heart transplantation may include pathogens like CMV.15

The present study suggests that CMV-seronegative recipients of seropositive hearts are of highest risk for development of endothelial dysfunction in small coronary vessels and have more cardiovascular-related events and death during follow-up. Documented CMV infection episodes are associated with deterioration of epicardial endothelial function, whereas endothelial dysfunction extends to the microcirculation in patients with symptomatic infections.

Independent determinants of endothelial activation in the proximal, distal, and resistance vessels of the cardiac allograft might help explain the partially absent association between epicardial and microvascular endothelial dysfunction in this and other studies.1,16,17

Because an intact coronary endothelial function relies on an intact nitric oxide synthase system, it is tempting to speculate that CMV initiates and/or accelerates endothelial dysfunction by impairing the endothelial nitric oxide synthase pathway.15,17 In fact, we have previously demonstrated that CMV infection in endothelial cells increases the endogenous nitric oxide synthase inhibitor asymmetric dimethyl arginine, most probably by reducing the activity of the oxidant stress-sensitive asymmetric dimethyl arginine-metabolizing enzyme dimethyl arginine dimethyl aminohydrolase.18 In addition, CMV infection of endothelial cells stimulates the expression of tumor necrosis factor-α; tumor necrosis factor-α has been reported to destabilize mRNA message for eNOS.19,20 Moreover, CMV infection promotes mononuclear adhesion, activation, and transendothelial migration within the allograft vasculature, typical hallmarks of an impaired endothelial function.21,22

Although we do not have data regarding CMV infection in the coronary endothelium of our patients, it is likely that such latent infection is present in individuals whose leukocytes are expressing the CMV antigen. It is well-established that circulating leukocytes harboring CMV can infect vascular endothelial cells, and several groups have provided evidence of human CMV infection of endothelial cells after transplantation.23–25

The recruitment of circulating monocytes infected with the CMV into allograft coronary vessels is the most likely mechanism by which CMV becomes associated with endothelial dysfunction.26 Alternatively, CMV-positive leukocytes may induce endothelial dysfunction by releasing proinflammatory cytokines, which in turn may directly diminish nitric oxide synthase activity.27

Importantly, we could not detect a prognostic impact of CMV serostatus or previous infection episodes on coronary intimal thickening. This may result from the fact that we included patients for the IVUS substudy at a relatively early phase after transplantation (median, 13 months). Induction of structural coronary alterations by CMV may take longer than accelerating coronary endothelial vasomotor dysfunction. In addition, limitations of the present study include the fact that it is retrospective and that subgroup analyses have been performed.

Moreover, routine detection of the immediate early CMV antigen pp65 was performed only during the first 12 months. It is therefore possible that some subclinical CMV infection episodes have been missed during longer follow-up.

Although we have found an association between CMV serostatus/infection and allograft endothelial dysfunction during follow-up, association does not imply causation. The present findings may warrant confirmation through a larger prospective study of an observational and/or interventional nature.

In summary, our data support the hypothesis that human CMV infection, one of the most common infectious complications in allograft recipients, may contribute to an impaired outcome after transplantation by accelerating allograft coronary endothelial dysfunction.

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