In atherosclerosis, inflammatory responses in the vessel wall control progression of atheroma, initiation of thrombotic complications, and development of restenosis after percutaneous revascularization procedures. Recently, the hypothesis that the atheromatous inflammation may be modified by angiotropic infectious agents, such as Chlamydia pneumoniae, Helicobacter pylori, or cytomegalovirus (CMV), has attracted attention.

CMV has received particular attention in interventional cardiology since Zhou et al reported that previous CMV infection increased the risk of restenosis after atherectomy. As a potential explanation, the investigators proposed inhibition of the eukaryotic protein p53, an inhibitor of cell cycle progression, by the CMV immediate/early gene product IE84. CMV immediate/early gene expression might have been initiated by reactivation of latent CMVs after mechanical irritation of the coronary plaque.

Inhibition of p53, however, is only 1 of the many cellular consequences of CMV reactivation. Others include increased surface expression of adhesion molecules and tissue factor expression as well as loss of natural anticoagulants, such as thrombomodulin, prostacyclin, and tissue plasminogen activator. Active CMV infection thus changes the endothelial phenotype from anticoagulant to procoagulant. It is therefore tempting to speculate that CMV infection promotes thrombotic complications after percutaneous coronary interventions. The impact of previous CMV infection on early outcome of coronary interventions, however, has not yet been addressed. We sought to investigate this issue by analyzing the effect of previous CMV infection on the early hazard of coronary stent placement.

**Methods**

Patients undergoing coronary stent placement were eligible for the study. All patients gave informed consent, and the study was approved by our institutional ethics committee. Stent placement was performed as described earlier. In patients with acute myocardial infarction, small target vessels (reference diameter <2.8 mm), or thrombus-containing lesions, we administered the glycoprotein IIb/IIIa receptor blocker abciximab in a bolus of 0.25 mg/kg body wt before the intervention, followed by continuous infusion of 10 μg/min for 12 hours. In addition, all patients received ticlopidine 250 mg BID for 4 weeks and aspirin 100 mg BID indefinitely. We obtained blood samples after successful stent placement and stored plasma aliquots at −70°C for later determination of CMV IgG titers by ELISA (Enzygnost, Dade Behring). Titers <1/230 were considered negative. For follow-up, the patients either presented at our clinic (82%) or were interviewed over the phone by trained medical personnel.

**Background**

Cytomegalovirus (CMV) infection induces upregulation of tissue factor and loss of anticoagulants, including thrombomodulin, prostacyclin, and tissue plasminogen activator. CMV infection may thereby increase the procoagulant properties of coronary artery plaques. This prospective study investigated the effect of previous CMV infection on the early hazard of coronary stent placement.

**Methods and Results**

In 551 consecutive patients with successful coronary stent placement, we determined CMV IgG titers. The end point was the composite rate of death, nonfatal Q-wave myocardial infarction, and urgent reintervention during 30-day follow-up. The study population represented the entire spectrum of coronary stenting; an acute coronary syndrome was present in 50% of the patients. A positive CMV IgG titer (≥1/230) was found in 340 patients (62%). Of these, 10 reached the end point during 30-day follow-up (2 deaths, 4 infarctions, 4 urgent reinterventions). In the group with negative CMV titer, thrombotic events did not occur (P=0.014 versus group with positive CMV titers). After correction for pertinent covariables, a significant relation between positive CMV titer and the 30-day end point prevailed (P<0.001).

**Conclusions**

Previous CMV infection may increase the risk of coronary thrombotic events after stent placement.

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**Key Words:** viruses ▪ stents ▪ thrombosis

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**Brief Rapid Communications**

**Previous Cytomegalovirus Infection and Risk of Coronary Thrombotic Events After Stent Placement**

Franz-Josef Neumann, MD; Adnan Kastrati, MD; Thomas Miethke, MD; Gisela Pogatsa-Murray, MD; Melchior Seyfarth, MD; Albert Schömig, MD

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**Citation:**

The study end point was the composite rate of death, Q-wave myocardial infarction, or urgent target-lesion reintervention during 30-day follow-up. Q-wave myocardial infarction was defined as new pathological Q waves plus an increase in creatine kinase (CK) to >240 U/L with a concomitant increase in its MB isoenzyme in the presence of typical symptoms. To meet this end-point criterion, patients who had initially presented with Q-wave myocardial infarction had to have suffered symptomatic recurrent ST-segment elevation with a rise in CK and/or angiographic verification of stent occlusion. CK levels were determined systematically for 48 hours after the intervention. End-point adjudication and collection of clinical, procedural, and angiographic data were completed before and after the intervention. The study end point (1/8800 versus 1/8200, \( P = 0.014 \)) reached an end point (Table 2). Patients who reached an end point did not differ significantly from the others in any of the clinical or procedural characteristics shown in Table 1. Within the group with positive CMV titers, median CMV titers were similar in those with and without an end point (1/8800 versus 1/8200, \( P = 0.89 \)).

Between the groups defined by CMV titer, most of the baseline characteristics were evenly distributed, and there were no significant differences in any of the procedural or angiographic variables (Table 1). Likewise, the peri-interventional use of glycoprotein IIb/IIIa blockade was shown in Table 1. A positive CMV titer was present in 62% of the study population.

During 30-day follow-up, none of the patients with negative CMV titers but 10 of the patients with positive CMV titers (\( P = 0.014 \)) reached an end point (Table 2). Patients who reached an end point did not differ significantly from the others in any of the clinical or procedural characteristics shown in Table 1. Within the group with positive CMV titers, median CMV titers were similar in those with and without an end point (1/8800 versus 1/8200, \( P = 0.89 \)).

Between the groups defined by CMV titer, most of the baseline characteristics were evenly distributed, and there were no significant differences in any of the procedural or angiographic variables (Table 1). Likewise, the peri-interventional use of glycoprotein IIb/IIIa blockade was shown in Table 1. A positive CMV titer was present in 62% of the study population.

The study included 551 consecutive patients with successful coronary stent placement, whose baseline characteristics are shown in Table 1. A positive CMV titer was present in 62% of the study population.

### Results

The study included 551 consecutive patients with successful coronary stent placement, whose baseline characteristics are shown in Table 1. A positive CMV titer was present in 62% of the study population.

### Study Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>CMV-Positive (n=340)</th>
<th>CMV-Negative (n=211)</th>
<th>P</th>
<th>Without Event (n=541)</th>
<th>With Event (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.7±11.3</td>
<td>63.3±11.8</td>
<td>0.02</td>
<td>64.8±11.6</td>
<td>62.8±10.2</td>
<td>0.59</td>
</tr>
<tr>
<td>Women</td>
<td>95 (27.9)</td>
<td>35 (16.6)</td>
<td>0.002</td>
<td>127 (23.4)</td>
<td>3 (0.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Active smoker</td>
<td>115 (33.8)</td>
<td>72 (34.1)</td>
<td>0.94</td>
<td>182 (33.6)</td>
<td>5 (0.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>209 (61.5)</td>
<td>124 (58.8)</td>
<td>0.53</td>
<td>325 (60.0)</td>
<td>8 (1.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>230 (67.6)</td>
<td>126 (59.7)</td>
<td>0.06</td>
<td>349 (64.5)</td>
<td>7 (1.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>55 (16.2)</td>
<td>34 (16.1)</td>
<td>0.98</td>
<td>87 (16.1)</td>
<td>2 (0.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>246 (72.3)</td>
<td>154 (73.0)</td>
<td>0.87</td>
<td>392 (72.5)</td>
<td>8 (1.6)</td>
<td>0.91</td>
</tr>
<tr>
<td>Previous balloon angioplasty</td>
<td>49 (14.4)</td>
<td>32 (15.2)</td>
<td>0.81</td>
<td>81 (15.0)</td>
<td>0 (0.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Previous coronary bypass operation</td>
<td>26 (7.6)</td>
<td>10 (4.7)</td>
<td>0.18</td>
<td>35 (6.5)</td>
<td>1 (0.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>78 (22.9)</td>
<td>43 (20.4)</td>
<td>0.48</td>
<td>121 (22.4)</td>
<td>0 (0.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Reduced left ventricular function</td>
<td>139 (40.9)</td>
<td>76 (36)</td>
<td>0.26</td>
<td>211 (39.0)</td>
<td>4 (0.8)</td>
<td>0.84</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>52 (15.3)</td>
<td>45 (21.3)</td>
<td>0.07</td>
<td>93 (17.2)</td>
<td>4 (0.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>113 (33.2)</td>
<td>63 (29.9)</td>
<td>0.41</td>
<td>175 (32.4)</td>
<td>1 (0.2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Complex lesions</td>
<td>288 (84.7)</td>
<td>169 (80.1)</td>
<td>0.16</td>
<td>488 (88.2)</td>
<td>9 (1.8)</td>
<td>0.93</td>
</tr>
<tr>
<td>Chronic occlusions</td>
<td>28 (8.2)</td>
<td>15 (7.1)</td>
<td>0.63</td>
<td>42 (7.8)</td>
<td>1 (0.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>Multiligation intervention</td>
<td>67 (19.7)</td>
<td>52 (24.6)</td>
<td>0.17</td>
<td>118 (21.8)</td>
<td>1 (0.2)</td>
<td>0.65</td>
</tr>
<tr>
<td>Lesion in venous bypass graft</td>
<td>18 (5.3)</td>
<td>8 (3.8)</td>
<td>0.42</td>
<td>25 (4.6)</td>
<td>1 (0.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Vessel size, mm</td>
<td>3.09±0.52</td>
<td>3.07±0.54</td>
<td>0.60</td>
<td>3.08±0.45</td>
<td>3.20±0.52</td>
<td>0.48</td>
</tr>
<tr>
<td>Balloon-to-vessel ratio</td>
<td>1.09±0.11</td>
<td>1.09±0.12</td>
<td>0.69</td>
<td>1.08±0.11</td>
<td>1.10±0.10</td>
<td>0.83</td>
</tr>
<tr>
<td>Inflation pressure, atm</td>
<td>14.4±2.7</td>
<td>14.4±2.5</td>
<td>0.88</td>
<td>14.4±2.6</td>
<td>14.1±2.7</td>
<td>0.70</td>
</tr>
<tr>
<td>Stented length, mm</td>
<td>23.6±14.0</td>
<td>22.7±14.0</td>
<td>0.47</td>
<td>22.9±13.6</td>
<td>28.8±14.9</td>
<td>0.18</td>
</tr>
<tr>
<td>Diameter stenosis after stenting, %</td>
<td>5.3±8.9</td>
<td>4.8±6.1</td>
<td>0.40</td>
<td>5.1±7.9</td>
<td>8.5±9.9</td>
<td>0.17</td>
</tr>
<tr>
<td>Periinterventional abciximab</td>
<td>99 (29.1)</td>
<td>65 (30.8)</td>
<td>0.67</td>
<td>161 (29.7)</td>
<td>3 (0.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Completed ticlopidine regimen</td>
<td>338 (99.4)</td>
<td>211 (100)</td>
<td>0.67</td>
<td>539 (99.6)</td>
<td>10 (1.9)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or number of patients (percentage).

### Table 2: Type and Timing of End-Point Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Number</th>
<th>Time After Stenting, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2</td>
<td>2, 28</td>
</tr>
<tr>
<td>Nonfatal infarction</td>
<td>4</td>
<td>1, 1, 1, 10</td>
</tr>
<tr>
<td>Urgent reintervention</td>
<td>4</td>
<td>1, 14, 15, 29</td>
</tr>
</tbody>
</table>

All end-point events occurred in patients with positive CMV titers. All reinterventions were due to angiographically documented occlusive (n=3) or nonocclusive stent thrombosis (n=1).
similar in both groups (Table 1). Nevertheless, the group with positive CMV titers was significantly older, comprised significantly more women, and tended to have a higher rate of hypertension and lower rate of acute infarction at presentation than the group with negative CMV titers (Table 1). To analyze a potential influence of the inhomogeneities between the groups defined by CMV titer, these variables, together with titer status, were entered into a multivariate regression model for the study end point. In this model, a positive CMV titer prevailed as a strong independent predictor of the composite 30-day end point. This result was also maintained (P=0.0002) after stented length and residual stenosis had been accounted for, which tended to be less favorable in patients with events (Table 1).

Discussion

Previous studies on the role of infectious agents in coronary artery disease focussed on the natural history of the disease or on restenosis after percutaneous revascularization procedures. Here, we present data suggesting that previous CMV infection increases the early risk of cardiac complications after coronary stent placement. Our study may thus elucidate a new role for CMV infection in coronary artery disease, i.e., promotion of coronary thrombotic events.

In our study, all major cardiac events during 30-day follow-up after stenting occurred in patients with previous CMV infection. In the entire population, our early event rate of 1.8% was within the expected range. It was disturbingly high, however, reaching 2.9%, in the group with previous CMV infection. This preponderance of patients with previous CMV infection for early adverse events after stenting cannot be explained by demographic, angiographic, or procedural covariates. Between the groups defined by CMV titers or occurrence of events, there were few inhomogeneities (Table 1) that might potentially confound the results. The relationship between previous CMV infection and early adverse outcome after stenting, however, remained significant after these potentially confounding effects had been adjusted for by multivariate analysis. Despite statistical significance, the low number of events prevents us from considering our results definitive. Rather, the conclusions of our study need further validation by larger trials.

The most likely explanation for a link between previous CMV infection and risk of early complications after stenting is the local procoagulant effect of vascular CMV reactivation, increasing the risk of postinterventional thrombotic events. As shown by earlier studies, it is intracoronary thrombosis, often leading to subacute stent occlusion, that determines the 30-day event rate after stenting. Likewise, in our present study, all end points in those surviving were attributable to intracoronary thrombotic events.

When confirmed by larger studies, our present findings may have pragmatic consequences. Although early thrombotic complications after stenting have become rare under treatment with aspirin plus ticlopidine, they are still dreaded for their devastating clinical consequences, with a mortality rate of >25%. Prediction of the risk of thrombotic complications after stenting is of utmost clinical interest. It should guide the decision for coronary intervention as well as allocation to expensive antithrombotic regimens, such as glycoprotein IIb/IIIa receptor blockade. In concert with other known predictors of thrombotic coronary complications, our new findings on the role of CMV infection may assist in tailoring treatment modalities to the individual patient’s needs.

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References

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