Cytomegalovirus Seropositivity and C-Reactive Protein Have Independent and Combined Predictive Value for Mortality in Patients With Angiographically Demonstrated Coronary Artery Disease

Joseph B. Muhlestein, MD; Benjamin D. Horne, MPH; John F. Carlquist, PhD; Troy E. Madsen, BS; Tami L. Bair, BS; Robert R. Pearson, BS; Jeffrey L. Anderson, MD

Background—The role of inflammation in coronary artery disease (CAD) is being increasingly recognized. Markers of inflammation (eg, C-reactive protein [CRP]) and infection (eg, seropositivity to Chlamydia pneumoniae, cytomegalovirus [CMV], and Helicobacter pylori) have been proposed as risk factors for CAD, but these associations require further evaluation.

Methods and Results—We prospectively tested whether CRP levels and IgG seropositivity to C pneumoniae, CMV, and H pylori are predictors of subsequent mortality in 985 consecutive patients with angiographically demonstrated CAD (stenosis $\geq 70\%$). Patients were followed for an average of 2.7 years (range 1.5 to 4.0 years). Patients averaged 65 years of age; 77% were men; and 110 (11.2%) died during follow-up. CRP levels were significantly elevated in nonsurvivors compared with survivors (mean CRP 3.1 mg/dL versus 1.5 mg/dL, $P=0.003$). After controlling for all known baseline variables, the 2nd and 3rd tertiles of CRP compared with the 1st produced a Cox hazard ratio (HR) for mortality of 2.4 ($P=0.001$). Of the 3 infectious markers tested, only seropositivity to CMV (HR=1.9, $P<0.05$) was predictive of mortality. The majority of mortality risk associated with elevated CRP or CMV seropositivity occurred when both risk factors were present ($P$ for trend $<0.0001$). Other independent predictors of increased risk of mortality were age (HR=1.07 per year, $P<0.0001$), left ventricular ejection fraction (HR=0.97 per percent, $P<0.0001$), and diabetes mellitus (HR=1.7, $P=0.02$).

Conclusions—CMV seropositivity and elevated CRP, especially when in combination, are strong, independent predictors of mortality in patients with CAD. This suggests an interesting hypothesis that a chronic, smoldering infection (CMV) might have the capacity to accelerate the atherothrombotic process. (Circulation. 2000;102:1917-1923.)

Key Words: coronary disease ■ risk factors ■ survival ■ antibodies ■ follow-up studies

Coronary artery disease, which frequently becomes manifest as myocardial infarction, continues to exact an enormous toll in Western society. Despite progress in its prevention, detection, and treatment, it continues to be a leading cause of death. Several risk factors for coronary artery disease have been well documented including hyperlipidemia, hypertension, smoking, diabetes, a positive family history, and obesity. However, these factors explain only part of attributable cardiovascular disease, and other factors must be involved.

A growing body of evidence supports the concept that local and systemic inflammation may play a role in the initiation and progression of atherosclerosis and its complications. C-reactive protein (CRP), an acute-phase reactant marker for underlying systemic inflammation, has long been known to be elevated in patients with acute myocardial infarction. It has also been shown to predict risk of recurrent ischemic events in patients with stable angina, prior myocardial infarction, and unstable angina. It has even been shown to predict risk for future ischemic events in previously healthy individuals.

The underlying cause of this chronic inflammation and how it specifically relates to coronary artery disease is unknown. CRP elevation might come from noninfectious sources such as oxidized LDL or other as-yet unknown noninfectious sources, but the possibility also exists that there is a chronic infectious or antigenic source. A distant infection might generate circulating cytokines. Alternatively, a persistent local infectious process within the atherosclerotic plaque might provide the ongoing stimulus. Chlamydia pneumoniae and cytomegalovirus (CMV) are intracellular pathogens that might serve as a source of chronic local infections.
infection. Helicobacter pylori, demonstrated to be a primary pathogen of peptic ulcer disease, is a candidate organism that might be a chronic source of distant inflammation.\textsuperscript{28,29} Seropositivity to each of these infectious agents has, to various degrees, been associated with the diagnosis of coronary artery disease. However, whether these markers of infection, either alone or in combination with CRP, predict risk of future adverse events among patients with angiographically documented coronary artery disease has not been adequately evaluated. Such knowledge might provide useful insight into the pathophysiology of and general risk factors associated with coronary artery disease.

**Methods**

**Study Hypothesis**

Our objectives were to determine whether, during long-term follow-up of patients with angiographically defined significant coronary artery disease, (1) higher levels of baseline CRP are predictive of mortality; (2) baseline seropositivity for C pneumoniae, CMV, or H pylori is predictive of mortality; and (3) whether there is any interaction between elevated plasma CRP levels, positive infectious serologies, and mortality.

**Patients**

Between August 15, 1994, and February 28, 1997, 1707 consenting patients undergoing coronary arteriography at LDS Hospital were enrolled in a cardiovascular registry (Intermountain Heart Study). Subjects were of unrestricted age and sex who gave written informed consent for blood to be drawn at angiography for use in confidential blood bank studies approved by the hospital’s institutional review board. Of these patients, 985 were found to have significant coronary artery disease as defined by a \( \geq 70\% \) stenosis of at least 1 major coronary artery and were included in the study.

Assessment of coronary artery disease was made by review of angiograms by the patient’s cardiologist and entered into the computer database in a format modified after the coronary artery surgery study (CASS) protocol.\textsuperscript{30} On the basis of this angiographic evaluation, the patients were determined to have single-, double-, or triple-vessel disease as defined by the presence of a \( \geq 70\% \) stenosis in each major vessel counted. Assessment of coronary artery disease was performed blinded to results of blood testing for inflammatory and serological markers. When available, and as determined by echocardiography or left ventriculography, the patient’s ejection fraction at the time of entry into the study was also recorded. Echocardiographic determination of the presence or absence of left ventricular hypertrophy was also recorded. Immediately after the baseline cardiac catheterization procedure and just before leaving the index hospitalization was categorized as stable angina (stable exertional symptoms only), unstable angina (progressive symptoms or symptoms at rest), or MI (creatine kinase [CK]-MB \( >6 \) mg/dL and CK-MB index \( >3\% \)). The clinical treatments at index hospitalization were categorized as medical therapy (only), percutaneous coronary interventions (including balloon angioplasty, atherectomy, and/or stenting), and CABG. Renal failure was regarded as present if serum creatinine was \( \geq 2.0 \) mg/dL.

**TABLE 1. Baseline Clinical Characteristics and Laboratory Values of the Population (\( n=985 \)) According to Survival Status, With Associated Probability Values From Univariate Cox Regression**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Survivors (( n=875 ))</th>
<th>Nonsurvivors (( n=110 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y (range)</td>
<td>65±11 y, 34–95 y</td>
<td>72±9 y</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>78% males</td>
<td>69% males</td>
<td>0.03</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute MI</td>
<td>23%</td>
<td>24%</td>
<td>0.23</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>33%</td>
<td>28%</td>
<td>0.97</td>
</tr>
<tr>
<td>Stable angina</td>
<td>44%</td>
<td>48%</td>
<td>Reference</td>
</tr>
<tr>
<td>Initial treatment approach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical management</td>
<td>42%</td>
<td>61%</td>
<td>Reference</td>
</tr>
<tr>
<td>Coronary bypass grafting</td>
<td>33%</td>
<td>25%</td>
<td>0.009</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>25%</td>
<td>14%</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>50%</td>
<td>32%</td>
<td>0.0006</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18%</td>
<td>27%</td>
<td>0.02</td>
</tr>
<tr>
<td>History of smoking</td>
<td>29%</td>
<td>19%</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53.5%</td>
<td>54.1%</td>
<td>0.80</td>
</tr>
<tr>
<td>Positive family history</td>
<td>34%</td>
<td>30%</td>
<td>0.45</td>
</tr>
<tr>
<td>Left ventricular hypertrophy on echocardiography</td>
<td>2.2%</td>
<td>3.7%</td>
<td>0.33</td>
</tr>
<tr>
<td>Lipid levels, mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC, mg/dL</td>
<td>184±47</td>
<td>178±47</td>
<td>0.87</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>120±38</td>
<td>117±38</td>
<td>0.55</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>33±13</td>
<td>36±21</td>
<td>0.19</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>155±108</td>
<td>133±95</td>
<td>0.02</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>6.7±5.5</td>
<td>6.8±6.7</td>
<td>0.16</td>
</tr>
<tr>
<td>Left ventricular function (available on 76% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean LVEF, mean±SD</td>
<td>61±16%</td>
<td>51±20%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proportion with LVEF =40%</td>
<td>9%</td>
<td>30%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary anatomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-vessel</td>
<td>37%</td>
<td>21%</td>
<td>Reference</td>
</tr>
<tr>
<td>Double-vessel</td>
<td>30%</td>
<td>28%</td>
<td>0.09</td>
</tr>
<tr>
<td>Triple-vessel</td>
<td>33%</td>
<td>51%</td>
<td>0.0004</td>
</tr>
<tr>
<td>History of renal failure, CK &gt;2.5</td>
<td>7%</td>
<td>10%</td>
<td>0.21</td>
</tr>
<tr>
<td>Inflammatory and infectious factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP, mg/dL, mean±SD</td>
<td>2.2±2.4</td>
<td>3.1±3.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CMV seropositive</td>
<td>74%</td>
<td>88%</td>
<td>0.002</td>
</tr>
<tr>
<td>C pneumoniae seropositive</td>
<td>81%</td>
<td>82%</td>
<td>0.84</td>
</tr>
<tr>
<td>H pylori seropositive</td>
<td>49%</td>
<td>55%</td>
<td>0.27</td>
</tr>
</tbody>
</table>
After successful discharge from the index hospitalization, long-term survival of each patient was determined by telephone contact or use of a computerized national death index. Through these two techniques, survival status was determined in 100% of cases. Deaths were not adjudicated between cardiac or some other cause.

Determination of CRP
Testing for CRP was performed with the use of a fluorescence polarization immunoassay (Abbott Diagnostics). All serum was analyzed by the high-sensitivity (0.05 mg/dL), low-range (0 to 6.5 mg/dL) CRP protocol (protocol C). Any serum with a CRP exceeding that range was reanalyzed by the lower-sensitivity (1.5 mg/dL), high-range (0 to 26 mg/dL) protocol A. After determination of all baseline CRP levels, the cohort was divided into tertiles (CRP 1st tertile <1.2 mg/dL; 2nd tertile 1.2 to 1.7 mg/dL; 3rd tertile >1.7 mg/dL), based on individual patient CRP values.

Testing for Infectious Serology
ELISA was used to determine levels of anti-cytomegalovirus IgG antibodies (Wampole Laboratories, Cranbury, NJ), species-specific anti-\textit{C pneumoniae} IgG antibodies (Savyon Diagnostics, Ashdod, Israel), and anti-\textit{H pylori} IgG antibodies (Meridian Diagnostics, Cincinnati, Ohio). Seropositivity or seronegativity was assigned according to the specifications of each product. Evaluable serological results for all 3 infectious agents were obtained in \( \geq 93\% \) of patients.

Statistical Considerations
Differences of average CRP levels and the prevalence of seropositivity for infectious markers, between survivors and nonsurvivors at long-term follow-up, were evaluated by univariate proportional hazards analysis through the generalized likelihood ratio test to determine whether an increased incidence of mortality was found in patients with elevated CRP (as defined by the upper two tertiles) or seropositivity to \textit{C pneumoniae}, CMV, or \textit{H pylori}.

To confirm the associations to mortality determined by univariate analysis, multivariate Cox Regression analysis (SPSS, version 9.0) was performed to determine hazard ratios corrected for confounding factors. Available baseline risk factors used in this adjustment model included age, sex, clinical presentation, initial form of cardiovascular treatment, history of diabetes, hyperlipidemia, hypertension, positive family history of cardiovascular disease, smoking, renal failure, prior myocardial infarction, prior coronary bypass grafting, left ventricular hypertrophy, LVEF, number of diseased coronary vessels, and baseline total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels.

To evaluate possible joint effect modification on mortality by CRP and seropositivity, a test of trend was performed for combined CRP/seropositivity variables that were coded as normal/seronegative, normal/seropositive, high/seronegative, and high/seropositive. The results are presented as a \( P \) for trend for only those infectious agents showing univariate significance. Two-tailed probability values are presented with 0.05 designated as nominally significant.

Results

Patient Population and Baseline Markers
The 985 subjects were followed for an average of 2.7 years (range 1.5 to 4.0 years), during which time 110 (11.2%) patients did not survive. Baseline clinical characteristics and laboratory values of the population (n=985) according to survival status, with the associated probability value from univariate Cox regression, are summarized in Table 1. In general, severity of illness varied greatly, ranging from a presentation with stable angina, single-vessel corre-
CRP and Survival

Figure 1 is a box-and-whisker plot showing CRP concentrations based on long-term survival. CRP levels were significantly elevated in nonsurvivors compared with survivors (mean CRP 3.1 ± 3.3 mg/L versus 1.5 ± 2.4 mg/L, P < 0.001).

Figure 2 shows the Kaplan-Meier survival curves of patients on the basis of CRP tertiles. There was nearly a 3-fold increase in mortality from the 1st to the 3rd tertile. The hazard ratio for mortality of these patients (1st compared with 2nd and 3rd CRP tertiles) by univariate analysis was 2.8 (95% CI 1.7, 4.8, P < 0.001). Figure 3 shows the effect of CRP levels on future mortality, based on initial clinical presentation. Interestingly, the effect of CRP was greater in patients with stable or unstable angina than with acute MI. After controlling for all known baseline variables, multivariate regression analysis produced a Cox hazard ratio of 2.4 (95% CI 1.4, 4.1, P = 0.001), verifying an independent effect.

Infectious Serology and Survival

Infectious serologies were frequently positive both in patients who survived as well as nonsurvivors (see Table 1). No significant differences in seropositivity to C pneumoniae or H pylori were detected in survivors versus nonsurvivors, but seropositivity to CMV was significantly higher in nonsurvivors (88% versus 74%, P = 0.002).

Figure 4 shows the Kaplan-Meier survival curves for patients on the basis of seropositivity to C pneumoniae, H pylori, or CMV. No significant hazard rate ratio increase was noted for seropositivity to C pneumoniae or H pylori. A significant hazard ratio of 2.5 (95% CI 1.4, 4.8, P = 0.001) by univariate analysis and 1.9 (95% CI 1.01, 3.6, P < 0.05) after multivariate Cox regression analysis was found for CMV.

TABLE 2. Cox Proportional Hazards Regression Model for Baseline Variables Associated With Independent Prediction of Mortality During Follow-Up

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>Cox Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.07 per year (1.04, 1.09)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.97 per % (0.96, 0.98)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP, 2nd and 3rd vs 1st tertiles</td>
<td>2.4 (1.4, 4.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>CMV seropositive</td>
<td>1.9 (1.01, 3.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.7 (1.1, 2.7)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
seropositivity. Figure 5 shows the frequency of seropositivity to the 3 infectious agents tested, stratified by CRP tertile. No significant association between CRP and seropositivity to any of the 3 agents, including CMV, was noted.

Other Predictors of Mortality
Table 2 lists all baseline variables found to be independent predictors of mortality in this study. The model was built beginning with all study variables, and the final model considered (but excluded because of age and LVEF) sex, hyperlipidemia, smoking, HDL, triglycerides, total cholesterol (TC)/HDL ratio, renal failure, index clinical treatment, and number of severe vessels. The only confounder of the inflammatory or infectious factors was age, which confounded CMV; despite this, however, CMV retained statistical significance. Interestingly, the independent predictive value of CRP and seropositivity to CMV on mortality was greater than a number of more traditional risk factors including diabetes, hyperlipidemia, hypertension, and a history of smoking. The effect on mortality of CRP and the 3 infectious serologies is shown for the whole study cohort as well as stratified by initial clinical presentation in Figure 6. No significant difference in the effects of CRP or CMV were noted, based on an initial presentation with stable or unstable angina or acute MI.

Interaction Between CRP and Seropositivity to CMV
Because seropositivity to neither C pneumoniae nor H pylori was found to be predictive of future mortality, further evaluation of these results was not performed. An evaluation of the effect of the combination of elevated CRP and seropositivity to CMV, however, was performed. Figure 7 shows the effect on mortality of seropositivity to CMV in those with high (2nd and 3rd tertiles) and low CRP (1st tertile) levels. The highest mortality rate was noted in seropositive patients with elevated CRP levels. In contrast, seropositivity to CMV or elevated CRP alone had little effect on mortality. Linear trend analysis of this interaction gives an adjusted hazard ratio of 2.2 ($P=0.0001$).

Discussion

Summary of Key Findings
In our prospectively studied, angiographically defined cohort with significant coronary artery disease, we demonstrated an independent association between future mortality and the inflammatory marker CRP. This association was important (>2-fold increase in mortality) and highly significant ($P<0.002$). Interestingly, the association between CRP and mortality was greater in patients with stable angina than with
acute MI, perhaps because the acute rise in CRP during MI actually diluted the predictive value of the baseline pre-MI CRP level.

In addition, seropositivity to CMV was found to be an independent predictor of mortality in this study group. An interaction between CRP and seropositivity to CMV was noted such that the majority of increased mortality came in those who were CMV seropositive and were not in the low range of CRP levels (tertiles 2/3). In contrast, seropositivity to neither C pneumoniae nor H pylori was predictive of mortality during long-term follow-up.

### Inflammation and Its Effect on Survival

In this study, the risk of mortality associated with elevations of CRP was independent of other known cardiovascular risk factors including smoking status, hypertension, diabetes, baseline lipid levels, and so forth. These data further extend previous reports that CRP predicts primary15,32–34 and secondary11–14 ischemic risk and adds further support to the inflammatory concept of coronary atherosclerosis. The fact that baseline CRP levels predict mortality in patients with existing coronary artery disease also suggests that chronic inflammation may, in some way, influence the individual progression rates of the atherosclerotic process.

### Infectious Serologies

Our study confirms previously reported findings of a high prevalence of seropositivity among patients with documented coronary artery disease for 3 agents (CMV, H pylori, and C pneumoniae) postulated to play a role in the pathophysiology of atherosclerosis. However, only seropositivity to CMV was predictive of increased mortality in patients with known coronary artery disease. This finding appears to contrast with results recently reported by Ridker et al, in which, among previously healthy patients enrolled in the Physicians’ Health Study, seropositivity to CMV did not appear to predict an increased risk of a first cardiovascular event. The interaction between inflammation and CMV seropositivity found in this study is similar to the findings of a cross-sectional angiographic study by Zhu et al, in which they correlated CMV seropositivity and CRP levels to the presence of coronary artery disease. There they noted that “CMV elicits a subclinical inflammatory response, but only in certain individuals, and individuals with an inflammatory response appear susceptible to the atherogenic effects of CMV, whereas those without appear resistant.” It is appealing to speculate that relative elevation of CRP in CMV-seropositive patients indicates an active, “smoldering” infectious/inflammatory process (arteritis?) that accelerates atherothrombotic progression, whereas low CRP in CMV-seropositive patients suggests a resolved or inactive infection. The actual pathophysiological mechanisms responsible for these findings are speculative, however, and remain to be conclusively demonstrated.

We also found that neither C pneumoniae nor H pylori seropositivity predicted increased mortality in patients with angiographically defined coronary artery disease. This does not eliminate the possibility, however, that they are associated with the initiation and early development of coronary atherosclerosis, as has been proposed by some prior studies.17–20,28,29 Additionally, lack of a serological association does not eliminate the possibility of a pathogenic association with chronic active infection because serological studies only document previous exposure rather than provide specific information regarding a resolved versus ongoing active infectious process.

### Potential Limitations and Strengths of the Present Study

This study, although prospective, is observational. Associations with mortality may be either causal or noncausal. Groups seropositive to CMV (or other agents) may have differed in other ways (eg, socioeconomically); therefore, a potential for confounding of variables exists. This limitation was addressed by the use of multivariate Cox regression analysis, taking into account all major recognized potential confounding variables. Although the study included nearly 1000 patients, there still exists the potential, if an even larger population were available, that other clinical variables, such as initial clinical presentation, might also demonstrate independent predictive value of future mortality. A strength of this study is that all patients were angiographically diagnosed at baseline with coronary artery disease. Also, all laboratory markers were performed by investigators blinded to the clinical results of the study. To obtain more complete information regarding the primary end point of all-cause mortality, a national death index was used to supplement telephone follow-up, which resulted in 100% follow-up.

### Conclusions

In a large, angiographically defined patient population, followed prospectively, the combination of seropositivity to CMV and relative elevation of CRP predicted future mortality. Although requiring validation, this finding suggests the possibility that chronic inflammation (represented by elevated CRP) caused by smoldering CMV infection is an independent risk factor for progression of the atherothrom-
botanic process to a fatal outcome. If true, this finding may have important implications for risk-stratification and intervention trials.

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References
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