Synergistic Effect of Persistent Chlamydia pneumoniae Infection, Autoimmunity, and Inflammation on Coronary Risk

Tiina Huittinen, MSc; Maija Leinonen, PhD; Leena Tenkanen, PhD; Hanna Virkkunen, MSc; Matti Mänttäri, MD, FESC; Timo Palosuo, MD, PhD; Vesa Manninen, MD, PhD; Pekka Saikku, MD, PhD

Background—Given the role of chronic infections, autoimmunity, and inflammation in atherosclerosis, we studied the joint effect of chronic Chlamydia pneumoniae infection, persistently elevated human heat-shock protein 60 (hHsp60) antibodies, and C-reactive protein (CRP) on coronary risk.

Methods and Results—The participants for this prospective nested case-control study were obtained from the Helsinki Heart Study, during which 241 nonfatal myocardial infarctions or coronary deaths occurred among 4081 dyslipidemic middle-aged men. Serum samples taken at baseline and 3 to 6 months before the coronary events that occurred during the 8.5-year period were analyzed for antibodies to C pneumoniae and hHsp60 and the CRP concentration. Compared with persistently low levels, the risk of coronary events was 2-fold for persistently elevated immunocomplex (IC)-bound and/or serum IgA antibodies to C pneumoniae (OR, 1.96; 95% CI, 1.14 to 3.36) and also for serum IgA antibodies to hHsp60 (OR, 2.11; 95% CI, 1.08 to 4.13). The risks associated with elevated antibodies were much higher when CRP was also elevated. Compared with low or transiently elevated levels, the risk of coronary events, with adjustment for age and smoking, was 4.5-fold for persistently elevated CRP and C pneumoniae IC/IgA antibodies together (OR, 4.47; 95% CI, 1.84 to 10.83) and was similar for CRP and hHsp60 IgA antibodies together (OR, 4.36; 95% CI, 1.53 to 12.39).

Conclusions—Persistently but not transiently elevated C pneumoniae IC/IgA and hHsp60 IgA antibodies, especially when present together with an elevated CRP level, predicted coronary events. (Circulation. 2003;107:2566-2570.)

Key Words: coronary disease ■ risk factors ■ infection ■ inflammation

Inflammation, infections, and autoimmunity to human heat-shock protein 60 (hHsp60) have emerged as novel risk factors for coronary heart disease during the past decade. Heat-shock proteins are a class of highly conserved proteins produced by all organisms to protect themselves from damage caused by, for instance, exposure to chemical and environmental factors, inflammation, and infections.1 Because of the high sequence homology between bacterial and human heat-shock proteins, they have been postulated to be critical antigens in autoimmune diseases. In particular, it has been proposed that the immune response to microbial Hsp60 may lead to autoimmunity to hHsp60 and by that means to the development of atherosclerosis.2

In our previous study,3 we showed that an elevated level of IgA antibodies to hHsp60 in baseline serum predicted the occurrence of a coronary event several years later. Although Chlamydia pneumoniae, a common respiratory pathogen throughout the world, has been associated with atherosclerosis,4 the above-mentioned study indicated that elevated levels of C pneumoniae antibodies were not alone a significant risk factor for coronary events. Instead, a 7-fold risk emerged when an elevated level of IgA antibodies to C pneumoniae in baseline serum was accompanied by factors related to autoimmunity and inflammation, such as elevated levels of hHsp60 IgA antibodies and C-reactive protein (CRP).

Given the role of chronic infections in atherosclerosis,5 we now studied the coronary risk in subjects with serological evidence of chronic C pneumoniae infection and persistently elevated levels of hHsp60 antibodies and CRP. The present study is a logical extension of our previous observations showing that elevated levels of CRP6 and C pneumoniae7 predict coronary events, especially when present persistently. However, the persistence of seropositivity to hHsp60 and, more importantly, the joint effects of all these factors together have not been studied previously.

Methods

Study Population

The participants in this prospective nested case-control study were obtained from the Helsinki Heart Study, which was a double-blind, randomized, placebo-controlled, coronary primary prevention trial to study the efficacy of gemfibrozil in dyslipidemic (non-HDL cholesterol level >5.2 mmol/L) middle-aged Finnish men.8,9 Persons with a history of coronary heart disease or other major illness were excluded. The study began in 1980, when the collection of baseline
sera from the 4081 participants was started. Altogether, 241 coronary events, either nonfatal myocardial infarctions or coronary deaths, were observed during the 8.5-year follow-up. The control patients (controls) were chosen from among the participants who completed the study without coronary events, and they were individually matched with the 241 case patients (cases) for gemfibrozil treatment and region of residence. Geographical matching was necessary because of the marked regional differences in the incidence of coronary heart disease and the regional exposure to some infectious agents studied. At baseline, the mean ages of the cases and the controls were 48.5 and 47.3 years, respectively, and 58% of the cases and 35% of the controls were current smokers. The means of systolic/diastolic blood pressure were 149/93 mm Hg for the cases and 143/90 mm Hg for the controls. The mean values of total cholesterol were 7.7 mmol/L for the cases and 7.5 mmol/L for the controls. In the present study, serum samples taken both at baseline and 3 to 6 months before the coronary events that occurred within 8.5 years after the baseline measurement were studied. However, only one sample was available from some participants because of coronary events that occurred very early during the follow-up period. In addition, not all measurements could be done in a portion of serum samples. Therefore, 235 case-control pairs had baseline measurements available for C pneumoniae antibodies, 230 for hHsp60 antibodies, and 214 for CRP; 172 case-control pairs had both baseline and pre-event measurements available for C pneumoniae antibodies, 148 for hHsp60 antibodies, and 151 for CRP. Finally, 135 case-control pairs had both baseline and pre-event measurements available simultaneously for all 3 of these factors.

**Laboratory Methods**

Immunoglobulin class-specific antibodies to hHsp60 were measured from the serum samples taken at baseline and 3 to 6 months before the coronary events by an enzyme immunoassay (EIA), as described in detail elsewhere. Briefly, microwell plates were coated with a recombinant human Hsp60 protein produced in Escherichia coli (Sigma Chemical Co) at a concentration of 5 μg/mL in PBS (pH 7.4) overnight at 37°C. Sera diluted 1:50 for IgA and 1:200 for IgG antibodies in PBS containing 10% FBS were added, and the plates were incubated for 2 hours at 37°C. The plates were then incubated for 2 hours at 37°C with alkaline phosphatase–conjugated anti-human IgA and anti-human IgG. Absorbance was measured against a blank at 405 nm. We considered values above the median to be elevated. The hHsp60 antibody levels were significantly higher at the second time point than at baseline both in cases and in controls. Therefore, time point–specific cutoff levels were used for the medians. For hHsp60 IgA antibodies, the cutoff level was 10.6 EIA units at baseline and 21.9 EIA units before the coronary event. For hHsp60 IgG antibodies, the cutoff levels were 26.7 and 17.7 EIA units, respectively.

Immunocomplex (IC)-bound and serum IgA and IgG antibodies to C pneumoniae were measured by the microimmunofluorescence (MIF) method, as described in detail elsewhere, using the elementary bodies of the Kajaani 6 strain of C pneumoniae as antigen. For IC-bound antibodies, we considered values above the median, ie, an MIF titer of 2 (both at baseline and before the coronary event), to be elevated. For elevated serum antibodies, we used the quartile 4 as a cutoff level, because our previous studies indicated that only the highest levels predict coronary events. The cutoff levels were an MIF titer of 40 for IgA antibodies and an MIF titer of 256 for IgG antibodies (both at baseline and before the coronary event). The diagnostic criteria suggestive of a chronic C pneumoniae infection included an elevated serum IgA and/or IC-bound antibody level.

Serum CRP concentrations were measured by EIA (Eucardio Laboratory). The CRP levels were significantly higher at the second time point than at baseline both in cases and in controls. Therefore, time point–specific cutoff levels were used for the medians, ie, 1.7 mg/L at baseline and 2.4 mg/L before the coronary event.

**Statistical Analysis**

Because of the skewed distributions, the variables were first categorized by quartiles. For descriptive purposes, no matching was done, and we used the pooled data to calculate the prevalences of the different combinations of potential risk factors among the cases and the controls. However, to estimate the coronary risks associated with these combinations, we calculated the ORs by conditional logistic regression analysis. This method was chosen to allow us to maintain the matching of the case-control design, but again, for additional description, the pooled data were used to calculate the number of cases and controls in the risk factor categories.

**Results**

**Prevalence of Persistent Risk Factors**

Using the above-mentioned cutoff levels, 45% of the cases and 31% of the controls had elevated C pneumoniae IC/IgA antibody levels both at baseline and before the coronary event, suggesting chronic C pneumoniae infections (Table 1). The prevalence of persistently elevated IgG antibodies to C pneumoniae did not differ between the groups (data not shown). Persistently elevated hHsp60 IgA antibody levels were present in 40% of the cases and in 32% of the controls, whereas persistently elevated hHsp60 IgG antibodies were equally common in both groups (data not shown). The greatest difference between the cases and the controls was seen in the prevalence of persistently elevated CRP levels, which were present in 44% of the cases and in 21% of the controls. Of the 47 controls and 65 cases with persistently elevated C pneumoniae IC/IgA antibody levels, 22 controls

**TABLE 1. Prevalence of Elevated* Levels**

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th></th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Available, n (%)</td>
<td>Missing, n</td>
<td>Available, n (%)</td>
<td>Missing, n</td>
</tr>
<tr>
<td>C pneumoniae IC/IgA antibody levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C pneumoniae IC/IgA antibody levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hHsp60 IgA antibodies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hHsp60 IgG antibodies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

C pneumoniae IC/IgA antibodies; hHsp60, human Hsp60 IgA antibodies; and CRP, C-reactive protein concentration.

*Quartiles 3 and 4 were considered elevated for hHsp60 IgA and C pneumoniae IC/IgA antibody levels, 22 controls
†Elevated levels present neither at baseline nor before the coronary event.
‡Elevated levels present only at baseline.
§Elevated levels present only before the coronary event.
||Elevated levels present both at baseline and before the coronary event.

Available, n (%); Missing, n
TABLE 2. Effect of Persistently Elevated* Levels on the ORs of Coronary Events

<table>
<thead>
<tr>
<th>Seropositivity</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted† OR (95% CI)</th>
<th>Cases/Controls, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No‡</td>
<td>1</td>
<td>1</td>
<td>69/87</td>
</tr>
<tr>
<td>Past§</td>
<td>0.85 (0.36–2.05)</td>
<td>0.89 (0.35–2.27)</td>
<td>11/15</td>
</tr>
<tr>
<td>New§</td>
<td>1.03 (0.49–2.16)</td>
<td>1.09 (0.50–2.36)</td>
<td>15/18</td>
</tr>
<tr>
<td>Persistent¶</td>
<td>1.98 (1.20–3.27)</td>
<td>1.96 (1.14–3.36)</td>
<td>77/52</td>
</tr>
<tr>
<td>hHsp60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No‡</td>
<td>1</td>
<td>1</td>
<td>44/60</td>
</tr>
<tr>
<td>Past§</td>
<td>1.58 (0.73–3.45)</td>
<td>1.95 (0.83–4.54)</td>
<td>24/23</td>
</tr>
<tr>
<td>New§</td>
<td>1.42 (0.65–3.11)</td>
<td>1.65 (0.70–3.86)</td>
<td>22/21</td>
</tr>
<tr>
<td>Persistent¶</td>
<td>2.03 (1.09–3.78)</td>
<td>2.11 (1.08–4.13)</td>
<td>58/44</td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No‡</td>
<td>1</td>
<td>1</td>
<td>34/69</td>
</tr>
<tr>
<td>Past§</td>
<td>2.56 (1.19–5.48)</td>
<td>1.73 (0.76–3.94)</td>
<td>26/23</td>
</tr>
<tr>
<td>New§</td>
<td>1.55 (0.73–3.27)</td>
<td>1.23 (0.56–2.70)</td>
<td>24/27</td>
</tr>
<tr>
<td>Persistent¶</td>
<td>4.48 (2.34–8.58)</td>
<td>2.89 (1.39–6.03)</td>
<td>67/32</td>
</tr>
</tbody>
</table>

*Quartiles 3 and 4 were considered elevated for hHsp60 IgA and Cpn IC antibodies and CRP concentrations and quartile 4 for Cpn serum IgA antibodies.
†Adjusted for age and smoking.
‡Elevated levels present at baseline.
§Elevated levels present only at baseline.
¶Elevated levels present both at baseline and before the coronary event.

and 19 cases had merely those antibodies present, whereas persistently elevated levels of hHsp60 IgA antibodies and CRP in addition to persistently elevated C pneumoniae IC/IgA antibody levels were seen in only 1 control but in 17 cases.

Univariate and Joint Effects of Persistence on Coronary Risk

Only persistently, not transiently, elevated antibody and CRP levels were associated with the risk of coronary events (Table 2). Compared with persistently low levels, the risk of coronary events was 2-fold both for a persistently elevated level of IC/IgA antibodies to C pneumoniae and for a persistently elevated level of IgA antibodies to hHsp60. The corresponding IgG antibodies were not associated with the risk (data not shown). The coronary risk was highest for a persistently elevated CRP level: OR was 4.48 (95% CI, 2.34 to 8.58) without adjustment and 2.89 (95% CI, 1.39 to 6.03) when adjusted for age and smoking. Adjustment for other coronary heart disease risk factors, such as serum total cholesterol or body mass index, did not essentially change the pattern of risk (data not shown).

Table 3 shows that when both C pneumoniae IC/IgA and hHsp60 IgA antibodies were persistently elevated, the risk of coronary events, compared with low or transiently elevated levels of both antibodies, increased (adjusted OR, 2.61; 95% CI, 1.23 to 5.53). Conversely, the risk associated with an elevated C pneumoniae IC/IgA antibody level alone (adjusted OR, 1.62; 95% CI, 0.87 to 3.00) increased prominently if CRP was elevated as well (adjusted OR, 4.47; 95% CI, 1.84 to 10.83). An elevated hHsp60 IgA antibody level was associated with the risk only when CRP was elevated (adjusted OR, 4.36; 95% CI, 1.53 to 12.39).

Even when both C pneumoniae IC/IgA and hHsp60 IgA antibodies were persistently elevated but the CRP level was low, the coronary risk was only 1.6-fold and statistically not significant (Table 4). Reciprocally, without either of the antibodies elevated, an elevated CRP level was only weakly associated with the risk. Only the participants who had a persistently elevated CRP level and either 1 or both of the antibody markers at persistently elevated levels had a significant risk. The group in which all 3 of these markers were persistently elevated included only 1 control but 17 cases.

Discussion

In our previous study, we showed that elevated IgA antibodies to C pneumoniae and Hsp60 in baseline sera predicted future cardiac events in the Helsinki Heart Study. In the present study, we also showed that only the antibodies that were persistently elevated in the sera of these middle-aged hypercholesterolemic men were associated with an increased risk, suggesting that chronic C pneumoniae infection and persistent production of autoimmune antibodies to Hsp60 may have played a role in the development of cardiac events. In addition, in agreement with our previous studies, the coronary risks associated with elevated levels of IgA antibodies to C pneumoniae and hHsp60 increased considerably in the presence of an elevated CRP level. The risk was
TABLE 4. Role of CRP in the Association Between Persistently Elevated* Antibody Levels and the Coronary Risk

<table>
<thead>
<tr>
<th>Persistence*</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted† OR (95% CI)</th>
<th>Cases/ Controls, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP−</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cpn− and hHsp60−</td>
<td>1</td>
<td>1</td>
<td>34/53</td>
</tr>
<tr>
<td>Cpn+ or hHsp60+</td>
<td>1.00 (0.51–1.96)</td>
<td>1.06 (0.53–2.13)</td>
<td>29/42</td>
</tr>
<tr>
<td>Cpn+ and hHsp60+</td>
<td>1.57 (0.64–3.86)</td>
<td>1.55 (0.62–3.91)</td>
<td>14/13</td>
</tr>
<tr>
<td>CRP+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cpn− and hHsp60−</td>
<td>2.00 (0.84–4.76)</td>
<td>1.78 (0.71–4.45)</td>
<td>17/13</td>
</tr>
<tr>
<td>Cpn+ or hHsp60+</td>
<td>2.60 (1.18–5.75)</td>
<td>2.26 (0.97–5.25)</td>
<td>27/16</td>
</tr>
<tr>
<td>Cpn+ and hHsp60+</td>
<td>23.87 (3.03–188.2)</td>
<td>16.87 (2.06–137.9)</td>
<td>17/1</td>
</tr>
</tbody>
</table>

Test for trend, P<0.001

Quartiles 3 and 4 were considered elevated for hHsp60 IgA and Cpn IC antibodies and for CRP concentrations and quartile 4 for Cpn serum IgA antibodies.

*Persistence, ie, elevated levels present both at baseline and before the coronary event.
†Adjusted for age and smoking.

increased by an increasing number of persistently elevated risk factors, being highest when all 3 factors, representing chronic *C pneumoniae* infection, inflammation, and autoimmunity to hHsp60, were elevated. Interestingly, only 1 participant who had all 3 of these markers was found among the 138 controls compared with 17 among the same number of cases.

Our finding is in agreement with a recent report by Kiechl et al,13 who showed that antibodies to mycobacterial Hsp65 predicted carotid atherosclerosis and that the association between chronic (respiratory, urinary tract, dental, and other) infections and the risk of atherosclerosis increased in the presence of an elevated CRP level, a marker of systemic inflammation. Another study, by Gattone et al,14 showed that seropositivity to both *C pneumoniae* and cytomegalovirus infections was associated with increased CRP and a risk of premature myocardial infarction. Atherosclerosis is currently accepted as an inflammatory disease,15 and several prospective studies have shown CRP to be a strong independent predictor of coronary events.16,17 The mechanisms by which CRP is involved in atherogenesis are under investigation.18,19 Given that the coronary risk associated with elevated *C pneumoniae* IC/IgA and hHsp60 IgA antibody levels increased in the presence of an elevated CRP level, the risk associated with elevated CRP also clearly increased when elevated antibody levels were involved.

In our previous study,3 by using single baseline serum samples of the same study population, we found a good correlation between human-specific and *C pneumoniae*-specific Hsp60 antibodies, but only the human-specific Hsp60 IgA antibodies were associated with the coronary risk. In addition, high levels of *C pneumoniae* IgA antibodies were associated with the risk. The association found between hHsp60 and *C pneumoniae* IgA antibodies suggests that the antibodies to hHsp60 may have resulted from chronic *C pneumoniae* infections. Human, chlamydial, and other bacterial heat-shock proteins share a high sequence homology, and it is thus possible that other bacterial agents, such as dental bacteria, that have been associated with coronary heart disease have also contributed to the development of autoimmunity to hHsp60.20 However, no association was found between *Helicobacter pylori* infection and coronary risk in our previous study.12

Chlamydial Hsp60 antibodies have been associated with the development of immunopathological damage after repeated and persistent *C trachomatis* infections,21 and the expression of Hsp60 is increased in these infections.22 In human atherosclerotic plaques, chlamydial Hsp60 and its human counterpart have been found to be colocalized and increasingly expressed compared with nonatherosclerotic tissues.23 In mice, only coimmunization with both mouse and chlamydial Hsp60 proteins was found to induce strong T- and B-cell autoimmune responses to mouse Hsp60.24 *C pneumoniae* and chlamydial Hsp60 have also been found to induce cellular oxidation of LDL.25 Furthermore, both chlamydial and human Hsp60 proteins have been shown to activate human vascular cell functions relevant to atherogenesis and lesion complications.26 These findings suggest that Hsp60 may have an important role in the pathogenesis of atherosclerosis.

The serological association between *C pneumoniae* antibodies and atherosclerosis has recently been disputed: some studies have revealed an association, but others have not (reviewed by Danesh et al.27,28). Although a lack of association has been observed primarily in the study of IgG antibodies,27 we have found IgA antibodies, especially when persistently elevated, to be more strongly associated with coronary heart disease and an increased risk of future coronary events.3,8,12 Although no causal association between *C pneumoniae* infection and atherosclerosis has been demonstrated, chronic *C pneumoniae* infection may be involved in atherogenesis by, for example, inducing inflammation and the development of autoimmunity to Hsp60. Our results suggest that a combination of elevated *C pneumoniae* IC/IgA antibodies and slightly elevated CRP values and/or elevated IgA antibodies to Hsp60 would be helpful when screening for persons at a high risk for a coronary event.

One shortcoming of the present study is the fact that some serum samples were missing, making the numbers too small for further analysis. Most missing samples were related to coronary events that occurred very early during the follow-up period, with only the baseline samples available. Because the present study was a logical extension of our previous studies,5,7,8,12 sufficient volumes of sera were no longer available in all cases. Some ORs would probably have reached statistical significance in a larger population. The participants with only 1 sample available, who were therefore excluded in the analyses, did not differ from those included in this study with respect to age, body mass index, serum total cholesterol, or blood pressure. However, this group of participants involved a larger number of smokers (53%) than the group included in the study (42%). The strong interaction between CRP and smoking observed in our previous study12 suggests a higher risk in the total study population compared with the risk found in this study. Another shortcoming is that the test of the post hoc hypothesis is based on dyslipidemic, middle-aged...
white men. Thus, the findings of the present study may not be
generalized to normocholesterolemic men or women or to
other races.

In conclusion, only persistently, not transiently, elevated C
pneumoniae IC/IgA and hHsp60 IgA antibodies predicted
coronary events in this study. Moreover, the coronary risk
associated with elevated antibody levels increased consider-
ably in the presence of an elevated CRP level, and vice versa.

Thus, it seems that chronic infection, autoimmunity, and
inflammation may have conspired in causing coronary events
in this study population.

Acknowledgments
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technical assistance.

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