High-sensitivity C-reactive protein affects central haemodynamics and augmentation index in apparently healthy persons

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Objective Among apparently healthy women and men, elevated levels of high-sensitivity C-reactive protein (hsCRP) predict the risk of cardiovascular events and may be useful for detecting subclinical atherosclerosis. The aim of this study was to investigate the associations between inflammatory markers, augmentation index (AIx), central pulse pressure and central systolic blood pressure in apparently healthy subjects.

Design and settings An observational study conducted at a university teaching hospital.

Methods and results Apparently healthy subjects (\(n=158\); 75 males, 83 females) passed a complete history and physical examination, blood tests and pulse wave analysis.

AIx was significantly higher in patients with hsCRP levels above 1 mg/l (24.5 $\pm$ 9.9 versus 18.1 $\pm$ 12.6\%, \(P<0.001\)). Central pulse pressure and central systolic blood pressure were significantly higher in the group with hsCRP levels above 1 mg/l. No differences between groups were shown for peripheral pulse pressure, peripheral blood pressures and estimated aortic pulse wave velocity. In multiple regression analysis, AIx correlated positively with age, female gender, short stature, mean arterial pressure, hsCRP (\(P=0.026\)) and white blood cell count (\(P=0.01\)), and negatively with heart rate.

Conclusions This study shows that plasma levels of hsCRP are positively correlated with AIx, central pulse pressure and central systolic blood pressure. Apparently healthy subjects with increased inflammatory markers have increased systemic arterial stiffness, which might reflect early atherosclerotic changes. Our results suggest that hsCRP and non-invasively measured arterial stiffness could serve as additional tools, beside conventional cardiovascular risk factors, for assessment of global arterial risk and preclinical atherosclerotic changes in arteries. J Hypertens 22:1133–1139 © 2004 Lippincott Williams & Wilkins.

Keywords: inflammation, atherosclerosis, arterial stiffness, augmentation index

Introduction Increased arterial stiffness is associated with atherosclerosis [1] and is recognized as an important cardiovascular risk factor [2]. It has been shown that arterial stiffness increases with age [3], and is higher in patients with coronary artery disease, hypertension, diabetes mellitus, hypercholesterolaemia and end-stage renal failure [4–7].

There are different methods for detecting arterial stiffness. Measurement of peripheral pulse pressure (PP), which is associated with increased risk of cardiovascular events [8,9], has been recognized as a surrogate marker for arterial stiffness. However, changes in peripheral PP do not always predict central PP [10] and cannot, therefore, be always considered a reliable indicator of systemic arterial stiffness [11]. Increased central systolic blood pressure and central PP are known to be more important determinants of left ventricular workload and mass, which independently predict cardiovascular mortality [12,13].

Pulse wave analysis (PWA) is a simple, non-invasive, reproducible method for assessing central blood pressure and the indices of systemic arterial stiffness (AIx – augmentation index) and estimated aortic pulse wave velocity (\(T\text{R} – \text{timing of the reflected waveform}\)). In stiffer vessels, pressure waves are reflected earlier in the aorta, which consequently augments central systolic blood pressure, central PP and AIx.

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Central systolic blood pressure, central PP, Alx and aortic pulse wave velocity are more precise indices for detecting increased arterial stiffness and have stronger associations with cardiovascular events than peripheral PP [14–16].

In our study, PWA was used to estimate both aortic and systemic arterial stiffness. Alx shows the proportion of central systolic blood pressure caused by wave reflection. It is considered to be the index of the reflective central systolic blood pressure [17]. $T_R$ is an additional tool in PWA, which provides a surrogate for aortic pulse wave velocity, measuring the timing of the start of wave reflection [18]. Hence $T_R$, serves as a marker of aortic stiffness. PWA has the capacity to differentiate between the changes related to stiffening of the aorta and those related to wave reflection.

Inflammatory processes play a principal role in the pathogenesis of atherosclerosis [19]. High-sensitivity C-reactive protein (hsCRP) and white blood cell count (WBC) are the markers for infection and/or inflammation in daily clinical practice, reflecting also the stage of atherosclerosis as a chronic inflammatory process [20]. Several large-scale prospective epidemiological studies have shown that plasma levels of hsCRP are strong independent predictors of the future risk of atherosclerotic events in apparently healthy men and women [21,22]. Elevated hsCRP is a marker for subclinical atherosclerosis [23], and is involved in development and progression of atherosclerosis [24–29].

We hypothesized that low-grade inflammation could be the earliest sign of atherosclerosis in apparently healthy persons, which affects wave reflection in small peripheral arteries and arterioles, rather than damaging the aorta or major conduit arteries. Therefore, these patients may have increased systemic arterial stiffness due to early wave reflection. The aim of the study was to test this hypothesis and to estimate the associations between inflammatory markers (hsCRP, WBC) and central and peripheral blood pressure values, $T_R$ and Alx.

### Methods

#### Subjects

The study population consisted of 158 healthy middle-aged subjects (age range 40–65 years) (Table 1). All subjects passed a routine medical evaluation including a complete history and physical examination, electro-

### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Female ($n = 83$)</th>
<th>Male ($n = 75$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.9 ± 5.6</td>
<td>50.6 ± 6.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.1 ± 4.2</td>
<td>25.6 ± 3.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 ± 0.06</td>
<td>1.8 ± 0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.2 ± 11.7</td>
<td>80.6 ± 11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSBP (mmHg)</td>
<td>116.7 ± 12.4</td>
<td>120.2 ± 11.3</td>
<td>0.03</td>
</tr>
<tr>
<td>PDPP (mmHg)</td>
<td>76.6 ± 8.9</td>
<td>78.2 ± 7.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Peripheral PP (mmHg)</td>
<td>39.6 ± 8.7</td>
<td>41.9 ± 8.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>91.3 ± 8.5</td>
<td>92.4 ± 8.5</td>
<td>0.4</td>
</tr>
<tr>
<td>CSBP (mmHg)</td>
<td>107.5 ± 11.6</td>
<td>109.1 ± 10.6</td>
<td>0.4</td>
</tr>
<tr>
<td>CDBP (mmHg)</td>
<td>77.7 ± 7.0</td>
<td>78.1 ± 7.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Central PP (mmHg)</td>
<td>29.8 ± 7.3</td>
<td>30.1 ± 7.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Augmentation index (%)</td>
<td>24.9 ± 9.8</td>
<td>16.8 ± 12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alx HR 75 (%)</td>
<td>25.1 ± 8.5</td>
<td>12.9 ± 10.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75.2 ± 10.7</td>
<td>67.2 ± 10.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$T_R$ (ms)</td>
<td>140.0 ± 11.1</td>
<td>148.5 ± 10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total serum cholesterol (mmol/l)</td>
<td>5.9 ± 1.0</td>
<td>5.7 ± 1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.6 ± 0.4</td>
<td>1.4 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>3.8 ± 0.9</td>
<td>3.7 ± 1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.1 ± 0.6</td>
<td>1.4 ± 1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Current smoking [n (%)]</td>
<td>14 (16.7)</td>
<td>13 (16.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cigarette (n/day)</td>
<td>10.4 ± 3.8</td>
<td>15.3 ± 8.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking history (years)</td>
<td>26.9 ± 6.1</td>
<td>29.0 ± 5.3</td>
<td>0.35</td>
</tr>
<tr>
<td>HS-CRP level (mg/l)</td>
<td>0.46 ± 0.5</td>
<td>0.47 ± 0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>WBC count ($×10^9$/l)</td>
<td>5.0 ± 1.2</td>
<td>5.37 ± 1.2</td>
<td>0.09</td>
</tr>
<tr>
<td>RBC count ($×10^12$/l)</td>
<td>4.4 ± 0.3</td>
<td>4.7 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>129.8 ± 9.6</td>
<td>144.8 ± 9.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>38.5 ± 2.5</td>
<td>42.3 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets ($×10^9$/l)</td>
<td>231.6 ± 53.7</td>
<td>223.4 ± 45.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.9 ± 0.5</td>
<td>5.2 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD unless otherwise indicated. PSBP, peripheral systolic blood pressure; PDPP, peripheral diastolic blood pressure; PP, pulse pressure; CSBP, central systolic blood pressure; CDBP, central diastolic blood pressure; Alx HR 75, augmentation index, correlated with heart rate 75; $T_R$, timing of the reflected pressure wave; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HsCRP, high-sensitivity C-reactive protein; WBC, white blood cell; RBC, red blood cell.
cardiography, and blood tests. The exclusion criteria were the following: clinically overt coronary artery disease or valve pathologies, arterial hypertension (blood pressure ≥ 140/90 mm Hg), cerebral and/or peripheral atherosclerotic disease, diabetes (fasting plasma glucose > 6.4 mmol/l), malignancies, chronic degenerative diseases, endocrine pathologies, and according to a self-reported questionnaire: regular use of vasoactive, anti-inflammatory or steroid substances during the past 2 months. Subjects above the upper limit of the normal range (>5 mg/l) of hsCRP were also excluded from analysis, as apparently having infection or inflammatory disorders.

The study protocol was approved by the Ethics Committee, University of Tartu. Informed written consent was obtained from each participant.

Study protocol
The subjects were studied and the plasma samples were collected between 0800 and 1000 h, after an overnight fast and abstinance from tobacco, alcohol, tea or coffee. After 15 min of rest, blood pressure was measured and PWA was performed. Thereafter, blood samples were drawn from the antecubital fossa for the measurement of plasma hsCRP, glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, WBC, red blood cell count, haematocrit, haemoglobin and platelets. Height and weight were recorded, and body mass index (BMI) was calculated.

Blood pressure
Systolic and diastolic blood pressure were measured in both arms at least twice with a mercury sphygmomanometer (Diplomat-Presameter, Riester, Germany). The first and the fifth Korotkoff sounds were recorded to determine peripheral systolic blood pressure and peripheral diastolic blood pressure. Peripheral PP was calculated as the difference between peripheral systolic blood pressure and peripheral diastolic blood pressure.

Pulse wave analysis
PWA was used to determine central blood pressure values, \(T_R\) and AIx. Applanation tonometry was used to record peripheral pressure waveforms at the surface of the skin, overlying the radial artery. The peripheral radial pulse was recorded continuously (the mean values of at least 20 pulse waves were used for analysis). On the basis of the collected data, an averaged peripheral waveform was generated. Thereafter, a corresponding averaged central pressure waveform and central AIx, the difference between the central first and second systolic peaks expressed as the percentage of central PP, were determined using a validated mathematical transfer function (SphygmoCor Px, Version 7.0, AtCor Medical, Australia) [17]. The timing of the reflected wave \(T_R\) was calculated as the time between the first systolic stand (inflection point). \(T_R\) provided the surrogate of aortic pulse wave velocity.

Laboratory assay
In all subjects, plasma samples were analysed immediately. Lipid levels were measured by the Hitachi 912 analyser (Roche Diagnostics GmbH, Germany). Plasma LDL and HDL cholesterol (Roche Diagnostics GmbH), total cholesterol (Human, Germany), and triglycerides (Biocon, Germany) were measured.

WBC, red blood cell count, haematocrit, haemoglobin and platelets were estimated by the Sysmex XE 2100 autoanlyser (Sysmex Corporation, Japan). hsCRP was determined by a latex particle-enhanced immunoturbidimetric assay (Roche Diagnostics GmbH) with an automated analyser, Hitachi 912. The measurement range was 0.1–20 mg/l.

Statistical analysis
The data were analysed using unpaired two-tailed Student’s \(t\)-test, Fisher’s exact test, Pearson correlation and multiple regression analysis (Software R, version 1.6.0 for Windows). Since the distribution of the hsCRP values was skewed to the left, logarithmic transformation and natural logarithm [\(\log(hsCRP)\)] were employed to achieve approximate normality. The values were expressed as mean ± SD or \(n\) (%). Significance was defined as \(P < 0.05\).

Results
Subjects
The baseline clinical characteristics of the 158 study subjects are summarized in Table 1. When the males and the females were compared, no differences were found between age, BMI, smoking status and smoking history or total cholesterol. Two groups differed significantly with regard to AIX (24.9 ± 9.8% for the female group versus 16.8 ± 12.5% for the male group, \(P < 0.001\)), heart rate and \(T_R\) (140.0 ± 11.1 ms for the female group versus 148.5 ± 10.4 ms for the male group, \(P < 0.001\)). Regarding serum glucose, significant differences were detected between the groups. Among the inflammatory markers, hsCRP \((P = 0.9)\) and WBC \((P = 0.09)\) did not differ significantly between the two groups.

hsCRP, central and peripheral haemodynamic data
The subjects were stratified into two groups according to hsCRP levels (Table 2). The AIx was significantly higher in patients with hsCRP levels above 1 mg/l (24.5 ± 9.9 versus 18.1 ± 12.6%, \(P < 0.001\), \(r = 0.28\)). When two hsCRP groups were compared, significant differences were revealed in central systolic blood pressure, central PP, and mean arterial pressure. No differences
were found between the groups regarding peripheral systolic blood pressure, peripheral PP or $T_R$.

**Data of central and peripheral haemodynamics and risk factors**

In multiple regression analysis (Table 3; $R^2 = 0.64$), AIx as a dependent variable correlated significantly with female gender, age, height, heart rate, mean arterial pressure, WBC ($P = 0.01$) and log(hsCRP) ($P = 0.026$). Adjusting additionally for weight, smoking, plasma glucose, LDL cholesterol, HDL cholesterol and triglycerides did not have any significant effect on the fitted regression model.

In sex-adjusted simple regression analysis, significant correlations were found between plasma hsCRP and AIx ($P < 0.0001$) (Fig. 1). Regarding the effect on AIx, hsCRP did not interact significantly with sex ($P = 0.16$).

In multiple regression analysis, central PP correlated significantly with age, heart rate, hsCRP and serum glucose (Table 4; $R^2 = 0.28$). Multiple regression analysis revealed no correlation between hsCRP and peripheral PP ($P = 0.09$) as a dependent variable.

Aortic $T_R$ as a dependent variable correlated only with height and mean arterial pressure (Table 5; $R^2 = 0.28$).

**Table 3 Results of the multiple regression analysis with augmentation index as the dependent variable**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>$P$ value</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.56</td>
<td>0.11</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Gender, female</td>
<td>9.57</td>
<td>1.82</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>–42.23</td>
<td>9.68</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>–0.58</td>
<td>0.06</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>WBC count ($\times 10^{12}$/l)</td>
<td>1.29</td>
<td>0.52</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Log(hsCRP)</td>
<td>1.93</td>
<td>0.86</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>0.42</td>
<td>0.08</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>2.78</td>
<td>1.67</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

$R^2 = 0.64$, $P < 0.0001$ for the entire study group ($n = 158$ subjects).

Log(hsCRP), natural logarithm of high-sensitivity C-reactive protein level; WBC, white blood cell; MAP, mean arterial pressure.
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Fig. 1

Scatter plot of log(hsCRP) (the natural logarithm of high-sensitivity C-reactive protein level) and AIx (the augmentation index), together with separate regression lines for males and females. \( r = 0.42 \) for males and \( r = 0.35 \) for females, \( P < 0.0001 \) for the entire study group (\( n = 158 \) subjects).

Table 4 Results of the multiple regression analysis with central pulse pressure (PP) as the dependent variable

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.30</td>
<td>0.09</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender, female</td>
<td>1.65</td>
<td>1.56</td>
<td>0.3</td>
</tr>
<tr>
<td>Height (m)</td>
<td>-8.64</td>
<td>7.08</td>
<td>0.5</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>-0.22</td>
<td>0.05</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>WBC count (( \times 10^9/\text{l} ))</td>
<td>-0.07</td>
<td>0.44</td>
<td>0.9</td>
</tr>
<tr>
<td>Log(hsCRP)</td>
<td>1.38</td>
<td>0.50</td>
<td>0.006</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>2.30</td>
<td>0.96</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.94</td>
<td>1.40</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\( R^2 = 0.28, P < 0.0001 \) for the entire study group (\( n = 158 \) subjects).

Log(hsCRP), natural logarithm of high-sensitivity C-reactive protein level; WBC, white blood cell.

Table 5 Results of the multiple regression analysis with \( T_R \) (timing of the reflected pressure wave) as the dependent variable

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.24</td>
<td>0.15</td>
<td>0.1</td>
</tr>
<tr>
<td>Gender, female</td>
<td>-4.42</td>
<td>2.51</td>
<td>0.08</td>
</tr>
<tr>
<td>Height (m)</td>
<td>32.36</td>
<td>13.36</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>-0.11</td>
<td>0.08</td>
<td>0.2</td>
</tr>
<tr>
<td>WBC count (( \times 10^9/\text{l} ))</td>
<td>-0.29</td>
<td>0.72</td>
<td>0.7</td>
</tr>
<tr>
<td>Log(hsCRP)</td>
<td>-0.98</td>
<td>1.19</td>
<td>0.4</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>-0.32</td>
<td>0.11</td>
<td>0.004</td>
</tr>
<tr>
<td>Smoking</td>
<td>-2.74</td>
<td>2.30</td>
<td>0.2</td>
</tr>
</tbody>
</table>

\( R^2 = 0.28, P = < 0.0001 \) for the entire study group (\( n = 158 \) subjects).

Log(hsCRP), natural logarithm of high-sensitivity C-reactive protein level; WBC, white blood cell; MAP, mean arterial pressure.

Our results confirm the previous findings that apparently healthy persons with higher values of inflammatory markers could represent a group at higher risk for developing cardiovascular events. This study suggests that increased hsCRP, WBC and AIx in apparently healthy persons could reflect the earliest (subclinical) stage of atherosclerotic changes, especially in small arteries. To the best of our knowledge, this is the first attempt to address the possible relationship between inflammatory markers and the affected wave reflection due to damaged small arteries and arterioles in apparently healthy persons.

The existing data of apparently healthy US adults have demonstrated an association between increased peripheral PP and an elevated C-reactive protein level [30]. This association has been suggested to be independent of peripheral systolic blood pressure, peripheral diastolic blood pressure and a number of other factors, including cholesterol, obesity, smoking status, alcohol consumption and physical activity. Although the present study revealed no correlation between peripheral PP and hsCRP, a correlation was demonstrated between central PP and hsCRP. Several explanations can be given for the discrepancies between the above study and ours. First, in our study C-reactive protein (CRP) was measured by high-sensitivity assay instead of standard methods for CRP. Standard assays for CRP lack the sensitivity needed to determine levels of inflammation within the normal range, which is necessary to detect subclinical changes in arteries. Therefore, clinical utility for standard CRP evaluation for vascular risk detection is extremely limited. Second, instead of peripheral blood pressure measurement, use of non-invasive PWA in this study offers the opportunity to analyse both central and peripheral haemodynamics. It has been shown that peripheral PP does not always predict central PP [10], which itself defines best left ventricular workload and hence left ventricular mass – an important and independent predictor of cardiovascular mortality [11–13]. We believe that the earliest changes preceding atherosclerosis could be detected by measurement of central haemodynamics and PP. As PP varies through the arterial tree, depending on the vessels’ compliance and wave reflection, measurement of peripheral blood pressure may not provide reliable information on central PP. In the case of stiffer vessels, the reflected pulse waves augment central haemodynamics, which also results in the reduction of PP amplification. Thirdly, in concordance with this as-
sumption, there has been found an association of central PP with several cardiovascular risk factors, such as intima–media thickness [31] and hypercholesterolaemia [6], whereas no such association has been revealed for peripheral PP.

Previous studies have shown an independent and statistically significant correlation between AIx and gender, age, height, mean arterial pressure and heart rate [6,32]. All these associations were also found in this study. After the correction of AIx for a heart rate of 75 beats per minute, the correlation between AIx and hsCRP became even higher in subjects with elevated levels of hsCRP.

As a novel finding, this study found a significant association between AIx and the inflammatory markers hsCRP and WBC. Previous studies have shown that higher WBC counts predict increased cardiovascular mortality independently of the other risk factors, both among men and women [33]. Evidence also suggests the pathogenic role of WBC in vascular injury [19,34,35].

HsCRP is an independent predictor of myocardial infarction, stroke and vascular death in a variety of settings [21,22,36,37]. According to recently published data, hsCRP predicts cardiovascular events more accurately than LDL cholesterol [36]. Many studies have demonstrated that CRP is not only a predictor of atherosclerotic events but is also involved in the pathogenesis of the atherosclerotic process, both directly and indirectly. At concentrations known to predict vascular disease, CRP stimulates the expression of endothelial cell adhesion molecules, production of chemotactic and inflammatory cytokines, and macrophage LDL uptake, and modulates production of endothelial-derived vasoactive factors, including downregulation of endothelial nitric oxide synthase [24–29]. CRP levels reflect the extent of inflammatory reactions in atherosclerotic vessels [38]. Patients with elevated plasma CRP levels have impaired endothelial vasoreactivity, and normalization of CRP levels over time is associated with a significant improvement in endothelial-dependent forearm blood flow responses [27]. Chronic inflammation and endothelial dysfunction stiffen arteries from the early stages of atherosclerosis. Previously, AIx and flow-mediated dilatation, which are considered to express endothelial dysfunction and ‘functional atherosclerosis’, have been shown to correlate strongly with early ‘structural atherosclerosis’ as assessed by carotid intima–media thickness [39].

In 2003, the Centers for Disease Control and Prevention and the American Heart Association published a scientific statement recommending the use of hsCRP in an adult population. According to the statement, the current cut-off points for low risk (hsCRP < 1 mg/l), average risk (hsCRP 1.0–3.0 mg/l) and high risk (> 3 mg/l) should be used in risk stratification [40]. In our study there was a significant difference between AIx at hsCRP < 1 mg/l and at hsCRP > 1 mg/l. Unfortunately, as the number of patients in the high-risk group was small, further studies are required to elucidate the relationship between the cut-off points for hsCRP and AIx.

Previously, associations have been described between several cardiovascular risk factors and AIx [6,41]. Wilkinson et al. [6] demonstrated that AIx, $T_R$ and central PP were significantly higher in subjects with hypercholesterolaemia, compared with the control group. Our study did not find significant correlations between AIx and LDL cholesterol, serum glucose, tobacco smoking or BMI. Different selection criteria, as well as the small number of study subjects, may serve as an explanation for these discrepancies. Future large studies are needed to confirm our results and to establish the effect of gender on AIx and the other cardiovascular risk factors.

The present study demonstrates increased AIx in asymptomatic subjects with higher values of hsCRP. However, it remains to be established to what extent this increased stiffness is caused by structural changes in the arterial wall or is due to dysfunctional endothelium. Therefore, to elucidate the role of the endothelium in the regulation of arterial stiffness, mechanistic studies are required to investigate the relationship between arterial stiffness and endothelial function.

This study shows that plasma levels of hsCRP are positively correlated with AIx, central PP and central systolic blood pressure. Apparently healthy persons with increased inflammatory markers have increased systemic arterial stiffness, which might reflect early atherosclerotic changes. Our results suggest that hsCRP and non-invasively measured arterial stiffness could serve as additional tools, beside conventional cardiovascular risk factors, for assessment of global arterial risk and preclinical atherosclerotic changes in arteries.

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