Antibodies to Endothelial Cells in Borderline Hypertension

Johan Frostegård, MD, PhD; Ruihua Wu, MD, PhD; Caroline Gillis-Haegerstrand, MD, PhD; Carola Lemne, MD, PhD; Ulf de Faire, MD, PhD

Background—Antibodies to endothelial cells (aECs) and to cardiolipin (aCLs) are implicated in autoimmune diseases like systemic lupus erythematosus vasculitis. β2-Glycoprotein 1 (β2GP1) is a cofactor for aCLs. The present study investigated the possible role of aECs, aCLs, and aβ2GP1 in borderline hypertension.

Methods and Results—Seventy-three men with borderline hypertension (BHT) and 73 age-matched normotensive (NT) men (diastolic blood pressure, 85 to 94 and <80 mm Hg, respectively) were recruited from a population screening program. Antibody levels were determined by ELISA. Presence of carotid atherosclerosis was determined by B-mode ultrasonography, and 29 individuals had atherosclerotic plaques. BHT men had significantly higher aEC and aβ2GP1 levels of IgG class than NT control subjects (P = 0.029 and P = 0.0001, respectively). aEC levels of IgM class were higher in BHT (P = 0.012), but not aβ2GP1 levels. There was no correlation between aCL levels and BHT. Individuals with atherosclerotic plaques had significantly higher aEC levels of both IgG (P = 0.042) and IgM subclasses (P = 0.018) than those without plaques, but no difference was found in aCL and aβ2GP1 levels. Endothelin and aECs of IgM class were significantly associated.

Conclusions—We demonstrate the first evidence of a significant elevation of aEC and aβ2GP1 levels in borderline hypertension. These findings provide a new link between hypertension and atherosclerosis and indicate that humoral immune reactions to the endothelium may play an important role in both conditions. (Circulation. 1998;98:1092-1098.)

Key Words: endothelium • antibodies • glycoproteins • atherosclerosis • hypertension
(NT), with the major change (13% to 15%) occurring already at the 1-year follow-up visit. After 3 years, 81 men were still within the range for BHT on the basis of repeated measurements over the entire time period.

These 81 individuals with BHT were invited to participate in the present investigation, together with 80 age-matched male control subjects from the original population who had a DBP \( \leq 80 \) mm Hg at the initial measurement. To obtain 80 age-matched control subjects, 105 NT men were asked to participate, of whom 23 declined to participate and 2 had a DBP \( > 80 \) mm Hg. The blood pressure of the control subjects was measured on 2 occasions a few weeks apart. For the subjects to participate in the study, their DBP had to be \( \leq 80 \) mm Hg on both occasions. All blood pressure measurements during the entire recruitment procedure and study period were performed by 1 person, a specially trained nurse.

The study was approved by the local ethics committee of Karolinska Hospital and was conducted in accordance with the Helsinki Declaration. All subjects gave informed consent before entering the program of which this study was a part. Of the 81 men with BHT and the 80 NT control subjects who agreed to participate in the program, 73 in the BHT and 73 in the NT group completed all procedures of the present study. None of the subjects had any other illnesses or were regularly using any drugs known to influence blood pressure, metabolic variables, or inflammatory variables.

**Study Program**

All subjects were investigated according to the same schedule. Men with BHT and their control subjects were investigated simultaneously when possible and never more than 4 weeks apart. All blood samples were taken between 8 and 9:30 AM, after 8 to 12 hours of fasting. All samples were drawn after 15 minutes of rest in the supine position.

**Analysis of Total Serum Immunoglobulin Levels**

Serum immunoglobulins, IgG, IgM, and IgA, were determined by immunoturbidimetry. Specific anti-IgG, anti-IgM, and anti-IgA reagents and calibrators were obtained from Dako. The turbidimetric reaction was quantified in a Hitachi 911 analyzer by measurement of light transmission at 340-nm wavelength.

**Cell Culture**

ECs were isolated and cultured from 3- to 5-cm-long segments of the saphenous vein derived from patients undergoing coronary bypass surgery, as described in detail previously. Briefly, the vein was rinsed and then filled with a collagenase solution (0.1%, Worthington). Harvested cells were routinely cultured in MEM (Gibco BRL) with the addition of 40% pooled heat-inactivated (56°C, 30 minutes) human serum, antibiotics, and cAMP-elevating compounds. Two days before the experiments, the ECs were gently detached with a 0.1% trypsin/0.02% EDTA (1:1) solution. The cells were seeded on gelatin-coated plastic wells (24-well plates, Costar) at a density corresponding to 100 000 cells/cm² in MEM containing only 30% human serum and antibiotics. The ECs were characterized as endothelial by immunohistochemical staining of von Willebrand factor–related antigen, PG1, production, and their typical cobblestone appearance. In each experiment, cells from a single donor from the fourth to seventh passages were used. The use of human great saphenous veins was approved by the ethics committee at the Karolinska Hospital.

**Detection of Antibody Levels**

Antibodies to ECs were detected essentially as described earlier. The ECs were suspended in the RPMI 1640 medium containing 20% heat-inactivated FCS and seeded on the 96-well flat-bottom tissue culture plates at a density of \( 1 \times 10^{5} \) cells/well. After the ECs were incubated for 2 days, the plates were washed 3 times with PBS, pH 7.4. The ECs were fixed for 15 minutes at room temperature with 0.2% glutaraldehyde. The fixed cells were washed 4 times in the washing buffer (PBS/0.2% BSA). The plates were blocked by 200 \( \mu \)L of blocking buffer (PBS/1% BSA and 0.1 mol/L glycine) for 1 hour at room temperature. The serum samples were diluted 1:50 in washing buffer, and 100 \( \mu \)L of this dilution was added to each well and incubated at 37°C for 2 hours. IgG and IgM antibodies to cardiolipin (CL) were determined by ELISA essentially as described.

Antibody reactivity to \( \beta 2 \)GP1 was detected by coating irradiated Titertek 96-well polystyrene microplates (Flow Laboratories) with 50 \( \mu \)L/well of 30 \( \mu \)g/mL \( \beta 2 \)GP1 (Calbiochem B 18287) dissolved in 10 mmol/L HEPES, 150 mmol/L NaCl, pH 7.4 (HEPES buffer), at 4°C overnight. The plates were blocked with 0.3% gelatin for 1 hour. After washing, the wells were incubated with 50 \( \mu \)L of 50-times-diluted samples for 1 hour at room temperature (2 mmol/L of EDTA was included in buffer). Control assays were performed in the absence of \( \beta 2 \)GP1.

After 3 washings with PBS, the plates were incubated with 50 \( \mu \)L/mL of alkaline phosphatase–conjugated goat anti-human IgG (Sigma A-3150) diluted 1:9000 or IgM (Sigma A-3275) diluted 1:7000 with PBS at 37°C for 2 hours. After 3 washings, 100 \( \mu \)L of substrate (phosphatase substrate tablets, Sigma 104; 5 mg in 5 mL diethanolamine buffer, pH 9.8) was added. The plates were incubated at room temperature for 30 minutes and read in an ELISA Multiskan Plus spectrophotometer at 405 nm. Each determination was done in triplicate. The coefficient of variation between triplicate tests was <5%. Investigators were blinded, and patient and control samples were mixed.

**Cross-Reactivity Between Antibodies**

To investigate whether there was an immunological cross-reactivity between antibodies tested, competition assays were performed. Sera at a dilution giving 50% of maximal binding to the compound coated were preincubated with ECs as indicated. The sera were incubated overnight with the different competitors at 4°C, and inhibition of binding to ECs was tested. The percentage of inhibition was calculated as follows: Percent inhibition = (OD control – OD with competitor × 100)/OD control, where OD is optical density.

**Analysis of Plasma Lipoprotein, Insulin, IGFbp-1, and Endothelin-1 Levels**

VLDL, LDL, HDL were determined as previously described. The insulin resistance was calculated by the formula IR = fasting insulin/22.5 \( e^{-0.02 \text{mean euglycemic clamp}} \). References 27 and 28. Insulin-like growth factor–binding protein-1 (IGFbp-1) was analyzed by radio-immunoassay. Endothelin-1 in plasma was analyzed by a competitive immunoassay as described in detail earlier.

**Blood Pressure Measurements**

An identical procedure was followed at each occasion during the entire recruitment period. All blood pressure measurements were performed with a mercury sphygmomanometer. The cuff was adjusted according to the circumference of the arm and placed at the level of the heart. Blood pressure was recorded as the mean of 2 measurements taken after 5 minutes of rest in the supine position. Systolic blood pressure (SBP) and DBP were defined according to the following: SBP, DBP 50 mm Hg, SBP 250 mm Hg, DBP > 250 mm Hg, and DBP > 30 mm Hg, and DBP > 150 mm Hg. No other editing was performed.

**Carotid Ultrasound**

The right and left carotid arteries were examined with a duplex scanner (Acuson 128XP/5) and a 7.0-MHz linear array transducer. The subjects were investigated in the supine position with the head turned slightly away from the sonographer, as described earlier. Plaque was defined as a localized intimal-medial thickening of
>1 mm and a 100% increase in thickness compared with normal, adjacent wall segments. Plaque occurrence was scored as present or absent. The cutoff point of 1 mm was based on results of a pilot study.32 Plaque was scored for in the common, internal, and external carotid arteries on both sides.

Body mass index (BMI) was calculated as weight in kilograms/height in meters)2 as described.33

Table 1. Basic Characteristics of Case and Control Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>NT (n=73)</th>
<th>BHT (n=73)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.0 (±6)</td>
<td>50.0 (±6)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>125/75 (±11/4)</td>
<td>141/89 (±10/2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.6 (±2.9)</td>
<td>25.9 (±2.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.90 (±0.05)</td>
<td>0.92 (±0.05)</td>
<td>0.022</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>37 (±5)</td>
<td>32 (±5)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>5.5 (±1.0)</td>
<td>5.5 (±0.9)</td>
<td>0.16</td>
</tr>
<tr>
<td>HDL</td>
<td>1.27 (±0.27)</td>
<td>1.16 (±0.28)</td>
<td>0.016</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>0.34 (±0.80)</td>
<td>1.57 (±0.77)</td>
<td>0.015</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.85 (±0.69)</td>
<td>1.0 (±0.68)</td>
<td>0.029</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>14.2 (±4.5)</td>
<td>17.4 (±5.7)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Endothelin, pmol/L</td>
<td>1.5 (±0.7)</td>
<td>2.0 (±0.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Statistical Methods

Variables were tested for skewness. For skewed variables, nonparametric tests were used for comparisons between the groups (Mann-Whitney U test), whereas Student’s t test was used for normally distributed variables. Categorical variables were compared by the χ² test. Spearman rank correlation coefficients were calculated to estimate interrelations between aECs, metabolic variables, and blood pressure levels. The significance level was set at P<0.05. Values in the text are given as mean±SD.

Results

Characteristics of Case and Control Subjects

Basic characteristics of the 2 study groups are presented in Table 1. The mean blood pressure level in the NT group was 125/75 (±11/±5) mm Hg compared with 141/89 (±10/±2) mm Hg in the BHT group, which indicates a significant difference. The BHT group also had a significantly higher BMI and waist-to-hip ratio. The 2 groups were well matched for age.

The BHT men had significantly altered metabolic profiles, with fasting hyperinsulinemia and dyslipoproteinemia, as previously presented (Table 1; Reference 33). In the BHT group, 26% of the subjects had plaque on one or both sides; the corresponding figure for the NT group was 14% (19 versus 10 subjects, P=NS). The basal level of endothelin-1 was significantly increased in the BHT group.

Antibody Levels

In the population as a whole, the aEC levels of both IgM and IgG types were significantly higher in the BHT group than in the NT group (Table 2). The aβ2GP1 levels of IgG type were significantly higher in the BHT group than in the NT group (P<0.0001), whereas there was no significant difference in IgM antibody levels (Table 2).

If individuals with carotid atherosclerotic plaques were excluded, the aEC levels of IgM were significantly higher in BHT men than in the NT group (0.24 versus 0.20; P=0.01). Likewise, the aβ2GP1s of IgG classes were significantly higher in BHT men than in the NT group (0.22 versus 0.18; P<0.0001). If individuals with BHT were excluded, the aEC levels of IgM were nonsignificantly higher in individuals with carotid atherosclerotic plaques than in those without (0.24 versus 0.20; P=0.09), whereas the aEC or aβ2GP1 levels of IgG type did not differ (data not shown).

Individuals with plaque (n=29) had higher aEC levels of both IgG and IgM types compared with individuals without (n=117). However, the aβ2GP1 levels of both IgG and IgM types did not differ between individuals with plaque and those without (Table 3).

Table 3. Antibody Levels to Ecs, β2GP1, and CL in Individuals With or Without Atherosclerotic Plaques

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ig Class</th>
<th>Without Plaque (n=113)</th>
<th>With Plaque (n=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>aEC</td>
<td>IgM</td>
<td>0.21±0.09</td>
<td>0.26±0.09</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>IgG</td>
<td>0.09±0.07</td>
<td>0.13±0.11</td>
<td>0.042</td>
</tr>
<tr>
<td>aβ2GP1</td>
<td>IgM</td>
<td>0.22±0.07</td>
<td>0.24±0.08</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>IgG</td>
<td>0.20±0.05</td>
<td>0.20±0.04</td>
<td>...</td>
</tr>
<tr>
<td>aCL</td>
<td>IgM</td>
<td>0.145±0.09</td>
<td>0.162±0.10</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>IgG</td>
<td>0.32±0.19</td>
<td>0.31±0.17</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are given as mean±SD. Group differences were determined by Student’s t test.
Antibody levels to CL did not differ between the BHT and NT groups or between individuals with plaque and those without. There was no difference in antibody levels to ECs, β2GP1, or CL between smokers and nonsmokers (data not shown).

To exclude the possibility that differences in antibody levels simply reflected enhanced total antibody levels, IgA, IgG, and IgM were determined. There was no difference between the BHT group and control subjects (IgG, 9.71 ± 1.86 versus 9.76 ± 2.31 mg/mL and IgM, 2.25 ± 0.81 versus 2.1 ± 0.88 mg/mL, respectively).

Correlations Between Antibody Levels

The correlation between aECs, aCLs, and aβ2GP1s are shown in Table 4. There were significant correlations between aEC, aCL, and aβ2GP1 levels against both the IgG and IgM isotypes. Furthermore, antibodies to HSP65, which we recently found to be elevated in BHT,12 correlated significantly with antibodies to ECs (P < 0.02) but not with antibodies to β2GP1 or CL.

Cross-Reactivity Between Antibodies

To study possible cross-reactivity between the antibodies, we performed competition experiments, with CL, β2GP1, and ECs and as a control an unrelated antigen, PPD. The sera were tested at a dilution that gave 50% of maximal binding to ECs. To test whether antibodies to ECs could be outcompeted by ECs themselves, serum was added to wells for 24 hours, and then the serum was moved to another plate coated with ECs. When inhibition >25% was considered positive, β2GP1 inhibited serum binding to ECs in 6 of 7 subjects tested but not with antibodies to β2GP1 or CL.

Correlations to Metabolic Variables

In the population as a whole and the 2 groups separately, there were no significant correlations between aECs, aβ2GP1s, or aCLs and lipoproteins, BMI, waist-to-hip ratio, or intimal-medial thickness (data not shown).

However, there were interesting correlations between aβ2GP1 but not aEC or aCL levels and other indicators of the metabolic syndrome, as shown in Table 5. aβ2GP1 levels of IgG type correlated with insulin, IGFbp1, and insulin resistance, and aβ2GP1 levels of IgM type correlated with IGFbp1. An intriguing finding was the correlation between aECs of IgM type and endothelin in the BHT group (R = 0.25, P = 0.039).

There was a significant association between 24-ABP determinations and aEC levels of IgG class in the BHT group (P = 0.037) and the 2 groups together (P = 0.0042) but not in the NT group alone. Smoking was not correlated to the antibodies tested (data not shown).

Effect of β2GP1 and an unrelated antigen, PPD, on serum binding to ECs. Sera were incubated with 100 μg/mL of antigens as indicated at 4°C overnight. After this, binding to ELISA plates coated with endothelial cells was investigated. Results are presented as mean of duplicate determinations.

TABLE 4. Correlations Between Antibody Levels in BHT and NT Groups (All Individuals)

<table>
<thead>
<tr>
<th>Regression, R</th>
<th>aEC/aCL</th>
<th>aEC/β2GP1</th>
<th>aβ2GP1/aCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM R</td>
<td>0.289</td>
<td>0.441</td>
<td>0.298</td>
</tr>
<tr>
<td>P</td>
<td>0.0003</td>
<td>0.0001</td>
<td>0.0003</td>
</tr>
<tr>
<td>IgG R</td>
<td>0.196</td>
<td>0.18</td>
<td>0.176</td>
</tr>
<tr>
<td>P</td>
<td>0.016</td>
<td>0.034</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD. Group differences were determined by Student's t test.

TABLE 5. Association Between Antibody Levels to β2GP1 and Metabolic Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression, R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>IgM R</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>IgG R</td>
<td>0.175</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.037</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>IgM R</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>IgG R</td>
<td>0.215</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.010</td>
</tr>
<tr>
<td>IGFbp1</td>
<td>IgM R</td>
<td>0.185</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>IgG R</td>
<td>0.176</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD. Group differences were determined by Student's t test.
Age was not associated with $\alpha_\beta$2GP1 or aCL levels; however, there was a correlation with aECs of IgM type ($P=0.039$) but not IgG type.

**Discussion**

The main finding in this report is that BHT is significantly associated with aEC antibody levels of both IgM and IgG types and with $\alpha_\beta$2GP1 levels of IgG type. Total antibody concentrations showed no difference between control subjects and BHT patients, indicating that the results do not simply reflect total Ig levels. Individuals with the presence of carotid atherosclerosis as determined by carotid ultrasound had significantly enhanced aEC levels compared with individuals without carotid atherosclerosis. This is in line with recent findings indicating that aEC levels are enhanced in individuals who had undergone surgery because of established atherosclerotic vascular disease. aECs of IgM but not IgG type were enhanced in BHT compared with NT individuals without atherosclerosis. These findings indicate that both BHT and atherosclerosis may be related to endothelial changes leading to B-cell activation and thus antibody formation, but the relative contribution of BHT and atherosclerosis remains to be elucidated.

BHT is a condition with only relatively minor cardiovascular alterations compared with normal individuals. The enhanced aEC level is therefore likely to reflect a humoral immune response associated with very early changes in the endothelium. Endothelial dysfunction has been described in hypertension, eg, as an impaired vasodilatation due to defective NO production, and changes in the endothelium including loss of heparan sulfate and sialic acid have been reported. It is thus possible that aECs react with neoepitopes formed or exposed on the endothelium, thus being secondary to changes induced by metabolic factors. aEC levels may therefore be a marker for endothelial dysfunction in apparently healthy individuals like those in the present study. These antibodies may initiate atherosclerotic lesions and also aggravate changes induced by metabolic factors, by activation of complement, deposition of immune complexes, induction of adhesion molecules, and attraction of phagocytic cells, which taken together may lead to aggravation and/or induction of atherosclerosis.

An intriguing finding was the strong association of aECs of IgM type with endothelin, the most potent vasoconstrictor described. This finding is in line with recent reports indicating that aECs from patients with autoimmune disorders are released in cultured human endothelial cells. Furthermore, endothelin levels in the BHT men studied here were also enhanced, as reported earlier. However, endothelin in sera has been suggested to be a marker of endothelial damage in individuals with autoimmune disorders, and it is possible that the statistical association noted here is also related to endothelial damage. However, the observation that aECs were highly related to endothelin levels in BHT clearly raises the possibility that aECs may actually induce hypertension via enhanced endothelin production. Whether or not aECs are a cause or effect of endothelial dysfunction or, most likely, a combination of both, these antibodies may activate and cause damage to the endothelium.

Chronic infections have been implicated as contributing factors for development of atherosclerosis. It is possible that aECs are formed during infections and exert a pathogenic effect on the endothelium, thus providing a link between infections and atherosclerosis. However, little is known about the role of chronic infections in hypertension. aECs, $\alpha_\beta$2GP1s, and aCLs all were present in most individuals. The physiological role of these antibodies is not well characterized, and it is not known whether under certain circumstances they also may protect the endothelium against noxious compounds. aECs present in hypertension may thus predispose to early atherosclerosis and also actively participate in the pathogenesis of atherosclerosis.

$\alpha_\beta$2GP1 levels of IgG type were enhanced in BHT, in contrast to aCLs, for which no significant differences were noted either for IgG or IgM antibody type. aCLs predispose to cardiovascular events, including both arterial and venous thrombosis in autoimmune disorders like SLE and in the antiphospholipid syndrome, and in young patients with myocardial infarction, enhanced aCL levels were detected. $\beta$2GP1 has been implicated as a cofactor in antibody binding to CL, and recent data indicate that $\beta$2GP1 is bound to oxidized phospholipids, thereby creating an immunogenic complex.

In autoimmune diseases, $\beta$2GP1 has been shown to be a cofactor also for aECs, and we demonstrate here that in BHT as well, $\beta$2GP1 is involved in the antigenicity of ECs, because $\beta$2GP1 competed with antibody binding to ECs, in addition to which, $\alpha_\beta$2GP1 and aEC levels correlated strongly.

In antiphospholipid syndrome and also in SLE, $\alpha_\beta$2GP1s are related to vascular complications, which may be predicted even better than by aCLs. An exaggerated immune response to $\beta$2GP1, associated with endothelium, platelets, lipoproteins, or other phospholipid-rich surfaces, may trigger local reactions, including complement activation and immune complex deposition, leading to increased risk of thrombosis.

$\alpha_\beta$2GP1s were correlated with plasma levels of insulin, IGFbp-1, and calculated insulin resistance, suggesting an association with the metabolic syndrome. This may reflect changes in immune reactions secondary to metabolic factors. aECs, on the other hand, were not significantly associated with metabolic factors, indicating a difference from $\alpha_\beta$2GP1s and possibly also that aECs do not only reflect metabolic changes.

Hypertension and BHT have been shown to be associated with increased carotid atherosclerosis. Several different mechanisms, including direct effects of the elevated blood pressure levels on the arterial wall, have been suggested. Conversely, however, atherosclerosis may also be causally related to hypertension by means of an impaired endothelial function leading to a defective secretion of nitric oxide. Clearly, the interaction between atherosclerosis and hypertension is complex, and the different possibilities are not mutually exclusive.

During recent years, the role of the immune system in atherosclerosis has attracted increasing attention. Activated T
cells and monocytes are present in the lesions, and oxLDL has been identified as a possible factor inducing the inflammatory component of atherosclerosis, because oxLDL activates lymphocytes and monocytes to antibody formation and secretion of proinflammatory cytokines.1–7 Furthermore, af2GP1 has been suggested to be involved in oxLDL-uptake by macrophages antibodies8 and may therefore also play a role in early atherosclerosis. Comparatively little is known about the role of the immune system in hypertension.10,11 One possibility is that immunogenic HSPs are induced at lesion-prone sites by mechanical stress, which may be enhanced in hypertension, and thus elicit an immune response in the artery wall; this hypothesis may provide an explanation of how mechanical stress, as in hypertension, may induce atherosclerosis.12 An intriguing finding was therefore the strong correlation between anti-oxLDL antibodies, which suggest that HSP60 may be involved in the antigenicity of ECs, and it is possible that increased stress to the vascular wall, as may be present in BHT, enhances the HSP60 expression in the endothelium, which triggers an immune reaction directed at HSP60 in endothelial cells.

Taken together, our results indicate that antibodies to endothelial cells and to an associated plasma protein, β2GP1, may play an important role in the early stages of both atherosclerosis and hypertension.

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References


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