Hypertension is a major cause of cardiovascular disease and was recently put forward as the leading risk factor for global disease burden.1 Long-term hypertension induces damage to the vasculature and myocardium,2 as well as to the kidneys.3 An increased turnover of the extracellular matrix has been suggested as a key element in the underlying pathophysiology of this hypertensive target-organ damage.3 However, until date, relevant endogenous biomarkers mirroring hypertension-related cardiovascular remodeling are scarce.

Endostatin is produced by the proteolytic cleavage of the C-terminal domain of collagen XVIII, a component of the extracellular matrix.5 Release of endostatin is mainly induced by the stimulation of elastase, metalloproteinases, and cathepsins.6–4 Endostatin plays a role in the local balance of angiogenesis as a potent inhibitor and has been suggested to be of particular importance in the growth and spreading of malignant diseases.9–12 The role of endostatin in the development of cardiovascular diseases, however, is less studied.

In short, Collagen XVIII increases in myocardial and renal tissues as well as in the arterial wall with hypertension.4,13,14 Meanwhile, extracellular matrix proteinases also increase in those tissues.5,15,16 Thus, endostatin, a cleaved product of collagen XVIII, could be an indicator of adverse extracellular remodeling in hypertension.

In the present study, we hypothesized that long-term exposure to hypertension induces extracellular matrix remodeling of the cardiovascular tree, which is reflected by elevated levels of circulating endostatin. Accordingly, we aimed to study the

**Key Words:** angiogenesis effects • antiangiogenesis effects • cohort study • endothelial cells • epidemiology • extracellular matrix • Sweden • vascular stiffness

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association between duration of hypertension and circulating endostatin levels in two community-based cohorts of elderly participants. As a second step, we also wanted to investigate the cross-sectional associations between endostatin and vascular, myocardial, and renal indices of hypertensive target-organ damage, namely endothelium-dependent vasodilation, left ventricular mass (LVM), and urinary albumin/creatinine ratio.

Methods

Study Populations

The Prospective Investigation of the Vasculature in Uppsala Seniors

All 70-year-old men and women, living in Uppsala, Sweden, between 2001 and 2004, were eligible for the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study13 (described in detail in http://www.medsci.uu.se/ivus/ivus.htm). Of 2025 invited individuals, 1016 agreed to participate. A second examination cycle was performed after 5 years when participants were ≥75 years old (2006–2009). Of 964 invited individuals, 827 agreed to participate at this follow-up. Of these, 15 participants were excluded because of missing data on endostatin, leaving 812 participants as the study sample. This second examination cycle was used as the baseline for the retrospective analyses between endostatin and the duration of hypertension and for the cross-sectional association between endostatin and urinary albumin/creatinine ratio, whereas the cross-sectional association between endostatin and LVM and endothelial function was assessed at the first examination cycle because these data were not available at the second examination cycle.

The Uppsala Longitudinal Study of Adult Men

The Uppsala Longitudinal Study of Adult Men (ULSAM) was initiated in 1970. All 50-year-old men, born during 1920–24 and living in Uppsala, Sweden, were invited to a health survey, focusing at identifying cardiovascular risk factors14 (described in detail in http://www.pubcare.uu.se/ULSAM). These present analyses are based on participants. As a second step, we also wanted to investigate endostatin levels in two community-based cohorts of elderly hypertensive medication at the first examination cycle 5 years earlier. Second, data on self-reported duration of hypertension, based on retrospective data on hypertension status, based on blood pressure measurements and use of antihypertensive medication, at examinations 6, 17, and 27 years before the baseline of examination cycle 4. At the first examination cycle of PIVUS, forearm blood flow (FBF) was measured by venous occlusion plethysmography (Elektromedicin, Kullavik, Sweden) with the strain-gauge technique. An arterial cannula was placed in the brachial artery. Resting FBF was measured 30 minutes after cannula insertion, and local intra-arterial drug-infusions were given during 5 minutes for each dose with a 20-minute washout period between the drugs. The infused dosages were 25 and 50 µg/min for acetylcholine (Clin-Alpha, Switzerland) and 5 and 10 µg/min for sodium nitroprusside (Nitropruss, Abbot, UK). The drugs were given in a random order at a maximal rate of 1 mL/min. Endothelium-dependent vasodilation with this technique was defined as FBF during infusion of 50 µg/min of acetylcholine minus resting FBF divided by resting FBF. Also, a comprehensive 2-dimensional and Doppler echocardiography was performed with an Acuson XP124 cardiac ultrasound unit (Acuson, Mountain View, CA). Left ventricular dimensions were measured with M-mode. LVM was determined from the Penn convention and indexed for height to obtain LVM index.15

In both ULSAM (fourth examination cycle) and PIVUS (second examination cycle), urine albumin was measured by nephelometry (Urine albumin, Dade Behring, Deerfield, IL) using a Behring BN ProSpec analyzer (Dade Behring). Urine creatinine was analyzed with a modified kinetic Jaffe reaction on an Architect Ci8200 analyzer (Abbott, Abbott Park, IL), and creatinine-related urine albumin was calculated.

Statistical Analysis

We initially investigated distributions of all variables. Serum endostatin was logarithmically transformed in all analyses to promote a normal distribution. We thereafter performed cohort-specific analyses in PIVUS and ULSAM of the association between the duration of hypertension and serum endostatin (modeled as a continuous variable expressed per SD increase) using linear regression in the following multivariable models:

Model A: Age and sex adjusted.
Model B: Lifestyle and cardiovascular risk factor model (age, sex, diabetes mellitus, smoking, body mass index, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering treatment, prevalent cardiovascular disease, level of physical activity).

In secondary analyses, we also added glomerular filtration rate to multivariable model B. Missing values for covariates were estimated by multiple imputation.

Moreover, we investigated the association between self-reported duration of hypertension and endostatin levels in PIVUS. Also, the cross-sectional association between systolic and diastolic blood pressure, per se, and serum endostatin were investigated in both cohorts using crude models and models adjusted for specific antihypertensive medication.

As a second step, we investigated the cross-sectional association between endostatin and markers of hypertensive end-target organ damage (LVM, endothelium-dependent vasodilation [PIVUS, examination cycle 1], and urinary albumin/creatinine [ULSAM and PIVUS, examination cycle 2]) in participants with prevalent hypertension using multivariable linear regression (Model A and B, as described above with the addition of the duration of hypertension to multivariable model B). A 2-sided P value <0.05 was considered as significant, and Stata 12.1 (Stata Corp College Station, TX) was used for all analyses.

Results

Baseline characteristics of both cohorts are shown in Table 1.

Serum Endostatin and the Duration of Hypertension

In examination cycle 2 of the PIVUS cohort, participants with >5 years of history of hypertension portrayed higher serum endostatin compared with normotensive participants, whereas
Body mass index, kg/m² 26.8±4.3 26.3±3.5
Age, y 75.3±0.2 77.6±0.8
No. of subjects 812 785

Table 1. Baseline Characteristics in the PIVUS and ULSAM Cohorts

<table>
<thead>
<tr>
<th>Variables</th>
<th>PIVUS</th>
<th>ULSAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>812</td>
<td>785</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>414 (51)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Age, y</td>
<td>75.3±0.2</td>
<td>77.6±0.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.8±4.3</td>
<td>26.3±3.5</td>
</tr>
<tr>
<td>Serum total cholesterol, mg/dL</td>
<td>5.4±1.1</td>
<td>5.4±1.0</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mg/dL</td>
<td>1.5±0.5</td>
<td>1.3±0.3</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>5.2±1.5</td>
<td>5.9±1.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>149±19</td>
<td>151±21</td>
</tr>
<tr>
<td>Serum endostatin, ng/mL</td>
<td>60±27</td>
<td>55±18</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>68±19</td>
<td>73±17</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>50 (6)</td>
<td>59 (8)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>112 (14)</td>
<td>112 (14)</td>
</tr>
<tr>
<td>Previous cardiovascular disease, n (%)</td>
<td>164 (20)</td>
<td>213 (27)</td>
</tr>
<tr>
<td>Lipid-lowering treatment, n (%)</td>
<td>216 (27)</td>
<td>131 (17)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>231 (28)</td>
<td>195 (25)</td>
</tr>
<tr>
<td>Ca-antagonists</td>
<td>133 (16)</td>
<td>121 (15)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>181 (22)</td>
<td>130 (17)</td>
</tr>
<tr>
<td>RAAS-blockade (ACE and ARB)</td>
<td>251 (31)</td>
<td>132 (17)</td>
</tr>
<tr>
<td>Leisure time physical activity, n (%)</td>
<td>99 (12)</td>
<td>62 (8)</td>
</tr>
<tr>
<td>Sedentary</td>
<td>498 (61)</td>
<td>274 (35)</td>
</tr>
<tr>
<td>Moderate</td>
<td>172 (21)</td>
<td>413 (53)</td>
</tr>
<tr>
<td>Regular</td>
<td>43 (5)</td>
<td>36 (5)</td>
</tr>
</tbody>
</table>

Data are mean±SD for continuous variables and n (%) for categorical variables. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HDL, high-density lipoprotein; PIVUS, the Prospective Investigation of the Vasculature in Uppsala Seniors; RAAS, renin-angiotensin-aldosterone system; and ULSAM, the Uppsala Longitudinal Study of Adult Men.

no endostatin increase was seen in participants with new-onset hypertension (0–5 years duration; Table 2) Associations were somewhat attenuated after adjustment for age, sex, established cardiovascular risk factors, and glomerular filtration rate, albeit still statistically significant (Models A–C; Table 2). Moreover, when using questionnaire-based data on the duration of hypertension dating back to repeated examinations since the 70s (range of duration of hypertension, 0–42 years), 1-year longer hypertension duration was associated with 0.01 SD; 95% confidence interval, 0.001–0.02; (P=0.03) higher endostatin in multivariable model C. When we compared the increase in endostatin between examination cycle 1 and 2 in PIVUS in those with persistent hypertension at both examinations compared with those who remained normotensive, the increase in endostatin was 55% higher in those with persistent hypertension versus those that remained normotensive (mean increase in endostatin 14.0 versus 9.0 ng/mL, respectively; (P=0.005).

The association between the longer duration of hypertension and higher serum endostatin was replicated in the ULSAM cohort in which participants with 27 years of hypertension had the highest levels of endostatin compared with normotensives (Table 2). There were no cross-sectional associations between systolic/diastolic blood pressure levels, per se, and serum endostatin in any cohort (P>0.29 for all, data not shown).

Serum Endostatin and Hypertensive End-Target–Organ Damage in Participants With Prevalent Hypertension

The mean±SD of endostatin in participants with prevalent hypertension at the first examination cycle of PIVUS was 48±14 ng/mL, and the mean endothelium-dependent vasodilation and LVM were 514%±298% and 46±13 g/m², respectively. Higher circulating endostatin was associated with lower endothelial function and higher LVM in age- and sex-adjusted models (Model A, Table 3). This association was, however, abolished when taking cardiovascular risk factors and duration of hypertension into account (Table 3).

The mean±SD of albumin/creatinine ratio in participants with prevalent hypertension in PIVUS (second examination cycle) and ULSAM was 7±30, 5±21 mg/µmol, respectively. Higher serum endostatin was significantly associated with higher urinary albumin/creatinine ratio in all multivariable models in both cohorts (Table 3).

As seen in Table S1 in the online-only Data Supplement, endostatin levels seem higher in all classes of antihypertensive drugs in both cohorts, which argues against an effect of any specific antihypertensive drug class as an explanation of our findings.

Discussion

In 2 independent community-based cohorts of elderly, participants with long-term hypertension portrayed elevated serum levels of endostatin, independently of established cardiovascular risk factors and kidney function. In addition, cross-sectional associations between circulating endostatin, and vascular, myocardial, and renal indices of hypertensive end-target–organ damage were found. To our knowledge, these associations have not been reported previously. Our data put forward serum endostatin as an interesting novel biomarker for hypertensive organ damage.

Circulating levels of endostatin have been suggested to be a marker of breakdown and remodeling of the extracellular matrix in various diseases, such as cancer or aortic aneurysms, however whether this is true also for hypertension is less studied. It is well known that long-term hypertension induces cardiovascular extracellular matrix remodeling. Mechanical stretch of the vasculature, as seen in hypertension, induces vascular extracellular remodeling by activation of metalloproteinase-2 and metalloproteinase-9, which both are proteases that play an important role in the degradation of collagen XVIII to endostatin. Moreover, experimental studies show that damages to the vasculature, the myocardium, and the kidneys lead to increased expression of endostatin in these tissues, and that circulating concentrations of endostatin are elevated in patients with prevalent cardiovascular diseases or chronic kidney disease. Thus, the fact that endostatin was both associated with the duration of hypertension and indices of vascular, myocardial, and renal hypertensive target-organ damage in the present study may indicate that higher circulating levels of endostatin mirror an increased extracellular remodeling that originates from these tissues. Still, based on the present observational study, no firm conclusions about from what tissue the elevated levels of endostatin originate should be drawn, nor can we establish the underlying mechanism that leads to higher circulating endostatin levels. Also, in the present study, it is not
possible to disentangle whether increased endostatin levels are a cause or a consequence of pathological processes. Till date, our understanding of a potential causal role for endostatin in these tissues is limited. Further mechanistic studies are needed to shed light on this issue.

In addition to the fact that endostatin is a break down product from collagen XVIII, endostatin is also a potent endogenous angiogenesis inhibitor and is regulated in balance with vascular endothelial growth factor. Because of this role endostatin has also found its place in the treatment of cancer, particularly small-cell lung cancer. Vascular endothelial growth factor levels, per se, would argue against a blood pressure regulating association was found between endostatin and blood pressure in patients with hypertension, and a disturbed vascular endothelial growth factor–mediated angiogenesis have been suggested to play a causal role in the development of vascular, cardiac, and renal hypertensive damage. Thus, a possible explanation could be that increased endostatin mirrors a systemic elevated angiogenic activity, reflecting increased neovascularization induced by vascular, myocardial, or renal ischemia, similar as the role suggested for vascular endothelial growth factor.

Endostatin has also been shown to exert acute reductions in blood pressure via a release of NO, and individuals with Down Syndrome have significantly higher circulating levels of endostatin and exhibit lower blood pressure compared with control subjects. This may indicate that endostatin, per se, may exert a blood pressure lowering effect. Thus speculatively, a possible explanation to our findings could be that endostatin is endogenously released to regulate the blood pressure as a response/protective mechanism to hemodynamic changes caused by remodeling of the extracellular matrix in the vascular tree or organs. However, the fact that no cross-sectional association was found between endostatin and blood pressure levels, per se, would argue against a blood pressure regulating role of endostatin as an explanation of our findings.

### Table 3. Association Between Endostatin and Different Indices of Hypertensive Target-Organ Damage (Endothelial Function, Left Ventricular Mass, and Urinary Albumin Creatinine Ratio) in Participants With Prevalent Hypertension in the PIVUS and ULSAM Cohorts: Multivariable Linear Regression

<table>
<thead>
<tr>
<th>End-Organ Damage</th>
<th>Model A</th>
<th>Model B</th>
<th>Model C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β Coefficient (95% CI)</td>
<td>P Value</td>
<td>β Coefficient (95% CI)</td>
</tr>
<tr>
<td>PIVUS cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelial function*</td>
<td>−0.09 (−0.16 to −0.01)</td>
<td>0.03</td>
<td>−0.32 (−0.11 to 0.05)</td>
</tr>
<tr>
<td>Left ventricular mass*</td>
<td>0.16 (0.08 to 0.23)</td>
<td>&lt;0.0001</td>
<td>0.06 (−0.02 to 0.15)</td>
</tr>
<tr>
<td>Urinary albumin/creatinine ratio</td>
<td>0.16 (0.08 to 0.24)</td>
<td>&lt;0.0001</td>
<td>0.13 (0.05 to 0.22)</td>
</tr>
<tr>
<td>ULSAM cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary albumin/creatinine ratio</td>
<td>0.22 (0.14 to 0.30)</td>
<td>&lt;0.0001</td>
<td>0.21 (0.13 to 0.29)</td>
</tr>
</tbody>
</table>

Regression (β) is expressed as SD increase of serum endostatin. Model A: Age and sex adjusted. Model B: Model A and cardiovascular risk factor model (age, diabetes mellitus, smoking, body mass index, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering treatment, prevalent cardiovascular disease, level of physical activity, and the duration of hypertension). CI indicates confidence interval; PIVUS, the Prospective Investigation of the Vasculature in Uppsala Seniors; and ULSAM, the Uppsala Longitudinal Study of Adult Men.

*Performed at the first examination cycle of PIVUS.
Finally, it is also possible that other cardiovascular risk factors that are closely associated with both endostatin, long-term hypertension and hypertensive target-organ damage, such as age, obesity, physical activity, glaucometabolic disturbance, and lipids, may mediate the present associations. This seemed true for the associations between endostatin and endothelial dysfunction and LVM but not for the association between endostatin and urinary albumin excretion rate or the duration of hypertension (Tables 2 and 3). The association between the duration of hypertension and endostatin was further attenuated, albeit still statistically significant, after adjustments for kidney function in both cohorts, suggesting that reduced renal clearance of serum endostatin can explain a portion of the present associations, or alternatively, that the reduced glomerular filtration rate is a yet another aspect of hypertensive renal damage that is reflected by endostatin levels.

Endostatin levels have been shown to be elevated in patients with various cardiovascular diseases, associations that also are supported by experimental data. For example, higher endostatin levels have been shown to be both a predictor of ischemic strokes, and with poorer outcomes in patients with stroke. Also in a recent study, we report that higher endostatin levels predict mortality from both cardiovascular disease and cancer in the present community-based cohort. Additional studies are warranted to determine whether endostatin levels can be considered a marker for subclinical cardiovascular damage used to identify hypertensive individuals at particularly increased cardiovascular risk.

One major strength of the present study is the replication of the results in an independent cohort. This approach increases the validity and generalizability of the results and limits the risk for reporting spurious associations. Also, with the use of two cohorts, it was possible to take advantage of the unique strengths of each cohort such as longitudinal data with up to 27 years follow-up, or a detailed characterization of participants with regard to subclinical vascular, myocardial, and renal organ damage.

Limitations include the limited generalizability to other age- and ethnic groups. Furthermore, as data on endostatin were only available at 1 examination cycle in ULSAM, it was not possible to investigate the interplay between the hypertension and changes in endostatin levels over time in this cohort. Also, because current knowledge on factors that influence circulating levels of endostatin is very limited, we cannot rule out that cohort-specific effects attributable to differences in handling of the samples (such as freezer time), or differences in sex, age, or the time of the baseline examination between the two cohorts may influence the absolute levels of endostatin. However, given the similarity of results between the two studies, this had most likely no major impact on our results.

Perspectives
Our data indicate that circulating endostatin is associated with the duration of hypertension as well as with vascular, myocardial, and renal indices of hypertensive target-organ damage. Studies evaluating the underlying mechanisms and the clinical relevance of our findings are warranted.

Sources of Funding
This study was supported by The Swedish Research Council (2006-6555, 2012-1727, 2012-2215), Swedish Heart-Lung foundation, Thüréus foundation, the Marianne and the Marcus Wallenberg Foundation, Dalarna University, and the Uppsala University.

Disclosures
The funding sources did not play any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the article. Dr. Arnlöv is the guarantor of this work, had full access to all the data, and takes full responsibility for the integrity of data and the accuracy of data analysis. The other authors report no conflicts.

References
Novelty and Significance

What Is New?

- An association between longer duration of hypertension and serum levels of endostatin was found and validated in 2 independent cohorts. Participants with >27 years of history of hypertension had the highest endostatin levels. Interestingly, in participants with prevalent hypertension, we found cross-sectional associations between higher circulating endostatin and impaired endothelial function, increased left ventricular mass, and higher urinary albumin/creatinine ratio.

What Is Relevant?

- Endostatin, a biologically active derivate of collagen XVIII, has been suggested to be a relevant marker for extracellular matrix turnover and remodeling in various diseases. However, the role of endostatin in hypertension and hypertensive target-organ damage is unclear.

Summary

Our data provide additional support for the importance of increased extracellular remodeling in hypertensive disease and put forward serum endostatin as a novel biomarker for hypertensive organ damage.
Association Between Circulating Endostatin, Hypertension Duration, and Hypertensive Target-Organ Damage

Axel C. Carlsson, Toraaph Ruge, Johan Sundström, Erik Ingelsson, Anders Larsson, Lars Lind and Johan Arnlöv

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The association between circulating endostatin, hypertension duration and hypertensive target organ damage

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Running short title: Endostatin, hypertension duration and organ damage

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Endostatin levels in individuals prescribed and not prescribed antihypertensive drugs (by main drug class)

<table>
<thead>
<tr>
<th></th>
<th>PIVUS</th>
<th></th>
<th>ULSAM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>No treatment</td>
<td>Treatment</td>
<td>No treatment</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>64.6 ± 27.7</td>
<td>57.8 ± 26.7</td>
<td>57.7 ± 16.4</td>
<td>53.8 ± 17.1</td>
</tr>
<tr>
<td>Ca-antagonists</td>
<td>60.5 ± 18.5</td>
<td>59.6 ± 28.5</td>
<td>60.4 ± 22.8</td>
<td>53.8 ± 15.5</td>
</tr>
<tr>
<td>Diuretics</td>
<td>67.1 ± 30.0</td>
<td>57.6 ± 25.9</td>
<td>63.3 ± 21.5</td>
<td>53.1 ± 15.3</td>
</tr>
<tr>
<td>RAAS-blockade (ACE and ARB)</td>
<td>64.5 ± 24.6</td>
<td>57.6 ± 27.9</td>
<td>61.6 ± 20.5</td>
<td>53.4 ± 15.8</td>
</tr>
</tbody>
</table>

Data are mean serum endostatin concentrations ± Standard deviations