Isolated Systolic Hypertension Is Characterized by Increased Aortic Stiffness and Endothelial Dysfunction

Sharon M.L. Wallace, Yasmin, Carmel M. McEniery, Kaisa M. Mäki-Petäjä, Anthony D. Booth, John R. Cockcroft, Ian B. Wilkinson

Abstract—Isolated systolic hypertension is associated with increased cardiovascular risk. It is thought to result from large artery stiffening, which is determined by structural components within the vasculature but also by functional factors including NO and endothelin-1. We hypothesized that endothelial dysfunction would account for increased arterial stiffness in patients with isolated systolic hypertension. The aim of this study was to investigate the relationship between endothelial function and arterial stiffness in these patients along with control subjects. We studied 113 subjects: 35 patients with isolated systolic hypertension (mean age±SD: 68±6 years), 30 age-matched control subjects (65±5 years), and 48 young control subjects (37±9 years). Aortic pulse wave velocity (PWV) was derived by sequential carotid/femoral waveform recordings. Conduit artery endothelial function was determined by flow-mediated dilatation. Aortic PWV was higher (9.65±2.56 m/s versus 8.26±0.85 m/s; \(P=0.009\)), and flow-mediated dilatation was lower (2.67±1.64% versus 4.79±3.1%; \(P=0.03\)) in patients with isolated systolic hypertension compared with age-matched control subjects. Similarly, aortic PWV was also higher, and flow-mediated dilatation lower, in older versus young control subjects (8.26±0.85 m/s versus 7.09±1.01 m/s and 4.79±3.1% versus 6.94±2.7%; \(P=0.004\) for both). Overall, aortic PWV correlated inversely with flow-mediated dilatation \((r=-0.3; P=0.001)\), which remained significant after adjustment for confounding factors \((P=0.01)\). Patients with isolated systolic hypertension have higher aortic PWV and decreased endothelial function compared with age-matched control subjects. Our results suggest that endothelial function contributes significantly to increased arterial stiffness in patients with isolated systolic hypertension and with age. (Hypertension. 2007;50:228-233.)

Key Words: arterial stiffness ■ endothelial function ■ isolated systolic hypertension ■ age

Hypertension is a common condition, which is increasingly prevalent with age.1 Indeed, 50% of those aged >60 years are hypertensive,2 of which the majority (80%), have isolated systolic hypertension (ISH). This is characterized by an increase in systolic blood pressure (SBP) but a normal or reduced diastolic blood pressure (DBP). Although initially considered a benign consequence of ageing,1 ISH is currently recognized as a key component of cardiovascular (CV) disease.1

In contrast to hypertension in younger subjects, ISH in older adults results from stiffening of the central (conduit) arteries,3,4 which normally serve to buffer the cyclic changes in pressure arising from intermittent left ventricular ejection. Traditionally, the structural components of the arterial wall were thought to be the major determinants of vessel stiffness. However, we5-8 and others9 have demonstrated recently that there is a "functional" regulation of conduit artery stiffness by smooth muscle tone, which is influenced by circulating and endothelium-derived vasoactive mediators, including NO and endothelin-1.

Endothelial dysfunction, or decreased NO bioavailability, characterizes a number of CV risk factors and also healthy ageing.10,11 We have demonstrated recently an independent correlation among endothelial function, arterial stiffness, and central blood pressure in healthy normotensive subjects.12 Although several studies have investigated endothelial function in essential hypertension, with controversial results,13 the relationship among endothelial function, arterial stiffness, and ISH is unknown. Endothelial function is associated with measures of arterial stiffness in healthy subjects12 and patients with CV disease.14 We hypothesized that ISH would be associated with endothelial dysfunction and that aortic stiffness would correlate with endothelial function. The aim of this study was to test these hypotheses in a group of subjects with ISH, age-matched normotensive control subjects, and younger control subjects.

Subjects and Methods

Overall, 113 subjects were recruited from the hypertension clinic at Addenbrooke’s Hospital and a community database of healthy volunteers. They were divided into 3 distinct groups: 35 patients with...
ISH (mean age: 68 ± 6 years; range: 57 to 79 years), 30 older aged-matched control subjects (mean age: 65 ± 5 years; range: 57 to 74 years), and 48 young healthy control subjects (mean age: 37 ± 9 years; range: 16 to 51 years). ISH was defined as SBP ≥140 mm Hg and DBP <90 mm Hg (on ≥3 occasions) as stated by the British Hypertension Society.15 Individuals in the 2 control groups were free from CV risk factors, including hypertension, and were not receiving any medication. The local ethics committee approved the study, and all of the participants gave written, informed consent. The procedures followed were in accordance with institutional guidelines and the Declaration of Helsinki.

Blood Pressure Measurement
Brachial blood pressure was recorded in the nondominant arm using a validated oscillometric technique (HEM-705CP; Omron Corporation).16 Both seated and supine readings were taken in duplicate or triplicate, if readings differed by 5 mm Hg.

Measurement of Arterial Stiffness
Aortic augmentation index (AIa) and central blood pressure were determined by pulse wave analysis using the SphygmoCor system (Atcor Medical, A high-fidelity micromameter was used to measure radial artery pressure in the nondominant arm. Twenty sequential waveforms were acquired, and integral software was used to generate a corresponding central waveform, from which augmentation pressure (AP), AIa, and central pressures were determined. AP was defined as the difference between the second and first peak of the central arterial waveform and was expressed as a percentage of the PP to give AIa. The pulse wave velocity (PWV) was derived as described previously17 by sequentially recording carotid and femoral waveforms for aortic PWV (aPWV) and carotid and radial for brachial PWV.

Measurement of Conduit Vessel Endothelial Function
Endothelial function was determined by recording the diameter changes in the brachial artery in response to increased blood flow generated during reactive hyperemia (FMD) and glyceryl trinitrate (GTN). The brachial artery was identified using high-resolution vascular ultrasound (Acuson XP 128/10) with a 7- to 10-MHz linear array transducer. A B-mode image of the artery was scanned in longitudinal section = 5 to 10 cm above the antecubital fossa. Once an optimal image of the vessel wall was obtained, the probe was fixed in place using a stertoclastic clamp. The image was then updated from the R-wave of the ECG. End-diastolic images of the vessel were then acquired every 3 seconds using data acquisition software (CVI analysis, Information Integrity) throughout the study and were stored offline for later analysis. Images were recorded for 1 minute before a pressure cuff, around the forearm, distal to the elbow, inflated above suprasystolic pressure for 5 minutes. After deflation of the cuff, the increase in blood flow was measured (reactive hyperemia) along with the change in vessel diameter (endothelial-dependent dilatation), which was measured for a further 5 minutes. Seven minutes after cuff deflation, a second baseline scan was recorded for 1 minute. Blood flow velocity was measured from the center of the vessel using continuous-wave Doppler. Heart rate and vessel area (centimeters squared) were used to calculate volumetric blood flow (milliliters per minute) at baseline and from 5 to 120 seconds after cuff deflation. Reactive hyperemia was calculated as the maximal percentage change in flow from baseline. A 25-μg dose of GTN was then administered sublingually, and the changes were measured over a period of 5 minutes (endothelial-independent dilatation). Vessel diameter changes were measured using edge detection software (Brachial Tools), and FMD was defined as the maximal percentage change in vessel diameter after reactive hyperemia and GTN-mediated dilatation after 25-μg sublingual GTN.

Protocol
All of the studies were conducted in a quiet, temperature-controlled room. Subjects were asked to attend fasting after having omitted any morning medication. Height and weight were recorded, and seated blood pressure was recorded, in duplicate, after 5 minutes of seated rest. After 10-minute supine rest, peripheral blood pressure was again recorded, followed by arterial stiffness, and then endothelial function was assessed. Finally, 10 mL of venous blood were drawn for determination of glucose, cholesterol, and electrolytes using standard laboratory assays.

Statistical Analysis
This study was powered (80%) to identify a 20% difference in FMD assuming an average value of 5 ± 1.8% (P < 0.05). Differences in baseline characteristics, measures of blood pressure, endothelial function, and arterial stiffness between the 3 groups were analyzed using 1-way ANOVA. Posthoc analyses were then conducted using the Bonferroni correction between 2 specific groups: patients with ISH versus older control subjects and older control subjects versus young control subjects. A P < 0.05 was considered significant. Multiple linear regression was undertaken using the enter approach with SPSS 12.02 and included all of the parameters with a univariate correlation with the dependent variable and any known or likely confounders. All of the data were presented as means ± SD, except for the variables that are skewed, in which case, values are represented as medians (interquartile range). C-reactive protein (CRP) was log transformed for correlation analyses, because it is not normally distributed. aPWV was corrected for mean arterial pressure (MAP) using linear regression.

Results
The baseline characteristics of the 3 groups are shown in Table 1. Of the subjects with ISH, 15 were on no treatment, 2 were receiving monotherapy with bendrofluazide, and 1 was taking a calcium channel blocker. The remainder of the ISH group were on combination therapy, which included a thiazide (n = 4), an angiotensin-converting enzyme inhibitor/angiotensin II receptor subtype 1 antagonist (3), a β-blocker (4), and a calcium channel blocker (2). Other medications included aspirin (2), thyroxine (1), and lansoprazole (1).

There was no difference in age between the 2 older groups. Triglycerides were significantly higher in the older group compared with the young control subjects. There were no other significant differences in the baseline demographics (Table 1).

ISH Patients Versus Older Control Subjects
Patients with ISH had significantly higher seated and supine peripheral SBP, PP, and central systolic pressure, but there were no differences in DBP or heart rate (Table 2). AP and aPWV were significantly higher in the subjects with ISH compared with age-matched control subjects (Table 3). After correcting for differences in MAP between the groups, aPWV remained significantly higher in the ISH group.

Brachial artery diameter did not differ significantly between the 2 groups, nor did the GTN response. However, endothelial-dependent dilatation was considerably lower in the ISH group. Neither baseline diameter nor peak flow was independently associated with FMD. The time to peak FMD dilation was 80 ± 37 seconds in the subjects with ISH and 82 ± 43 seconds in the age-matched control subjects (not significant).

Older Versus Young Control Subjects
Older subjects had significantly higher peripheral and central SBP and supine peripheral DBP than younger subjects, but
there was no difference in heart rate (Table 2). AP, AIA, brachial PWV, and aPWV were all significantly lower in the younger subjects compared with older control subjects (Table 3). Even after correcting for differences in MAP, aPWV remained significantly different between the groups. In contrast, GTN responses did not differ between the 2 groups. Again, differences in FMD were not associated with baseline diameter or peak flow (data not shown). Time to peak FMD dilatation in the older control subjects was 82 ± 43 seconds compared with 57 ± 29 seconds in the younger subjects (P = 0.06).

Regression Analyses
Data from all of the subjects were then combined. Using univariate analysis, peripheral PP and central PP (Figure 1) were both found to be negatively associated with FMD along with aPWV (−0.3; P = 0.001; Figure 2). Log-CRP was negatively associated with FMD (r = −0.33; P < 0.001) but not with aPWV. Because a number of factors are known to influence arterial stiffness, multiple regression analysis was then used to identify the independent predictors of aPWV. MAP, HR, AIA, lipid fractions, glucose, smoking status, sex, age, body mass index, FMD, GTN response, and resting artery diameter were all entered into the model. aPWV was positively and independently associated with age and inversely associated with FMD (R² = −0.3; P = <0.01).

Discussion
Both endothelial function and arterial stiffness are considered surrogate measures of CV disease and future risk. Interestingly, a number of factors known to impair endothelial vasomotor function have also been associated with increased

**TABLE 1. Baseline Demographics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients With ISH (n=35)</th>
<th>Older Control Subjects (n=30)</th>
<th>Young Control Subjects (n=48)</th>
<th>Overall ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68±6</td>
<td>65±5</td>
<td>37±9*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>21/14</td>
<td>16/14</td>
<td>21/27</td>
<td>—</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.7±12.7</td>
<td>76.3±12.3</td>
<td>74.6±17.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.70±0.11</td>
<td>1.69±0.10</td>
<td>1.70±0.10</td>
<td>0.8</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.2±1.2</td>
<td>5.2±1.2</td>
<td>4.8±0.8</td>
<td>0.1</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.42±0.45</td>
<td>1.35±0.55</td>
<td>1.54±0.40</td>
<td>0.2</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.98±0.90</td>
<td>3.08±0.79</td>
<td>2.67±0.85</td>
<td>0.1</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.87±1.05</td>
<td>2.13±1.27</td>
<td>1.35±0.84*</td>
<td>0.006</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.6±3.5</td>
<td>5.3±1.4</td>
<td>4.4±0.7</td>
<td>0.1</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>2.62 (1.52 to 4.41)†</td>
<td>2.64 (1.51 to 3.97)</td>
<td>1.14 (0.55 to 2.40)</td>
<td>0.03</td>
</tr>
<tr>
<td>Smokers, n</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are expressed as means±SD or number, except for variables that were skewed, in which case the values are represented as median (interquartile range). LDL indicates low-density lipoprotein; HDL, high-density lipoprotein. One-way ANOVA was used to identify significance between the groups; patients with ISH vs older control subjects; posthoc analyses were conducted using the Bonferroni method.

*P<0.05, older and young control subjects.
†P<0.05, patients with ISH vs older control subjects.

**TABLE 2. Blood Pressure Measurements**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients With ISH (n=35)</th>
<th>Older Control Subjects (n=30)</th>
<th>Young Control Subjects (n=48)</th>
<th>Overall ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seated peripheral SBP, mm Hg</td>
<td>147±13*</td>
<td>128±13</td>
<td>120±10†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Seated peripheral DBP, mm Hg</td>
<td>80±9</td>
<td>78±8</td>
<td>76±8</td>
<td>0.06</td>
</tr>
<tr>
<td>Supine peripheral SBP, mm Hg</td>
<td>147±12*</td>
<td>126±12</td>
<td>117±11†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Supine peripheral DBP, mm Hg</td>
<td>79±9</td>
<td>76±7</td>
<td>72±8‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Supine MAP, mm Hg</td>
<td>102±11*</td>
<td>93±7</td>
<td>85±9†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Supine peripheral PP, mm Hg</td>
<td>68±11*</td>
<td>50±10</td>
<td>45±9‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Supine heart rate, bpm</td>
<td>61±12</td>
<td>65±11</td>
<td>65±11</td>
<td>0.3</td>
</tr>
<tr>
<td>Supine central SBP, mm Hg</td>
<td>137±13*</td>
<td>116±10</td>
<td>104±10†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Supine central DBP, mm Hg</td>
<td>81±10</td>
<td>77±7</td>
<td>72±8‡</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values represent mean±SD. One-way ANOVA was used to identify significance between the groups. Posthoc analyses were conducted using the Bonferroni method.

*P<0.01, patients with ISH vs older control subjects.
†P<0.01, ‡P<0.05, older vs young control subjects.
arterial stiffness. The aim of this study was to investigate the relationship between endothelial function and arterial stiffness using ISH as a model of increased stiffness. In particular, we hypothesized that ISH would be associated with decreased endothelial function compared with age-matched control subjects. The main findings of the current study are that endothelium-dependent vasomotor function was decreased in subjects with ISH compared with age-matched, normotensive control subjects and that aPWV was independently associated with endothelial function. We also confirmed previous observations that ISH is associated with increased aortic stiffness independent of MAP and that ageing, per se, is associated with decreased endothelial function and increased arterial stiffness, even in healthy, normotensive individuals.

PP depends on 3 main factors: stroke volume, the elasticity of the large arteries, and wave reflection. Thus, PP is often considered a “surrogate” measure of arterial stiffness. Two groups have demonstrated previously that reduced vasomotor endothelial function is associated with peripheral PP in untreated hypertensive subjects and subjects undergoing coronary angiograph. However, PP varies throughout the arterial tree, and we and others have demonstrated that PP in the brachial artery is a relatively poor surrogate of aortic stiffness. In the present study, we assessed both brachial and aortic PP and aPWV, the current “gold-standard” measure of arterial stiffness. PWV is inversely related to the square root of vessel distensibility by the 1922 Bramwell and Hill equation: the higher the PWV, the less distensible or stiffer the vessel. In the present study, aPWV, but not brachial PWV, was increased in subjects with ISH compared with age-matched control subjects, which confirms our previous observations that ISH is primarily associated with stiffening of the central, rather than peripheral, conduit arteries. This difference persisted after correction for differences in MAP.

### TABLE 3. Arterial Stiffness and Endothelial Function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients With ISH (n=35)</th>
<th>Older Control Subjects (n=30)</th>
<th>Young Control Subjects (n=48)</th>
<th>Overall ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine AP, mm Hg</td>
<td>17±7*</td>
<td>11±5</td>
<td>4±5†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Supine Ala, %</td>
<td>32±9</td>
<td>27±8</td>
<td>14±13†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Brachial PWV, m/s</td>
<td>9.59±1.97</td>
<td>8.81±1.97</td>
<td>6.53±1.30†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>aPWV, m/s</td>
<td>9.65±2.56‡</td>
<td>8.26±0.85</td>
<td>7.09±1.01†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted aPWV, m/s</td>
<td>8.66±0.58*</td>
<td>8.19±0.39</td>
<td>7.80±0.44‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline artery diameter, mm</td>
<td>4.58±0.87</td>
<td>4.18±0.81</td>
<td>3.89±0.72</td>
<td>0.01</td>
</tr>
<tr>
<td>Basal flow, mL/min</td>
<td>20.3±13.7</td>
<td>18.5±10.2</td>
<td>14.2±8.34</td>
<td>0.4</td>
</tr>
<tr>
<td>FMD response, %</td>
<td>2.67±1.64*</td>
<td>4.79±3.16</td>
<td>6.94±2.7†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GTN response, %</td>
<td>6.44±3.60</td>
<td>8.62±4.69</td>
<td>9.49±5.27</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values represent mean±SD. One-way ANOVA was used to identify significance among the 3 groups. Posthoc analyses were conducted using the Bonferroni method.

*P<0.01, patients with ISH vs older control subjects.
†P<0.01, older control vs young control subjects.
‡P<0.05, older control vs young control subjects.

Figure 1. Relationship between central PP and FMD for all patients. ●, subjects with ISH; ○, older control subjects; △, younger control subjects. R=−0.50; P<0.001 for the linear regression of all data.

Figure 2. Relationship between aPWV and FMD for all patients. ●, subjects with ISH; ○, older control subjects; △, younger control subjects. R=−0.3; P<0.001 for the linear regression of all data.
suggesting an increase in isobaric stiffness rather than a passive rise because of an increase in mean pressure. Interestingly, AlA did not differ between the 2 groups, despite a higher augmented pressure. AlA is a measure of wave reflection, and our findings suggest that large artery stiffness rather than enhanced wave reflection is the abnormality in ISH, which is in agreement with our previous data.5

The response to reactive hyperemia (FMD) in the brachial artery was significantly reduced in subjects with ISH compared with age-matched healthy control subjects, despite preservation of the endothelium-independent GTN response. This suggests that ISH is associated with vasomotor endothelial dysfunction. Previous groups have reported both normal13 and abnormal25 endothelial function in younger subjects with hypertension. The difference in endothelial function was not explained by variation in peak flow or brachial artery diameter. Interestingly, FMD was lower in the older control subjects compared with younger healthy subjects in our cohort, confirming a previous observation of an age-related decline in endothelial function26 and suggesting that ISH may represent an exaggeration of the “usual” ageing process. We also found a significant, inverse correlation between endothelial function and aPWV, which remained significant even after correcting for potential confounding factors, including age and MAP. Endothelial function was also inversely related to both brachial and aortic PP.

We have previously demonstrated that conduit vessel stiffness is, in part, regulated by smooth muscle tone, which is under the influence of a number of local circulating mediators, including NO5 and endothelin-1.6 The data from the present study suggest that endothelial dysfunction and reduced NO bioavailability may contribute to increased arterial stiffness and potentially to the development of ISH. Indeed, oral nitrates are known to reduce PP and arterial stiffness and potentially to the development of ISH.27,28 However, because we conducted an observational cross-sectional study, we cannot distinguish between cause and effect, and an alternative explanation is that arterial stiffening results in endothelial dysfunction or that common processes drive the 2 phenomena.

We also assessed endothelial function in a muscular large artery rather than the more elastic aorta, because there are no established techniques to assess endothelial vasomotor function in the aorta. However, previous studies have demonstrated that endothelial dysfunction is a systemic effect and is not confined to 1 specific region. Moreover, FMD is known to correlate significantly with invasive coronary endothelial function.29

Perspectives

We have shown for the first time that aPWV is independently associated with endothelial function in patients with ISH. These findings compliment previous observations suggesting that local endothelium-derived factors contribute to increased arterial stiffness and, therefore, to the development of CV risk factors, such as ISH. This may have important implications for the management of patients with ISH, because improving NO bioavailability may reduce arterial stiffness, therefore, reducing CV risk.

Sources of Funding

S.M.L.W., Y., C.M.M., A.D.B., J.R.C., and I.B.W. received grants from the British Heart Foundation. K.M.M-P. and I.B.W. have received grants from GlaxoSmithKline. S.M.L.W. holds a British Heart Foundation studentship. I.B.W. is a British Heart Foundation WE Parkes Senior Clinical Fellow. C.M.M. holds a British Heart Foundation Intermediate Fellowship. This work was performed in a British Heart Foundation–sponsored vascular research laboratory at Addenbrooke’s Hospital, Cambridge, United Kingdom.

Disclosures

None.

References


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Hypertension. 2007;50:228-233; originally published online May 14, 2007;
doi: 10.1161/HYPERTENSIONAHA.107.089391
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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