Acute Reduction of Blood Pressure by Nitroglycerin Does Not Normalize Large Artery Stiffness in Essential Hypertension

Andrew D. Stewart, Benyu Jiang, Sandrine C. Millasseau, James M. Ritter, Philip J. Chowienczyk

Abstract—Stiffness of large elastic arteries is elevated in subjects with hypertension, an effect that could potentially be explained by increased distending pressure. We examined effects of an acute change in blood pressure on carotid-femoral pulse wave velocity and carotid artery distensibility (inversely related to stiffness) in normotensive control subjects (n=20, mean age 42) with mean arterial pressure (MAP) 84±1.7 mm Hg (mean±SE) and subjects with essential hypertension (n=20, mean age 45, MAP 104±2.0 mm Hg). Normotensive subjects received intravenous nitroglycerin (NTG) and angiotensin II to lower/increase blood pressure. Hypertensive subjects received NTG to lower blood pressure. Pulse wave velocity was 24% (95% CI: 12% to 35%) higher and carotid distensibility 47% (95% CI: 32% to 63%) lower in hypertensive subjects compared with controls. In normotensive subjects, acute changes in blood pressure produced expected changes in stiffness. However, in hypertensive subjects, despite reducing MAP by 22 mm Hg to the same level as in normotensive subjects, there was no detectable reduction in arterial stiffness: pulse wave velocity remained 24% (95% CI: 10% to 38%) higher and carotid distensibility 48% (95% CI: 31% to 63%) lower in hypertensive compared with normotensive subjects. Because blood pressure–independent effects of NTG are, if anything, to reduce stiffness, these results indicate that elevated carotid and aortic stiffness in hypertensive subjects is not explained by elevated blood pressure but relates to structural change in the arterial wall. (Hypertension. 2006;48:404-410.)

Key Words: arterial pressure ■ carotid arteries ■ hypertension, arterial

Carotid-femoral pulse wave velocity (PWV), a measure of the functional stiffness of large elastic arteries, is increased in hypertensive subjects1,2 and, in such subjects,3–5 as well as in other groups at high cardiovascular risk6,7 and in older subjects in the general population,8 predicts future cardiovascular events. Arterial stiffness is determined both by the structure of the arterial wall and by the loading conditions on the wall, particularly mean distending pressure, which is closely related to mean arterial pressure (MAP).9,10 An acute elevation of blood pressure results in increased arterial stiffness in both animal models and in human subjects.9,11,12 However, in hypertensive subjects it is not clear whether increased stiffness occurs as a result of elevated blood pressure or whether there is an intrinsic change in the elasticity of the arterial wall so that, when compared at the same operating pressure, it is stiffer than that in normotensive subjects. Previous studies to address this issue have examined the relationship of arterial pressure to diameter of the common carotid artery throughout the cardiac cycle with extrapolation to a common pressure. This approach suggests that, when compared at the same operating pressure, stiffness of the common carotid artery is similar in hypertensive and in normotensive subjects13–15 but makes assumptions regarding the form of the pressure/diameter relationship and homogeneity of the arterial wall.

In the present study, we examined whether acute reduction of blood pressure in subjects with sustained hypertension to levels seen in normotensive subjects normalizes carotid-femoral PWV and common carotid artery stiffness. We reduced blood pressure by intravenous infusion of nitroglycerin (NTG), an agent that, in the absence of a change in blood pressure, has small effects on stiffness of muscular arteries (tending to reduce stiffness)16–18 but little or no effect on large elastic arteries.19,20 We also examined effects of an acute increase in blood pressure on stiffness in normotensive subjects using angiotensin II (Ang II) and also effects of blood pressure reduction in normotensive subjects using NTG.

Methods

Subjects
Subjects with essential hypertension (n=20) in whom blood pressure had not been controlled to a systolic blood pressure <140 mm Hg and/or diastolic pressure <85 mm Hg on their last office reading
despite appropriate lifestyle and (in 17 of 20 subjects) pharmacological treatment were recruited from Guy’s and St Thomas’ Hospital hypertension clinic. All of the subjects had had hypertension diagnosed on the basis of ≥3 readings of systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg for ≥12 months before the study. All of the subjects were screened by physical examination and appropriate investigations and were excluded if they were current smokers, had evidence of clinically significant coronary artery, cerebrovascular or peripheral arterial disease, suffered from diabetes or renal insufficiency (serum creatinine ≥140 μmol L\(^{-1}\)) or had evidence of secondary hypertension.

Subjects were also excluded if they had evidence of carotid artery plaque on ultrasound scanning. Drug treatment included diuretics (9 of 20 subjects), angiotensin-converting enzyme inhibitors or receptor blockers (9 of 20), calcium channel blockers (7 of 20), \(\alpha\)-adrenergic antagonists (4 of 20), and \(\beta\)-adrenergic antagonists (1 of 20). Normotensive subjects of similar age were recruited from the local community. The study was approved by St Thomas’ Hospital local research ethics committee, and all of the subjects gave written informed consent.

**Protocol**

Subjects were asked to attend in the morning after having refrained from caffeine and alcohol for 12 hours. Measurements were made in a quiet temperature-controlled vascular laboratory. Subjects lay supine and an intravenous cannula was placed in the left antecubital fossa and normal saline infused at 1 mL min\(^{-1}\). After 30-minute baseline measurements of blood pressure (using an oscillometric method, Omron 705, Omron, according to British Hypertension Society guidelines), carotid-femoral PWV and carotid artery distensibility (as described below) were determined. Normotensive and hypertensive subjects then received vasoactive drugs as detailed below.

**Normotensive Subjects**

After baseline measurements 16 of the normotensive subjects received a cumulative rising dose infusion of Ang II (Clinafla, 75, 150, and 300 ng min\(^{-1}\), a dose that, in pilot studies, increased MAP by ≈20 mm Hg). Each dose was given for 20 minutes. Measurements of blood pressure, carotid-femoral PWV, and carotid distensibility were made over the last 15 minutes of the infusion. Another group (\(n=15\)) of the normotensive subjects received NTG (10, 30, and 100 μg min\(^{-1}\), each dose for 20 minutes). Subjects receiving both Ang II and NTG were studied on 2 occasions separated by ≥1 week, receiving either NTG or Ang II on each study day. All of the infusions were given at 1 mL min\(^{-1}\).

**Hypertensive Subjects**

After baseline measurements, hypertensive subjects received a cumulative dose infusion of NTG (Faulding Pharmaceuticals, 10, 30, and 100 μg min\(^{-1}\), each dose for 20 minutes). In pilot studies, this dose reduced MAP by ≈20 mm Hg. Measurements of blood pressure, carotid-femoral PWV, and carotid distensibility were performed as in the protocol for normotensive subjects.

**Carotid-Femoral PWV**

Stiffness over the carotid-femoral portion of the arterial tree was assessed by measuring carotid-femoral PWV using the SphygmoCor system (Atcor). ECG-referenced sequential carotid and femoral tonometry was used to measure foot-to-foot carotid-femoral transit time and PWV calculated from the carotid-femoral path length divided by transit time. Path length was estimated from linear distance from the sternal notch to the femoral artery at the point of extrapolation. The same distance was used for all of the measurements in each subject. PWV of an arterial segment is inversely related to the distance from the sternal notch to the femoral artery at the point of extrapolation. The same distance was used for all of the measurements in each subject. PWV of an arterial segment is inversely related to the distance from the sternal notch to the femoral artery at the point of extrapolation. The same distance was used for all of the measurements in each subject. PWV of an arterial segment is inversely related to the distance from the sternal notch to the femoral artery at the point of extrapolation. The same distance was used for all of the measurements in each subject.

**Statistics**

Subject characteristics are summarized as mean (SD), and results are summarized as mean±SE. Comparison between groups was performed using Student unpaired \(t\) test or a \(\chi^2\) test as appropriate. Changes in hemodynamic and stiffness measures in response to vasoactive drugs were analyzed using repeated-measures ANOVA. Potential effects of heart rate and age were examined by seeking an interaction between these variables and the response to drugs. SPSS (version 13.0) was used for all of the analyses. A \(P<0.05\) was taken to be significant, and all of the tests were 2-tailed.

**Results**

**Subject Characteristics**

Subject characteristics, including baseline measurements of PWV and common carotid distensibility, are summarized in Table 1. Hypertensive and normotensive subjects were similar with respect to age, gender, ethnicity, renal function, and lipid profiles, but hypertensive subjects had a higher body mass index. As expected, PWV was higher and carotid distensibility lower in hypertensive subjects compared with controls (Table 1). The size of the difference between the groups was considerable, PWV being 24% (95% CI: 12% to 35%) higher and carotid distensibility 47% (95% CI: 32% to 63%) lower in hypertensive subjects compared with controls.

**Effects of Acute Modulation of Blood Pressure**

**Normotensive Subjects**

Hemodynamic changes during infusion of Ang II in normotensive subjects are summarized in Table 2. The highest dose of Ang II (300 ng min\(^{-1}\)) increased MAP from 83±1 to 103±2 mm Hg, this value being similar to the mean baseline MAP in hypertensive subjects (104±2 mm Hg). Ang II increased PWV and decreased carotid distensibility (Figure 1; each \(P<0.001\) for trend). At the highest dose of Ang II, when MAP in the normotensive subjects was similar to that in hypertensive subjects at baseline, the mean value of PWV in normotensive subjects approached that in hypertensive subjects (9.4±0.3 versus 9.9±0.4 m s\(^{-1}\); \(P\) not significant). Carotid
TABLE 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normotensive (n=20)</th>
<th>Hypertensive (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>13/7</td>
<td>14/6</td>
</tr>
<tr>
<td>Age, y</td>
<td>42.2 (10.5)</td>
<td>45.3 (10.5)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.71 (0.08)</td>
<td>1.71 (0.08)</td>
</tr>
<tr>
<td>Body mass index, kg m⁻²</td>
<td>26 (2.9)</td>
<td>29 (4.5)*</td>
</tr>
<tr>
<td>Total-cholesterol, mmol L⁻¹</td>
<td>4.8 (0.9)</td>
<td>5.1 (0.8)</td>
</tr>
<tr>
<td>HDL-cholesterol mmol L⁻¹</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>Triglycerides mmol L⁻¹</td>
<td>1.3 (0.7)</td>
<td>1.7 (1.2)</td>
</tr>
<tr>
<td>Creatinine, μmol L⁻¹</td>
<td>94 (18.5)</td>
<td>96 (24.7)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>112 (11)</td>
<td>136 (16)†</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>70 (7.0)</td>
<td>86 (7.3)†</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>84 (7.5)</td>
<td>104 (9.1)†</td>
</tr>
<tr>
<td>Carotid systolic BP, mm Hg</td>
<td>100 (9.2)</td>
<td>126 (14.1)†</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>62 (8.8)</td>
<td>62 (9.5)</td>
</tr>
<tr>
<td>Carotid-femoral PWV, m s⁻¹</td>
<td>8.0 (1.0)</td>
<td>9.9 (1.7)†</td>
</tr>
<tr>
<td>CC distensibility, mm Hg×10⁻³</td>
<td>3.63 (0.6)</td>
<td>1.91 (1.0)†</td>
</tr>
</tbody>
</table>

Values are mean (SD). BP indicates blood pressure; CC, common carotid.

*P<0.05 vs normotensive subjects.
†P<0.001 vs normotensive subjects.

Distensibility, however, remained significantly greater in normotensive subjects than the mean baseline value in hypertensive subjects, even when blood pressure in the normotensive subjects was elevated to the level of that in hypertensive subjects (2.7±0.24 versus 1.9±0.13 mm Hg⁻¹×10⁻³; P<0.01). Infusion of NTG in normotensive subjects reduced MAP from 84±2 to 70±1 mm Hg (P<0.001), and this was associated with a significant reduction in PWV (from 8.1±0.3 to 7.7±0.3 m s⁻¹; P<0.05). The relationship between the change in PWV and change in MAP produced by NTG and Ang II was curvilinear (Figure 2) with a greater change in PWV at higher MAP, a similar relationship to that noted in previous studies using other vasoactive drugs to modulate MAP.12 There was no significant change in carotid distensibility in response to NTG, but 95% CIs for this (−0.4 to 0.7 mm Hg⁻¹×10⁻³) included the change predicted from the change in MAP and the PWV versus MAP relationship (0.4 mm Hg⁻¹×10⁻³), this being calculated from the best-fit curve shown in Figure 2 and by assuming an inverse square relationship between distensibility and PWV.

Hyptertensive Subjects

Hemodynamic changes during NTG infusion in hypertensive subjects are summarized in Table 2. The highest dose of NTG reduced MAP from 104±2 to 82±2 mm Hg, a value similar to baseline MAP in normotensive subjects (84±2 mm Hg). Despite this reduction in MAP, there was no significant effect of NTG to lower PWV or to increase carotid distensibility. At the highest dose of NTG, when blood pressure in the hypertensive subjects was similar to baseline blood pressure in normotensive subjects, the difference between PWV in hypertensive and normotensive subjects (9.9±0.5 versus 8.0±0.3 m s⁻¹; difference: 1.9±0.6 m s⁻¹) was similar to that between the 2 groups at their usual operating blood pressures (9.9±0.4 versus 8.0±0.3 m s⁻¹; difference: 1.9±0.5 m s⁻¹). The difference between carotid distensibility in hypertensive and normotensive subjects, at the same MAP (1.9±0.12 versus 3.7±0.3 mm Hg⁻¹×10⁻³; difference: 1.8±0.3 mm Hg⁻¹×10⁻³), was also similar to that between the 2 groups at their usual operating blood pressures (1.9±0.13 versus 3.7±0.3 mm Hg⁻¹×10⁻³; difference: 1.8±0.3 mm Hg⁻¹×10⁻³). Thus, PWV remained 24% (95% CI: 10%

TABLE 2. Hemodynamic Measurements During Blood Pressure Reduction/Elevation by NTG/Ang II in Normotensive Subjects and Blood Pressure Reduction in Hypertensive Subjects by NTG

<table>
<thead>
<tr>
<th>Drug</th>
<th>Normotensive subjects</th>
<th>Hypertensive subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NTG, μg min⁻¹</td>
<td>Ang II (ng min⁻¹)</td>
</tr>
<tr>
<td></td>
<td>HR, min</td>
<td>SBP, mm Hg</td>
</tr>
<tr>
<td>(vehicle)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>64±2</td>
<td>115±3</td>
</tr>
<tr>
<td>30</td>
<td>66±2</td>
<td>110±2</td>
</tr>
<tr>
<td>100</td>
<td>72±3*</td>
<td>108±2*</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(vehicle)</td>
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<td></td>
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<tr>
<td>75</td>
<td>58±2</td>
<td>119±2</td>
</tr>
<tr>
<td>150</td>
<td>58±2</td>
<td>124±2</td>
</tr>
<tr>
<td>300</td>
<td>58±3*</td>
<td>132±3*</td>
</tr>
</tbody>
</table>

Values are mean±SE. HR indicates heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; cSBP, carotid systolic blood pressure.

*P<0.001 for trend with dose.
to 38%) greater and distensibility 48% (95% CI: 31% to 63%) lower in hypertensive subjects than in normotensive subjects when compared at the same MAP (equal to that in the normotensive subjects). There was no significant interaction between age and response to NTG, nor between heart rate and response to NTG.

**Relationship Among Carotid Distensibility, Diastolic Diameter, and Compliance**

Values of carotid pulse pressure, diastolic diameter, distensibility, and compliance in normotensive and hypertensive subjects at baseline and at similar MAP (achieved by infusion of Ang II in normotensive subjects and NTG in hypertensive subjects) are shown in Table 3. During infusion of NTG, carotid distensibility in hypertensive subjects remained constant as a result of a parallel reduction of pulse pressure and distension and also an increase in diameter. The increase in diameter led to a significant increase in cross-sectional compliance despite the lack of change in distensibility.

**Discussion**

Arterial stiffness is strongly associated with age and blood pressure but not with other risk factors. Indeed, several studies have shown a weak association, inverse association, or no association between large artery PWV and risk factors including smoking, hyperlipidemia, and diabetes. In the present study and despite any clinical evidence of atherosclerosis or plaque deposition in the carotid arteries, there were marked differences in carotid and carotid-femoral stiffness between hypertensive and normotensive control subjects. This is consistent with the overwhelming importance of blood pressure as a determinant of arterial stiffness. If measured at the same site, the inverse square relationship between distensibility and PWV would be expected to lead to a 2-fold greater difference in distensibility than in PWV between the hypertensive and control groups, and in hypertensive subjects, carotid-femoral PWV was 24% greater and carotid distensibility 47% lower than in normotensive subjects. Although methodologic influences cannot be excluded, these increases in stiffness in the carotid and carotid-femoral path suggest that both territories are affected by hypertension to a similar degree.

Whether the effect of elevated MAP alone accounts for increased arterial stiffness in subjects with hypertension is a fundamental question that has received surprisingly little attention. Early work on rat aortae suggested that, at normal operating pressures (ie, usual MAP), young hypertensive rats actually have less stiff vessels, as determined by calculation of Young’s incremental elastic modulus ($E_{inc}$, a measure of the intrinsic elasticity of the vessel wall) than normotensive controls. A study of the static and dynamic mechanical properties of the carotid artery in rats suggested that, whereas in static conditions, hypertensive rats had stiffer vessels, when measured in dynamic conditions, the stiffness of the 2 groups was similar. Human studies using mathematical techniques to compare isobaric distensibility (distensibility at the same pressure) have shown similar carotid artery distensibility in hypertensive subjects compared with normotensive subjects at the same blood pressure. In these studies, simultaneous pressure and diameter data were acquired to create a pressure–diameter hysteresis loop. Hysteresis was then eliminated by iteration, the resultant pressure–diameter curve fitted to a logarithmic model and carotid distensibility evaluated at a pressure common to both hypertensive and control groups. A similar approach using an arc tangent function to model the pressure–diameter relationship and to calculate $E_{inc}$ has suggested similar intrinsic stiffness of the carotid artery wall in hypertensive subjects and control subjects when measured at the same pressure. Comparison of distensibility at the same pressure relies on an overlap of arterial pressure in the 2 groups (ie, a measurement taken
close to diastolic in the hypertensive group and close to systolic in the normotensive group). The interpretation of the result is, therefore, critically dependent on assumptions regarding the form of the pressure–diameter relation during the cardiac cycle and whether this differs in hypertensive and normotensive subjects. Calculation of $E_{\text{sa}}$ requires measurement of wall thickness and assumes that elasticity of the arterial wall is constant throughout the thickness of the wall and that intima–medial thickness (used to estimate the relevant wall thickness) is representative of the part of the wall that determines its overall elastic behavior. In reality, increased intima–medial thickness in hypertension may result from both intimal and medial thickening.

In the present study, we have used an entirely different approach, that of pharmacological manipulation of blood pressure with functional measures of stiffness. PWV is particularly important as a functional measure of stiffness, because it is known to predict future cardiovascular outcome. In interpreting the results of these studies, it is important to consider direct, blood pressure–independent effects of vasoactive drugs on arterial stiffness mediated through a change in the tone of smooth muscle and resulting change in diameter. In particular, there is the possibility that dilation of smooth muscle accompanies blood pressure reduction alters the load on the arterial wall resulting in a null effect on distensibility. This is a theoretical possibility if smooth muscle is arranged in parallel with stiffer elements, such as collagen. However, in studies in the brachial artery where smooth muscle tone and transmural pressure can be manipulated independently, incremental elastic modulus and PWV depend mainly on transmural pressure despite large changes in brachial artery diameter induced by alterations in smooth muscle tone. Bank et al have suggested that the artery behaves as if smooth muscle elements are in series with stiffer elements, so that relaxation of smooth muscle by NTG increases intrinsic elasticity, distensibility, and PWV (although effects of transmural pressure predominate). It is likely that the behavior of muscular and elastic arteries will differ with less effect of smooth muscle relaxation in more elastic arteries. Previous studies in the sheep iliac artery suggest that the effect of NTG, in the absence of any change in blood pressure, is to decrease PWV by $\approx 5\%$ for high local concentrations of NTG. In human studies, we have previously found no evidence of a blood pressure–independent effect on carotid-femoral PWV when using drugs that have differential effects on smooth muscle tone. Thus, direct blood pressure–independent effects of NTG on large artery stiffness would either produce no detectable change or a small decrease in PWV. Similarly, direct effects of Ang II would be expected to either produce no detectable change or a small increase in PWV.

The findings of the present study in normotensive subjects confirm the potential importance of mean arterial blood pressure in determining functional stiffness. In normotensive subjects, intravenous infusion of Ang II increased in MAP and produced a concomitant increase in both carotid-femoral PWV and carotid stiffness. Similarly, reduction of MAP with NTG reduced carotid-femoral PWV. The decrease in PWV was of smaller magnitude than the increase but was consistent with the expected decrease given the curvilinear relation between PWV and MAP observed in previous studies involving the acute modulation of blood pressure in normotensive subjects. When MAP was increased to a level similar to that in hypertensive subjects, carotid-femoral PWV and carotid stiffness approached that in the hypertensive subjects. However, at the same MAP, PWV still tended to be lower in normotensive subjects compared with hypertensive subjects, and carotid stiffness was significantly lower (distensibility greater) in normotensive subjects compared with hypertensive subjects. This suggests that, although the level of blood pressure may contribute to elevated functional stiffness in

<table>
<thead>
<tr>
<th>Variable</th>
<th>MAP, mm Hg</th>
<th>$D$, mm</th>
<th>$\Delta D$, mm</th>
<th>$\Delta P$, mm Hg</th>
<th>Compliance, mm² mm Hg⁻¹</th>
<th>Distensibility, mm Hg×10⁻³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive baseline</td>
<td>84±2</td>
<td>5.7±0.14</td>
<td>0.58±0.04</td>
<td>28.8±0.9</td>
<td>0.19±0.01</td>
<td>3.6±0.24</td>
</tr>
<tr>
<td>Hypertensive baseline</td>
<td>104±2</td>
<td>6.4±0.23</td>
<td>0.46±0.03</td>
<td>39.3±2.2</td>
<td>0.13±0.01</td>
<td>1.9±0.13</td>
</tr>
<tr>
<td>Normotensive (Ang II)</td>
<td>103±2</td>
<td>6.3±0.15</td>
<td>0.54±0.04</td>
<td>34.1±1.7</td>
<td>0.17±0.01</td>
<td>2.6±0.17§</td>
</tr>
<tr>
<td>Hypertensive (NTG)</td>
<td>82±2</td>
<td>7.2±0.25</td>
<td>0.37±0.03</td>
<td>28.1±1.9</td>
<td>0.16±0.01</td>
<td>1.9±0.12†</td>
</tr>
</tbody>
</table>

$D$ indicates carotid diameter during diastole; $\Delta D$, change in carotid diameter (maximum—minimum); $\Delta P$, carotid pulse pressure.

$^aP<0.05$, $^bP<0.01$ relative to normotensive at baseline.

$^cP<0.05$, $^dP<0.01$ relative to hypertensive at baseline.
hypertensive subjects, additional factors, such as a structural alteration in the wall, are implicated.

The most persuasive evidence that the difference in functional stiffness between normotensive and hypertensive subjects relates to a difference in structural properties between the 2 groups is provided by the reduction of blood pressure in hypertensive subjects by NTG. Despite reducing MAP by 22 mm Hg to a level similar to that in normotensive subjects, NTG had no significant effect on carotid-femoral PWV or carotid stiffness. Carotid distensibility remained 48% lower and PWV 24% higher in hypertensive subjects compared with normotensive subjects. There was a small but significant increase in heart rate after NTG and in other studies, using pacing to alter heart rate over a wide range, we and others have found PWV to increase modestly with heart rate (0.05 m/s per unit change in heart rate). However, the change in heart rate observed in the present study (4 to 8 min for the highest 2 doses of NTG) would be expected to have only a minor influence on PWV, and we found no significant association between PWV and heart rate. Because the direct effect of NTG on the arterial wall is, if anything, to reduce stiffness, the lack of change in PWV in hypertensive subjects after normalizing blood pressure strongly suggests that difference in stiffness between hypertensive and normotensive subjects is not explained by the level of the blood pressure but by a structural change induced by sustained hypertension. Indeed, because acute blood pressure reduction had no observable effect on PWV, these results suggest that structural alterations in hypertensive subjects may render the wall less sensitive to acute changes in blood pressure and that elevated stiffness in hypertension is almost entirely attributable to a structural change. Although treatment with NTG did not reduce PWV or increase distensibility in hypertensive subjects, it did result in an increase in cross-sectional compliance consistent with previous observations with isosorbide dinitrate. This increase in cross-sectional compliance was because of an increase in arterial diameter rather than a change in the intrinsic elasticity of the arterial wall (this being related to PWV and distensibility). However, an increase in compliance is likely to be of functional importance, because it will reduce pulse pressure. It is notable that novel NO donors have an even greater effect on brachial artery compliance and distensibility than classic nitrovasodilators, and it is possible that such drugs could be used to increase compliance and to reduce pulse pressure.

Perspectives
Previous studies using mathematical techniques to compare large artery stiffness at the same blood pressure have suggested that elevated stiffness in hypertension may be explained solely by the level of blood pressure. In the present study, we normalized blood pressure in hypertensive subjects by infusion of NTG, and there was no detectable reduction in arterial stiffness: carotid-femoral PWV remained 24% (95% CI: 10% to 38%) higher and carotid distensibility 48% (95% CI: 31% to 63%) lower in hypertensive compared with normotensive subjects. Because blood pressure–independent effects of NTG are, if anything, to reduce stiffness, these results indicate that elevated carotid and aortic stiffness in hypertensive subjects is not explained by elevated blood pressure but relates to structural change in the arterial wall. They suggest that arterial stiffness is not simply a “measure of blood pressure” but rather a measure of the longer-term influence of blood pressure on the arterial wall as observed in animal models of hypertension. Secondly, they suggest that any reduction in stiffness that accompanies a reduction in blood pressure is associated with structural remodeling, and it will be important to characterize the time course of such an effect and the degree to which it is determined by the level of blood pressure control. Subjects in this study had elevated blood pressure for ≥12 months despite treatment, and results in untreated subjects with hypertension of shorter duration or in subjects with hypertension that has been well controlled on treatment might differ.

In conclusion, in subjects with essential hypertension that is not controlled despite antihypertensive treatment, acute reduction of blood pressure by NTG to normotensive levels does not normalize large artery distensibility or PWV. Large artery stiffness in such subjects is likely to be elevated as a result of structural changes in the arterial wall.

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None.

References


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