Flow-Mediated Vasodilation and Distensibility in Relation to Intima-Media Thickness of Large Arteries in Mild Essential Hypertension

Michael Barenbrock, Martin Hausberg, Markus Kosch, Sergey A. Golubev, Klaus Kisters, and Karl-Heinz Rahn

Whether endothelial dysfunction in essential hypertension is a cause or a consequence of structural vessel wall alterations is not known. The purpose of the present study was to compare flow-mediated vasodilation and mechanical vessel wall properties of large arteries between never treated mild essential hypertensive patients with normal intima-media thickness (IMT) and those exhibiting intima-media thickening. We measured brachial and carotid artery diameter and distension by Doppler frequency analysis of vessel wall movements in M-mode in ten essential hypertensive patients with normal carotid artery IMT (HYP1), in ten patients with increased IMT (HYP2), and in 13 normotensive control subjects (CON).

Therefore, we measured changes in brachial artery (BA) diameters during distal reactive hyperemia after 4 min of forearm occlusion. Nitroglycerin-mediated vasodilation was measured to assess endothelium-independent vasodilation, and BA blood flow was estimated using a pulsed Doppler system. Intima-media thickness of the carotid arteries was examined by high resolution B-mode ultrasound. IMT was 0.66 ± 0.02 mm in the HYP1 group, 0.84 ± 0.03 mm in the HYP2 group (P < .01 v HYP1, P < .01 v CON), and 0.71 ± 0.04 mm in the CON group. Forearm occlusion was reduced in both the HYP1 group (3.4% ± 3.6%, P < .01 v CON) and the HYP2 group (6.4% ± 1.5%, P < .05 v CON) when compared with the CON group (16.5% ± 2.8%). Nitroglycerin-mediated vasodilation and BA blood flow were not different between study groups. BA distension (as well as carotid artery distension) was significantly lower in the HYP1 group (52 ± 6 μm, P < .05 v CON), but not in the HYP2 group (72 ± 10 μm) when compared with the CON group (88 ± 13 μm). The data suggest that endothelial dysfunction and reduced distensibility of large arteries in patients with essential hypertension occur in the absence of structural vessel wall alterations. Am J Hypertens 1999;12:973–979 © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: Intima-media thickness, flow-mediated vasodilation, arterial distensibility, essential hypertension

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Several experimental and clinical studies have shown that the vascular endothelium is altered in the presence of arterial hypertension. This is manifest as reduced vasodilation or paradoxical vasoconstriction in response to acetylcholine and to increased blood flow. In response to various types of injury, the vessel wall responds by constricting, thickening, or developing lesions. These processes are consequences of the damaging effects of hypertension. It has therefore been suggested that hypertension is associated with parallel alterations of endothelial function, vessel wall composition, and clinically undetectable atherosclerosis. However, whether endothelial dysfunction is a cause or a consequence of structural vessel wall alterations remains controversial. High resolution ultrasound imaging has emerged as an adequate tool to directly examine and quantify structural vessel wall changes of large arteries. It has been demonstrated that these newer ultrasound techniques can reliably identify the intima and media of arteries and detect very early arterial lesions. The presence of intima-media thickening of larger arteries has been documented in essential hypertension. To date, there have been no data on the relationship between intima-media thickening and endothelial dysfunction in these patients. Flow-mediated vasodilation is a useful index of endothelial function. The purpose of the present study was to investigate flow-mediated vasodilation in mild essential hypertensive patients with no evidence of structural vessel wall changes in high resolution B-mode ultrasound, and compare the results with those from essential hypertensive patients exhibiting intima-media thickening, and from normotensive control subjects. The mechanical vessel wall properties of large arteries were investigated in the study groups as well.

METHODS

Subjects Thirty-six patients with newly diagnosed and untreated mild essential hypertension, who presented consecutively in our outpatient clinic, were screened for intima-media thickening. Each subject gave informed consent. All patients had diastolic blood pressure values exceeding 90 mm Hg in the sitting position on three different occasions. None of the patients had clinical evidence of atherosclerotic disease, renal disease, hypercholesterolemia, diabetes mellitus, valvular heart disease, or heart failure. In ten of these patients (HYP1), intima-media thickness (IMT) was within the 95% CI for the IMT of normotensive controls. The remaining 26 patients had intima-media thickness above the 95% CI of normal controls. The ten essential hypertensive patients with normal IMT (HYP1) and ten age-matched patients with increased IMT of the common carotid artery (HYP2) were enrolled in the study. Thirteen age-matched normotensive volunteers served as control subjects (CON). The normotensive control subjects had a normal physical examination, ECG, chest x-ray, echocardiography, and routine biochemical parameters. None of the patients or controls had evidence of plaque formation or calcifications in the carotid bifurcation, common carotid artery, or brachial artery, as observed by high resolution B-mode ultrasound. Standard laboratory assays were performed in the fasting state. Demographic data of patients and subjects are represented in Table 1.

The following assessments were performed: blood pressure measurements, measurement of intima-media thickness, determination of flow-mediated and nitroglycerin-mediated vasodilation, and measurement of arterial distensibility. All determinations of intima-media thickness were performed by one observer and all determinations of distensibility and flow-mediated vasodilation were performed by another investigator. Investigators were blinded to the subjects’ group (HYP I, HYP II, or CON).

Blood Pressure Measurements Left brachial artery blood pressure was measured using an automatic sphygmomanometer (Dinamap model 1846 SX, Critikon Inc, Tampa, FL). Heart rate was determined using an ECG monitor.

Ultrasound B-Mode Imaging Imaging of both carotid arteries was performed in all subjects with a real-time high resolution B-mode ultrasound system (Biosound 2000 II s.a., Biosound Inc., Indianapolis, IN) equipped with an 8 MHz linear transducer. This system provides images of adequate quality to measure carotid artery wall thickness. The carotid arteries were examined bilaterally at the level of the common carotid artery, the bifurcation, and the internal

<table>
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<tr>
<th>TABLE 1. DEMOGRAPHIC AND BIOCHEMICAL DATA</th>
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<td>Age (years)</td>
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<tr>
<td>Male/Female</td>
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<tr>
<td>Smokers/Nonsmokers</td>
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<tr>
<td>Body Mass Index (kg/m²)</td>
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<td>Serum creatinine (mg/dl)</td>
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<td>Total cholesterol (mg/dl)</td>
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<td>Serum triglyceride (mg/dl)</td>
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Demographic and biochemical data in essential hypertensive patients with normal intima-media thickness (HYP1, n = 10), increased intima-media thickness of the carotid arteries (HYP2, n = 10), and in healthy controls (CON, n = 13). Body mass index was calculated as weight/weight². None of these variables were significantly different between the three groups.
carotid artery. The intima-media complex had to be lined out clearly in each carotid segment in a sequential manner. In a longitudinal B-mode image, three arterial interfaces associated with both far wall and near wall are present. The first echogenic line between arterial wall and lumen is the intima-lumen interface, followed by the media-adventitia and adventitia-peri-adventitia layer (the second and the third interfaces). The distance between the first and second interface corresponds to the intima-media complex. The visualization of these three interfaces in all carotid segments from the anterior, the posterior, and the lateral angles is necessary to measure the maximum of the combined thickness of the intima-media complex. In each segment, the intima-media complexes of the far wall and the near wall were recorded on videotape. The linear distance from the first to the second echogenic line was measured in millimeters after twofold augmentation by an image analysis system data base (KS 100, Kontron Elektronik, Munich). The maximum thickness of intima media of all arterial sites and angles was evaluated. Mean of IMT was calculated. The coefficient of variation for IMT measurements of the carotid arteries was 7.3% ± 1.4% (n = 26) in our study. Furthermore, each segment of the carotid artery and the brachial artery was scanned for occurrence of atherosclerotic plaques. Plaque was defined as an echo-genic structure encroaching into the lumen. Subjects with plaques were excluded from study.

Doppler Analysis of Vessel Wall Movements The brachial artery of the right arm was visualized in a longitudinal section 2 to 6 cm above the elbow using a 7.5 MHz linear array transducer and a standard Toshiba Sonolayer α SSA-270A system (Toshiba Medical Systems, Neuss, Germany). The brachial artery was displayed in B- and in M-Mode. Vessel diameter and distension were then analyzed using a multigate pulsed Doppler system.13,14 Low frequency Doppler signals originating from the sample volumes coinciding with the anterior and posterior vessel walls were processed. The resolution for a 6.1 MHz Doppler system is equivalent to a displacement of 31.25 μm (assuming a speed of sound of 1525 miles/sec). Using the ECG trigger, the enddiastolic diameter and distension of the brachial artery were measured over three consecutive cardiac cycles and the results averaged to a single value. Coefficients of variation were 4.5% ± 0.7% (n = 26) for the enddiastolic diameter and 9.6% ± 1.6% (n = 26) for the relative distension of the brachial artery. The same system was used to assess left carotid artery enddiastolic diameter and distension 2 cm below the carotid bifurcation.

Protocol All studies were performed between 8 and 12 AM in supine position after at least 15 min of rest. First imaging of both carotid arteries was performed using high resolution B-mode ultrasound. Thereafter, enddiastolic diameter and distension of the carotid and brachial arteries were measured using the multigate Doppler system. After two measurements of enddiastolic diameter and distension of the brachial artery at baseline were taken, a forearm cuff was inflated downstream from the site of arterial measurements at 300 mm Hg for 4 min. During the last minute of cuff inflation, and 1, 3, 5, 7, and 10 min after cuff release, further measurements of brachial artery enddiastolic diameter were taken. Brachial artery blood flow at baseline and during the initial 15 sec of reactive hyperemia was estimated using pulsed Doppler. At 11 min after cuff release, 400 μg of glycerol trinitrate were administered sublingually and further scans of the brachial artery were taken after 1, 3, and 5 min.

Analyses From the enddiastolic diameter (d), the systolic increase of vessel diameter (distension = Dd) and from the systolic (SBP) and diastolic (DBP) blood pressure, arterial wall distensibility was calculated (distensibility coefficient DC = 2 Dd × d⁻¹ × (SBP−DBP)⁻¹ [10⁻³ kPa]) for the carotid and brachial arteries. Because continuous blood pressure recordings were not performed, distensibility calculations could not be obtained at a range of different blood pressure levels. Flow-mediated vasodilation of the brachial artery was calculated as the maximum absolute and relative increase in brachial artery enddiastolic diameter after reactive hyperemia. Nitroglycerin-mediated vasodilation was accordingly calculated as the maximum absolute and relative increase in brachial artery enddiastolic diameter after sublingual glycerol trinitrate. The coefficients of variation were 11.4% ± 4.5% (n = 12) for flow-mediated vasodilation and 8.2% ± 3.1% (n = 12) for nitroglycerin-mediated vasodilation. Statistical analysis was performed by analysis of variance for continuous variables. Post-hoc between groups comparison was performed using Fisher’s PLSD. Nominal variables were compared by χ² test. Additionally, ANCOVA was performed for key variables. Correlation analyses were performed using Spearman rank correlation. Statistical significance was assumed at P < .05, where ns means statistically not significant. Data are presented as mean ± SEM.

RESULTS

Demographic and biochemical data of patient groups and control subjects are shown in Table 1. There were no significant differences in age, smoking habits, gender ratio, or body mass index between groups. Serum creatinine, total cholesterol, and triglyceride levels did not differ significantly between groups. HYP1 and HYP2 did not differ significantly in systolic and diastolic blood pressure values or heart rates; both had significantly elevated systolic and diastolic
blood pressures and heart rates as compared with control subjects (Table 2).

Intima-media thickness of the carotid arteries was significantly elevated in HYP2 when compared with HYP1 and CON, whereas HYP1 and CON did not differ significantly in carotid artery intima-media thickness (Figure 1, Table 2). Carotid and brachial artery enddiastolic diameter at baseline did not differ significantly between groups. Brachial and carotid distensions and distensibility coefficients were lower in HYP1 than in HYP2, but the differences between both groups failed to reach statistical significance. Distension of the brachial and the carotid artery were significantly lower in HYP1 than in CON, but did not differ significantly between HYP2 and CON (Figure 1). Brachial and carotid distensibility coefficients were significantly lower in both HYP1 and HYP2 when compared with CON (Table 2).

During reactive hyperemia, the increase in brachial artery enddiastolic diameter (flow-mediated vasodilation) was significantly blunted in both essential hypertensive groups. This was true when diameter changes were expressed both as absolute and as relative values (Table 2, Figure 1). However, brachial artery flow-mediated vasodilation was not significantly different in patients with or without carotid artery intima-media thickening.

Brachial artery vasodilation after sublingual glycerol trinitrate as a measure of endothelium independent vasodilation was similar in both patient groups and control subjects. Brachial artery flow was comparable in patients and controls at baseline and during reactive hyperemia. Analysis of covariance revealed that the differences in brachial artery flow-mediated vasodilation between patient groups and control subjects remained statistically significant (HYP1 v CON, \( P = .008 \); HYP2 versus CON, \( P = .02 \)) independent of age (\( P = .93 \)) and brachial artery enddiastolic diameter (\( P = .10 \)). Analysis of covariance also demonstrated a significant reduction in brachial artery distension in HYP1 (HYP1 v CON, \( P = .008 \); HYP2 v CON, \( P = .39 \)) when compared with CON independent of age (\( P = .44 \)) and enddiastolic diameter (\( P = .008 \)). Moreover, brachial artery distensibility coefficients between both patient groups and normotensive volunteers (HYP1 v CON, \( P = .003 \); HYP2 v CON, \( P = .03 \)) were significantly different independent of age (\( P = .50 \)) and brachial artery enddiastolic diameter (\( P = .59 \)).

There was no correlation between brachial artery flow-mediated vasodilation and intima-media thickness of the common carotid artery (\( \rho = -0.15, P = .38 \)) (Figure 2). This was also true for the correlation between the carotid artery intima-media thickness and carotid (\( \rho = -0.17, P = .32 \)) or brachial (\( \rho = 0.10, P = .60 \)) artery distensibility coefficients. We observed a significant correlation between brachial artery flow-mediated vasodilation and distensibility coefficient of the brachial artery (\( \rho = 0.39, P = .02 \)).

**DISCUSSION**

Several studies have suggested that endothelium is dysfunctional in hypertension.\textsuperscript{1–4} With intact endothelium, arteries exhibit endothelium-dependent dilation in response to increased flow. This is mediated by

**TABLE 2. BLOOD PRESSURE AND PARAMETERS OF VESSEL PROPERTIES**

<table>
<thead>
<tr>
<th></th>
<th>HYP1</th>
<th>HYP2</th>
<th>CON</th>
</tr>
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<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>148</td>
<td>149</td>
<td>122</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>94</td>
<td>87</td>
<td>74</td>
</tr>
<tr>
<td>Heart Rate (/min.)</td>
<td>74</td>
<td>71</td>
<td>61</td>
</tr>
<tr>
<td>IMT carotid (mm)</td>
<td>0.66</td>
<td>0.84</td>
<td>0.71</td>
</tr>
<tr>
<td>Diameter carotid (mm)</td>
<td>5.8</td>
<td>6.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Distension carotid (µm)</td>
<td>316</td>
<td>418</td>
<td>473</td>
</tr>
<tr>
<td>DC carotid (10 (^{-3})/kPa)</td>
<td>15.0</td>
<td>18.1</td>
<td>25.1</td>
</tr>
<tr>
<td>Diameter brachial (mm)</td>
<td>3.8</td>
<td>3.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Distension brachial (µm)</td>
<td>52</td>
<td>72</td>
<td>88</td>
</tr>
<tr>
<td>DC brachial (10 (^{-3})/kPa)</td>
<td>4.2</td>
<td>5.3</td>
<td>8.3</td>
</tr>
<tr>
<td>FMD brachial (mm)</td>
<td>0.13</td>
<td>0.23</td>
<td>0.51</td>
</tr>
<tr>
<td>FMD brachial (%)</td>
<td>3.4</td>
<td>6.4</td>
<td>16.5</td>
</tr>
<tr>
<td>NMD brachial (mm)</td>
<td>0.50</td>
<td>0.50</td>
<td>0.72</td>
</tr>
<tr>
<td>NMD brachial (%)</td>
<td>13.9</td>
<td>16.2</td>
<td>19.0</td>
</tr>
<tr>
<td>Baseline Flow brachial (ml/min)</td>
<td>88</td>
<td>106</td>
<td>84</td>
</tr>
<tr>
<td>Peak Flow brachial (%)</td>
<td>448</td>
<td>441</td>
<td>481</td>
</tr>
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</table>

Values for systolic and diastolic blood pressure (BP), heart rate, enddiastolic diameter, distension, and distensibility coefficient (DC) of the carotid and brachial arteries, flow-mediated vasodilation (FMD) and glycerol-trinitrate-mediated vasodilation (NMD), blood flow at baseline, and peak blood flow (% increase) of the brachial artery during reactive hyperemia in essential hypertensive patients with normal (HYP1 \( n = 10 \)) and increased (HYP2 \( n = 10 \)) intima media thickness (IMT) and healthy controls (CON, \( n = 13 \)). * \( P < 0.05 \), ** \( P < 0.01 \) versus CON, § \( P < 0.05 \), §§ \( P < 0.01 \) HYP1 versus HYP2.
endothelial release of nitric oxide after shear stress. The data of the present study confirm previous evidence that flow-mediated vasodilation is decreased in patients with essential hypertension. Furthermore, the data show that flow-mediated vasodilation occurs independent of intima-media thickening. 

Flow-mediated vasodilation was reduced in both essential hypertensive groups when compared to healthy control subjects. Endothelial dysfunction seems, therefore, to precede adaptive vessel wall changes in response to high blood pressure. Moreover, the study shows that distension of the brachial and carotid artery is significantly reduced in essential hypertensive patients with normal intima-media thickness as compared to patients with vessel wall thickening and healthy controls. Arterial wall hypertrophy may attenuate increases in wall stress, thereby improving the reduction of arterial distensibility with increasing distending pressure.

There is debate as to whether intima-media thickening reflects early atherosclerosis preceding advanced lesions or medial hypertrophy due to pressure effects. The ultrasound imaging method does not allow for differentiation between the intima atherosclerotic process and medial hypertrophy. Atherosclerosis is focal, primarily intimal, and leads to occlusive arterial disease, whereas arterial wall thickening that occurs with high blood pressure is primarily diffuse, resulting from medial hypertrophy. In the present study, patients with hypercholesterolemia, overt atherosclerotic disease, or with local lesions detectable by high resolution B-mode ultrasound were not included. Therefore, vessel wall changes in the essential hypertensive group with increased IMT are likely the consequence of arterial wall hypertrophy. The data of the present study suggest that endothelial dysfunction precedes arterial wall hypertrophy that occurs with high blood pressure. Apart from flow-mediated vasodilation, mechanical vessel wall properties of the carotid artery were also disturbed in essential hypertensive patients without evidence of intima-media thickening in high resolution B-mode ultrasound. The study shows that distension of the brachial and carotid
artery was significantly reduced in essential hypertensive patients with normal intima-media thickness when compared with healthy controls, whereas no significant reductions were observed between essential hypertensive patients with intima-media thickening and healthy controls. Vessel wall hypertrophy might attenuate increases in distending wall stress resulting from elevated intravascular pressure. Arterial wall hypertrophy could therefore improve the reduction of arterial compliance that occurs as a mechanical consequence of the increased distending pressure. This may explain why arterial distensions did not differ significantly between essential hypertensive patients with intima-media thickening and healthy controls in our study.

It has to be noted that distensibility calculations were only performed at a single blood pressure in each patient. True comparisons of distensibility are best done in pressure-independent fashion; that is, when calculated at a range of different blood pressures. Therefore, we cannot exclude the possibility that isobaric distension is similar in the three groups and thus the reduction of arterial distensibility in the hypertensive groups is a mechanical consequence of higher distending pressure. However, although systolic blood pressure was similar in both hypertensive groups and pulse pressure tended even to be higher in the hypertensive group with intima-media thickening, distension and distensibility tended to be higher in this group when compared to the hypertensive group with normal intima-media thickness.

The mechanism for endothelial dysfunction in essential hypertensive patients is not known. The present study suggests that endothelial dysfunction precedes structural vascular alterations. The absence of detectable structural vessel wall changes in a subgroup of essential hypertensive patients with endothelial dysfunction supports the hypothesis of a functional phase of arterial involvement. Studies indicate the occurrence of a diminished basal and stimulated nitric oxide production.20,21 Impaired endothelial function with essential hypertension assessed by ultrasonography. Am Heart J 1996; 132:779–782.

The data of the present study showed that flow-mediated vasodilatation is similarly reduced in essential hypertensive patients without intima-media thickening when compared to patients with increased vessel wall thickness. Endothelial dysfunction in essential hypertension seems, therefore, to occur in the absence of structural vessel wall alterations. Moreover, the study shows a reduction in arterial distension and distensibility when structural vessel wall changes are not detectable in B-mode ultrasound.

CONCLUSION

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REFERENCES


