Endothelial Function Is Associated With Pulse Pressure, Pulse Wave Velocity, and Augmentation Index in Healthy Humans


Abstract—Arterial stiffness is an independent predictor of mortality and is regulated by a number of factors, including vascular smooth muscle tone. However, the relationship between endothelial function and definitive measures of arterial stiffness and wave reflections has not been described in healthy individuals. Therefore, we tested the hypothesis that endothelial function is inversely correlated with aortic pulse wave velocity (PWV), central pulse pressure, and augmentation index in healthy individuals. Peripheral and central pulse pressure and augmentation index were determined at rest, and global endothelial function was measured using pulse wave analysis and administration of sublingual nitroglycerin and inhaled albuterol. Aortic PWV was also determined at baseline in a subset of 89 subjects. In a separate group of subjects (n=89), aortic PWV was measured and brachial artery flow-mediated dilatation assessed as a measure of conduit artery endothelial function. Global endothelial function was significantly and inversely correlated with aortic PWV (r = -0.69; P<0.001), augmentation index (r = -0.59; P<0.001), and central (r = -0.34; P<0.001) and peripheral pulse pressure (r = -0.15; P=0.03). Moreover, there was a stronger correlation between central rather than peripheral pulse pressure. After adjusting for potential confounders, global endothelial function remained independently and inversely associated with aortic PWV and augmentation index. There was also a significant, inverse relationship between conduit artery endothelial function and aortic PWV (r=0.39, P<0.001), which remained independent after adjusting for confounding factors. In healthy individuals, a decline in endothelial function is associated with increased large artery stiffness, wave reflections, and central pulse pressure. (Hypertension. 2006; 48:602-608.)

Key Words: nitric oxide ■ endothelium-derived factors ■ blood pressure ■ pulse ■ arteries

Endothelial dysfunction, characterized by a reduced bioavailability of endothelium-derived NO, is an important step in the progression of atherosclerosis. Indeed, resistance vessel, conduit artery, and coronary endothelial dysfunction independently predict all-cause and cardiovascular mortality. A number of risk factors for cardiovascular disease, including age, hypertension, obesity, hypercholesterolemia, diabetes, and smoking, are associated with systemic endothelial dysfunction. Interestingly, these risk factors are also associated with increased elastic artery stiffness, which is itself an important predictor of outcome in a number of patient groups. Removal of the vascular endothelium alters arterial stiffness in animal models, and we have demonstrated recently that blocking NO synthesis increases local arterial stiffness, suggesting that endothelium-derived NO contributes to the regulation of large artery stiffness in vivo.

Support for this hypothesis stems from the observation that brachial artery pulse pressure, a surrogate measure of large artery stiffness, correlates with coronary and resistance vessel endothelial function in hypertensive patients and controls. However, direct evidence of a relationship between endothelial function and more definitive measures of arterial stiffness is largely limited to studies in patients with cardiovascular disease and risk factors, and the relationship between endothelial function and aortic (carotid–femoral) pulse wave velocity (PWV), the current “gold-standard” measure of stiffness, in healthy normotensive individuals, who are free of the potentially confounding influence of cardiovascular disease, has not been well-described. Moreover, as we and others have shown previously, brachial pulse pressure does not always provide an accurate indication of central pulse pressure, and the relationship between endothelial function and central pulse pressure is unclear. This is

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likely to be important clinically, because the left ventricle, kidney, and brain are influenced by central, not peripheral pulse pressure,29,30 and central pulse pressure is a stronger predictor of all-cause mortality in patients with cardiovascular disease.31 To our knowledge, there are no data describing the relationship between endothelial function and central pulse pressure, PWV, and augmentation index (AIx) in a large group of healthy individuals.

We hypothesized that global endothelial function, which includes conduit and resistance vessel endothelial function, is associated with aortic wall properties and wave reflection. Therefore, the aim of this study was to test this hypothesis in a group of healthy individuals using a validated, noninvasive method with which to assess endothelial function32,33: pulse wave analysis coupled with the administration of the endothelium-dependent β2 adrenoceptor agonist albuterol and the endothelium-independent vasodilator nitroglycerin (NTG). To confirm our findings, we also examined the relationship between arterial stiffness and flow-mediated dilatation, a widely used technique to assess conduit vessel endothelial function, in a separate group of healthy individuals.

Methods

Subjects
In all, 309 healthy volunteers, across a wide age range (18 to 81 years), were recruited from a community-based volunteer database. All of the subjects were free of cardiovascular disease, risk factors, and medication. Approval for the study was obtained from the local research ethics committee, and written informed consent obtained from each participant.

Hemodynamics
Brachial blood pressure was recorded in duplicate in the nondominant arm using a validated oscillometric sphygmomanometer (HEM 705-CP, Omron Corp).34 Radial artery waveforms were recorded with a high-fidelity micromanometer (SPC-301, Millar Instruments). A validated transfer function35,36 was then used to generate a corresponding central aortic pressure waveform (SphygmoCor, AtCor Medical) as described previously.37 From this, mean arterial pressure (MAP) and heart rate (HR) were determined using the function, in a separate group of healthy individuals.

Assessment of Conduit Artery Endothelial Function

Global endothelial function was assessed by recording the diameter changes in the brachial artery to increased blood flow generated during reactive hyperemia (flow-mediated dilatation) and NTG. Briefly, 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 a longitudinal section ~5 to 10 cm above the antecubital fossa and updated from the R wave of an ECG. End-diastolic images of the vessel were then acquired every 3 seconds and stored offline for later analysis using edge detection software (Brachial Tools). Images were recorded for 1 minute before a pressure cuff, around the forearm distal to the elbow, was 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 (endothelium-dependent dilatation), which was measured for a further 5 minutes. NTG (25 μg) was then administered sublingually, and the changes were measured over a period of 5 minutes (endothelium-independent dilatation). Flow-mediated and NTG-mediated dilatation were defined as the maximal percentage changes in vessel diameter after reactive hyperemia and administration of NTG, respectively.

Protocol
All of the studies were conducted in a quiet, temperature-controlled room (22±2°C). Heart rate, blood pressure, and arterial waveforms were all recorded in duplicate.

Study 1 Assessment of Global Endothelial Function
In 220 individuals, 3 sets of recordings were made during a 30-minute period of supine rest, with the last taken as baseline. Global endothelial function was assessed as the ratio of the change in AIx after drug administration, and global endothelial function was defined as the ratio of the change in albuterol relative to NTG. Therefore, a reduction in the albuterol:NTG ratio (ie, less fall in AIx with albuterol compared with NTG) is indicative of worse endothelial function.

TABLE 1. Clinical Characteristics and Baseline Hemodynamic Responses of Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A (n = 220)</th>
<th>B (n = 89)</th>
<th>C (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45±17</td>
<td>48±20</td>
<td>41±16</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>132/88</td>
<td>68/41</td>
<td>41/48</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.72±0.09</td>
<td>1.71±0.10</td>
<td>1.71±0.11</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76±143</td>
<td>75±13</td>
<td>74±16</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.5±4.2</td>
<td>25.4±3.7</td>
<td>25.0±4.4</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.16±1.15</td>
<td>4.90±0.83</td>
<td>4.94±0.91</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.36±0.35</td>
<td>1.44±0.96</td>
<td>1.39±0.93</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.97±0.85</td>
<td>4.90±0.80</td>
<td>4.90±1.26</td>
</tr>
<tr>
<td>Peripheral SBP, mm Hg</td>
<td>121±16</td>
<td>125±16</td>
<td>119±12</td>
</tr>
<tr>
<td>Peripheral DBP, mm Hg</td>
<td>70±10</td>
<td>69±8</td>
<td>72±8</td>
</tr>
<tr>
<td>Peripheral PP, mm Hg</td>
<td>51±12</td>
<td>56±13</td>
<td>47±10</td>
</tr>
<tr>
<td>Central SBP, mm Hg</td>
<td>108±17</td>
<td>110±17</td>
<td>107±11</td>
</tr>
<tr>
<td>Central DBP, mm Hg</td>
<td>71±10</td>
<td>70±8</td>
<td>73±8</td>
</tr>
<tr>
<td>Central PP, mm Hg</td>
<td>37±11</td>
<td>40±12</td>
<td>34±8</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>87±11</td>
<td>87±11</td>
<td>88±9</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>65±9</td>
<td>63±10</td>
<td>63±10</td>
</tr>
<tr>
<td>Augmentation index, %</td>
<td>15±16</td>
<td>18±16</td>
<td>16±13</td>
</tr>
<tr>
<td>Aortic PWV, m/s</td>
<td>—</td>
<td>8.31±3.65</td>
<td>7.37±1.75</td>
</tr>
<tr>
<td>Cigarette smokers, n</td>
<td>40</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>

Column A refers to all subjects included in study 1 (NTG/albuterol). Column B refers to those individuals in study 1 in whom aortic PWV was measured at baseline. Column C refers to those individuals included in study 2. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.
endothelial function was then assessed. In a subset of 89 individuals, aortic PWV was measured at baseline, before the administration of NTG.

**Study 2 Assessment of Conduit Artery Endothelial Function**

In a separate group of individuals (n = 89), conduit artery endothelial function was assessed after baseline measurements of blood pressure and aortic PWV.

In all of the subjects, 10 mL of blood were then drawn from the antecubital fossa into plain tubes. The samples were centrifuged at 4°C (4000 rpm for 20 minutes) and the serum separated and stored at −80°C for subsequent analysis. Cholesterol, triglycerides, and glucose were determined using standard methodology in an accredited laboratory.

**Statistical Analysis**

Differences in the response to NTG and albuterol (study 1) or flow-mediated and NTG-mediated dilatation (study 2) were analyzed using paired Student t tests. Stepwise multiple regression analyses were then conducted using SPSS software (version 11.0). Variables for the stepwise linear regression model were chosen based on univariate correlation analyses and those variables known or thought to be associated with arterial stiffness, from published observations. All of the values represent mean±SD, and a P < 0.05 was considered significant. R² change indicates the percentage change for each parameter.

**Results**

The baseline characteristics of the subjects studied are shown in Table 1. The mean ages of the groups were similar: 45±17 years (study 1), 48±20 years (study 1 subset), and 41±16 years (study 2).

**Study 1: Global Endothelial Function**

Administration of NTG and albuterol caused a significant fall in AIx of -14±6% (P < 0.001) and -8±5% (P < 0.001), respectively (Figure 1). Importantly, there were no changes in
MAP or HR in response to either drug. With univariate analyses, endothelial function was most strongly correlated with aortic PWV \((r = 0.69; P < 0.001; \text{Figure 2A})\), AIx \((r = -0.59; P < 0.001)\), and age \((r = -0.56; P < 0.001)\). Similar relationships were observed when these analyses were performed separately in “younger” and “older” individuals based on the median age of the group (45 years). When these analyses were performed on the whole group, using the responses to albuterol and NTG separately rather than as a ratio, only the response to albuterol remained significantly correlated. There was also a significant correlation between endothelial function and central pulse pressure \((r = 0.34; P < 0.001)\) and, to a lesser extent, peripheral pulse pressure \((r = 0.15; P = 0.03)\). Other variables that were significantly associated with endothelial function were total cholesterol \((r = 0.37; P < 0.001)\) and body mass index \((\text{BMI}) r = -0.18; P < 0.01)\). When all of these parameters were included in a stepwise multiple regression model to examine the major independent determinants of endothelial function, together with gender, low-density lipoprotein cholesterol, triglycerides, and smoking, only age and BMI remained significantly associated. When this analysis was repeated using the response to albuterol, again only age and BMI remained significantly associated. Baseline values of AIx or PWV did not enter either model.

To determine whether global endothelial function influences aortic PWV and AIx, stepwise multiple regression models were constructed for each parameter to control for possible confounding variables (Table 2). Aortic PWV was independently and positively associated with age and blood glucose level and negatively with endothelial function. Augmentation index was also independently and positively associated with age and MAP and negatively associated with endothelial function, height, and HR. When the same regression models were constructed using the response to albuterol and NTG separately, the response to albuterol remained independently associated with both aortic PWV and AIx, whereas the response to NTG was not significantly associated. In post hoc analyses, exclusion of smokers did not meaningfully alter any of the regression models.

Subjects were then stratified into quartiles of age and global endothelial function to examine the interaction between each parameter and aortic stiffness (Figure 3). For a given quartile of age, aortic PWV increased as endothelial function declined and vice versa.

**Study 2: Conduit Vessel Endothelial Function**
The mean baseline artery diameter was 4.03±0.78 mm before inflation of the forearm occlusion cuff and 3.99±0.79 mm before the administration of NTG \((P\) not significant). The maximal change in diameter was 5.80±3.03% after ischemia and 9.59±5.08% after NTG. There was a significant and inverse correlation between flow-mediated dilatation and aortic PWV \((r = -0.39; P < 0.001; \text{Figure 2B})\), which remained independent even after correcting for confounding variables (Table 2).

**Discussion**
Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in selected patient groups.12–15 Physiologically, the stiffness of the large arteries depends on 3 main factors: structural elements within the arterial wall, such as elastin and collagen; distending pressure; and vascular smooth muscle tone. Changes in smooth muscle tone alter the distribution of forces within the arterial wall, providing functional regulation of arterial stiffness. We have shown recently in both animals17 and humans18 that the endothelium-derived vasodilator NO contributes to the regulation of local conduit artery stiffness in vivo. The aim of the current study was to investigate the relationship between endothelial function and large artery stiffness and associated wave reflection characteristics in a group of healthy individuals. Our major findings were that global endothelial function correlates more strongly with central rather than peripheral
pulse pressure and is independently and inversely correlated with aortic PWV (a measure of large artery stiffness) and AIx as measured by AIx. In addition, we found that aortic PWV was significantly and inversely correlated with flow-mediated dilatation in the brachial artery, which is an established and widely used measure of conduit artery endothelial function. Together, these data suggest that endothelial function is an important determinant of central hemodynamics and large artery stiffness and lend further support to the importance of NO in the regulation of large artery stiffness in vivo.

Previous studies indicate that peripheral pulse pressure, frequently considered as a surrogate measure of large artery stiffness, is associated with arteriolar endothelial dysfunction and conduit artery endothelial dysfunction in hypertensive animals and patients and coronary endothelial dysfunction in hypertensive and normotensive individuals undergoing diagnostic angiography. A number of other studies have described a relationship between various indices of arterial stiffness and endothelial dysfunction in selected patient groups. However, these studies require invasive procedures and/or highly specialized equipment and operators. Moreover, only a limited number of studies assessed aortic PWV, the current gold-standard measure of large artery stiffness, and wave reflection characteristics. Furthermore, many of the patients studied had cardiovascular risk factor, and, to our knowledge, no previous data have explored the relationship among arterial stiffness, wave reflections, and endothelial function in a sufficiently large group of healthy individuals.

In the current study, global endothelial function, which includes conduit and resistance vessel endothelial function, was assessed using a previously validated, noninvasive method, which couples the technique of pulse wave analysis with the administration of a β2-adrenoceptor agonist as an endothelium-dependent vasodilator and NTG as an endothelium-independent NO donor. This technique is reproducible and correlates with the response to acetylcholine and sodium nitroprusside in the forearm vascular bed, assessed using venous occlusion plethysmography. Global endothelial function, obtained using the above technique, was inversely associated with peripheral pulse pressure, but there was a much stronger correlation with central pulse pressure, which is a better surrogate measure of central artery stiffness and left ventricular afterload and is a stronger predictor of all-cause

### TABLE 2. Stepwise Linear Regression Analyses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression Coefficient</th>
<th>SE</th>
<th>β</th>
<th>P</th>
<th>R² Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aortic PWV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables excluded: gender, BMI, total cholesterol, HR, MAP, and triglycerides (R²=0.81, P&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.120</td>
<td>0.012</td>
<td>0.667</td>
<td>&lt;0.001</td>
<td>75</td>
</tr>
<tr>
<td>Global endothelial function</td>
<td>−2.221</td>
<td>0.590</td>
<td>−0.258</td>
<td>&lt;0.001</td>
<td>4</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.574</td>
<td>0.230</td>
<td>0.125</td>
<td>0.015</td>
<td>2</td>
</tr>
<tr>
<td><strong>Augmentation index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables excluded were gender, total cholesterol, smoking, and BMI (R²=0.69; P&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.446</td>
<td>0.050</td>
<td>0.478</td>
<td>&lt;0.001</td>
<td>57</td>
</tr>
<tr>
<td>Global endothelial function</td>
<td>−8.177</td>
<td>1.630</td>
<td>−0.239</td>
<td>&lt;0.001</td>
<td>5</td>
</tr>
<tr>
<td>Height</td>
<td>−0.336</td>
<td>0.072</td>
<td>−0.195</td>
<td>&lt;0.001</td>
<td>3</td>
</tr>
<tr>
<td>HR</td>
<td>−0.308</td>
<td>0.067</td>
<td>−0.181</td>
<td>&lt;0.001</td>
<td>3</td>
</tr>
<tr>
<td>MAP</td>
<td>0.230</td>
<td>0.065</td>
<td>0.164</td>
<td>0.001</td>
<td>1</td>
</tr>
<tr>
<td><strong>Aortic PWV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables excluded: MAP, gender, BMI, total cholesterol, HR, smoking, baseline arterial diameter, and NTG-mediated vasodilatation (R²=0.21; P&lt;0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Conduit artery</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelial function</td>
<td>−0.221</td>
<td>0.076</td>
<td>−0.362</td>
<td>&lt;0.01</td>
<td>14</td>
</tr>
<tr>
<td>Age</td>
<td>0.030</td>
<td>0.014</td>
<td>0.259</td>
<td>0.05</td>
<td>7</td>
</tr>
</tbody>
</table>

**Figure 3.** Influence of age and endothelial function on aortic PWV. Endothelial function refers to the ratio of response to albuterol versus NTG, with quartile 4 representing superior and quartile 1 representing inferior endothelial function. There were no individuals in the highest quartile of age in whom endothelial function was also in the highest quartile.
mortality in patients with cardiovascular disease than peripheral pressure. Moreover, we have shown previously that assessing peripheral pulse pressure does not always provide a reliable estimate of central (aortic) pulse pressure. To explore further the relationship between endothelial function and large artery stiffness and wave reflection, we also assessed aortic PWV, which provides a robust measure of arterial stiffness, and AIx, which provides a composite measure of elastic plus muscular artery stiffness and wave reflection. Both of these indices are independent predictors of cardiovascular risk in selected patient populations. Global endothelial function was significantly and negatively correlated with aortic PWV and AIx. However, both indices are influenced by a number of factors, and to control for potential confounding influences, a multiple regression model was constructed for each parameter, including known or likely determinants of arterial stiffness and wave reflection. As expected, age was independently associated with aortic PWV, but there was also an independent, negative association with global endothelial function, indicating that as endothelial function declined, the aortic PWV increased. Indeed, this association was evident within each quartile of age in the present study. In addition, plasma glucose concentration was also independently associated with aortic PWV, suggesting that even in healthy individuals, glucose tolerance may influence arterial stiffness. Concerning AIx, age, gender, height, HR, and MAP were all independently associated, in line with previously published findings. However, global endothelial function emerged as an additional, independent determinant of AIx, suggesting that a decline in endothelial function in smaller, preressistance arteries may lead to enhanced wave reflection and a rise in AIx.

We also determined the relationship between aortic PWV and another, widely used method of assessing endothelial function, flow-mediated dilatation in the brachial artery (conduit artery endothelial function), in a separate group of healthy individuals. Flow-mediated dilatation emerged as a significant and independent determinant of aortic PWV, suggesting that as conduit artery endothelial function declines, large artery stiffness increases. Although flow-mediated dilatation is known to correlate with invasively measured coronary endothelial function, ultrasound-based measures of endothelial function require highly specialized equipment and operators, making them unsuitable for inclusion in large-scale population studies. In contrast, PWA coupled with administration of NTG and albuterol provides a simple and repeatable method with which to assess global endothelial function in large numbers of patients. Nevertheless, the observed relationship between flow-mediated dilatation and aortic PWV in the current study confirms our findings using NTG and albuterol and lends further support to our hypothesis that endothelial function is associated with large artery stiffness.

Limitations
Although global endothelial function was associated with arterial stiffness, aging also exerts a marked effect on both parameters, and the cross-sectional nature of the current study limits our ability to infer a causal relationship. Therefore, further studies are required to determine whether a decline in endothelial function per se leads to arterial stiffening. Also, we did not observe any independent relationship between cholesterol and arterial stiffness, which is perhaps surprising in light of previously published work from our laboratory and others, but may reflect the a priori exclusion of patients with hypercholesterolemia.

Perspectives
NO is a potent antiatherogenic molecule, and the importance of endothelial function as a surrogate marker of risk has become increasingly recognized following the results of studies in which endothelial dysfunction predicts all-cause and cardiovascular mortality. Arterial stiffening is also associated with a number of adverse hemodynamic effects, including a rise in central pulse pressure, as observed in the current study, leading to increased cyclic stress on the arterial wall, increased left ventricular afterload, and decreased myocardial perfusion. Interestingly, conditions associated with endothelial dysfunction, such as aging, smoking, hypercholesterolemia, hypertension, and diabetes, are also associated with increased arterial stiffness, suggesting that impaired NO bioavailability may be the link. Therefore, a more thorough understanding of the relationship among endothelial function, arterial stiffness, and wave reflections may promote better risk stratification and targeting of therapies, particularly those that restore NO bioavailability.

Conclusions
Endothelial function and large artery stiffness are independent determinants of all-cause and cardiovascular mortality. The results of the current study demonstrate that even in healthy individuals, a decline in global endothelial function is associated with increased aortic stiffness (PWV) and AIx. In addition, we have also shown that global endothelial function correlates more strongly with central, rather than peripheral pulse pressure. These data suggest that large artery stiffness and central hemodynamics are influenced by endothelial function and support our previous findings describing the importance of NO in the regulation of large artery stiffness in vivo. Therefore, therapeutic strategies that restore NO bioavailability may reduce arterial stiffness and its adverse cardiovascular consequences.

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Disclosures
None.

References


