Plasma norepinephrine is an independent predictor of vascular endothelial function with aging in healthy women

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Kaplon RE, Walker AE, Seals DR. Plasma norepinephrine is an independent predictor of vascular endothelial function with aging in healthy women. J Appl Physiol 111: 1416–1421, 2011. First published September 8, 2011; doi:10.1152/japplphysiol.00721.2011.—We tested the hypothesis that reductions in vascular endothelial function (endothelium-dependent dilation, EDD) with age are related to increases in sympathetic activity. Among 314 healthy men and women, age was inversely related to brachial artery flow-mediated dilation (FMD) (r = −0.30, P < 0.001), a measure of EDD, and positively related to plasma norepinephrine concentrations (PNE), a marker of sympathetic activity (r = 0.49, P < 0.001). Brachial FMD was inversely related to PNE in all subjects (r = −0.25, P < 0.001) and in men (n = 187, r = −0.17, P = 0.02) and women (n = 127, r = −0.37, P < 0.001) separately. After controlling for PNE (multiple regression analysis), brachial FMD remained significantly related to age in all subjects (r = −0.20, P < 0.001) and in men (r = −0.23, P < 0.01), but not women (r = −0.16, P = 0.06). Consistent with this, brachial FMD remained significantly related to PNE when controlling for age (r = −0.24, P < 0.01) and menopause status (r = −0.24, P < 0.01) in women. Indeed, PNE was the strongest independent correlate of brachial FMD in women after controlling for conventional cardiovascular disease risk factors (r = −0.22, P = 0.01). This relation persisted in a subset of women (n = 113) after further accounting for the effects of plasma oxidized low-density lipoprotein (P < 0.05), a circulating marker of oxidative stress. Endothelium-independent dilation was not related to age in either men or women (P > 0.05). These results provide the first evidence that EDD is inversely related to sympathetic activity, as assessed by PNE, among healthy adults varying in age. In particular, our findings suggest that sympathetic nervous system activity may be a key factor involved in the modulation of vascular endothelial function with aging in women.

endothelium-dependent dilation; flow-mediated dilation; oxidative stress

Moreover, several metabolic and cardiovascular disorders are associated with both increased resting sympathetic activity and reduced endothelium-dependent dilation (2, 5, 15, 27, 41, 42). Importantly, sympathetic activity increases with age in the absence of disease (35, 48). However, it is unknown if reductions in endothelium-dependent dilation with age are related to increases in sympathetic activity among healthy adults. If endothelium-dependent dilation and sympathetic activity are related with aging, it is possible that the nature of the relation may not be the same for men and women. Although endothelium-dependent dilation decreases on average with age in both men and women, it is possible that some of the factors involved may differ between the sexes (32, 33), as they do for other forms of vascular dysfunction with aging (9, 29).

In the present study we tested the hypothesis that reductions in endothelium-dependent dilation with age are related to increases in sympathetic activity among healthy men and women. To do so, we assessed brachial artery flow-mediated dilation (FMD), a measure of endothelium-dependent dilation (3), and plasma norepinephrine (PNE), a marker of sympathetic activity (35, 48), in a large group of adults varying in age, but free of metabolic and cardiovascular disease. We first determined the simple relations among age, brachial FMD, and plasma norepinephrine in the overall group and separately in men and women. We then assessed the independent effects of PNE on brachial FMD using multiple regression and partial correlation analyses. Finally, we examined the potential role of oxidative stress by assessing the influence of plasma oxidized low-density lipoprotein (LDL), a circulating marker of oxidant modification of lipids (6).

METHODS

Subjects. A cohort from our laboratory database (n = 314) previously assessed for endothelial function were used for the analysis. All subjects were healthy, nonsmoking adults (187 men, 127 women) between the ages of 18 and 79 yr who were free of clinical disease as assessed by medical history, physical examination, blood chemistry, electrocardiogram, resting blood pressure, and cardiovascular responses to a graded exercise test. Subjects were not taking medications and refrained from all dietary supplements for 2 wk prior to participation in the study. All procedures were approved by the Institutional Review Board at the University of Colorado at Boulder. The nature, risks, and benefits of all study procedures were explained to volunteers and their written informed consent was obtained before participation in the study.

Procedures. All testing was performed at the Clinical Translational Research Center (CTRC) at the University of Colorado at Boulder following a 12-h fast from food and caffeine and 24-h abstention from exercise and alcohol. All premenopausal women were tested during the low follicular phase of the menstrual cycle to account for possible confounds of circulating reproductive hormones. Postmenopausal status was confirmed by follicular stimulating hormone levels > 40 IU/L.

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**Subject characteristics.** Arterial blood pressure was measured over the brachial artery during seated rest using a semiautomated device (Dynmap pro 100, GE, Health Care). Total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and fasting glucose were measured using standard assays, and plasma norepinephrine by high-performance liquid chromatography (BioRad Laboratories) at the University of Colorado CTRC core laboratory. Plasma oxidized LDL was assessed by ELISA (ALPCO) as described previously (19, 20, 43). All blood samples were drawn from an intravenous catheter placed in the left antecubital fossa. Blood samples for norepinephrine measurements were drawn after 20 min of supine rest. Habitual physical activity levels were calculated from estimates of daily energy expenditure using the Stanford Physical Activity Questionnaire (34).

**Duplex ultrasonography (Power Vision 6000, Toshiba; multi-frequency linear-array transducer) was used to assess brachial artery FMD and endothelium-independent dilation (i.e., brachial artery dilation in response to 0.4 mg sublingual nitroglycerin) as described previously by our laboratory (12, 19, 20). To ensure subject safety, endothelium-independent dilation was only assessed in individuals with a systolic blood pressure ≤ 160 mmHg. FMD measurements were reported as absolute and percent change in accordance with recent guidelines (10, 16). In a subset of subjects (men: n = 48, women: n = 30), peak hyperemic shear rate was calculated as (4 × time-averaged peak velocity/occlusion diameter based on a small, centered sample volume from the first 10 velocity envelopes (first 15 s) following cuff release per recent recommendations (16).

**Data analysis.** Statistical analyses were performed in SPSS (IBM SPSS Statistics 19). The strength of the linear relations between age, PNE, and brachial FMD were assessed using Pearson product-moment correlation analyses. Differences in correlation coefficients were assessed using Fisher’s z-transformation. Multiple linear regression analysis was used to further assess relations while controlling for additional variables. Partial correlation analysis was used to statistically remove such variables and assess the independent bivariate relation of interest. Statistical significance was set at P < 0.05.

### RESULTS

**Clinical characteristics of subjects.** Clinical and vascular characteristics are presented in Table 1 and Table 2, respectively. Mean PNE concentrations were 243 ± 3 pg/ml for all subjects, 220 ± 8 pg/ml for men, and 275 ± 11 pg/ml for women. Plasma oxidized LDL was 55 ± 1, 58 ± 1, and 51 ± 2 U/l for all subjects, men, and women, respectively.

**Age-associated changes in brachial FMD and PNE.** In all subjects, age was inversely related to brachial FMD (%Δ: r = −0.30, P < 0.001; mmΔ: r = −0.31, P < 0.001) and positively related to PNE (r = 0.49, P < 0.001). These relations also were observed in men (FMD%Δ: r = −0.28, P < 0.001; FMDmmΔ: r = −0.31, P < 0.001; PNE: r = 0.50, P < 0.001) and women (FMD%Δ: r = −0.33, P < 0.001; FMDmmΔ: r = −0.31, P < 0.001; PNE: r = 0.51, P < 0.001) when assessed separately (Fig. 1).

Brachial FMD was inversely related to PNE in all subjects (%Δ: r = −0.25, P < 0.001; mmΔ: r = −0.29, P < 0.001) and in men (%Δ: r = −0.17, P = 0.02; mmΔ: r = −0.16, P = 0.03) and women (%Δ: r = −0.37, P < 0.001; mmΔ: r = −0.37, P < 0.001) separately (Fig. 2), although the relation trended toward being stronger in women than in men (P = 0.06). Baseline brachial artery diameter and peak shear rate were not related to age or PNE in men or women (P > 0.05 for all relations).

**Relation between brachial FMD and age when controlling for PNE.** In a multiple linear regression model, brachial FMD remained significantly related to age in all subjects (%Δ: r =

### Table 1. Clinical characteristics of subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>314</td>
<td>187</td>
<td>127</td>
</tr>
<tr>
<td>Age, yr</td>
<td>48 ± 1</td>
<td>47 ± 1</td>
<td>48 ± 2</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>117 ± 1</td>
<td>120 ± 1</td>
<td>113 ± 1</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>69 ± 1</td>
<td>71 ± 1</td>
<td>67 ± 1</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60 ± 1</td>
<td>59 ± 1</td>
<td>61 ± 1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.2 ± 0.2</td>
<td>26.0 ± 0.3</td>
<td>23.9 ± 0.3</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.84 ± 0.01</td>
<td>0.89 ± 0.01</td>
<td>0.76 ± 0.00</td>
</tr>
<tr>
<td>Physical activity, MET h/wk</td>
<td>68 ± 4</td>
<td>68 ± 4</td>
<td>69 ± 7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>191 ± 2</td>
<td>187 ± 3</td>
<td>198 ± 3</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>54 ± 1</td>
<td>47 ± 1</td>
<td>64 ± 1</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>115 ± 2</td>
<td>114 ± 2</td>
<td>116 ± 3</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>110 ± 3</td>
<td>125 ± 6</td>
<td>92 ± 4</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dl</td>
<td>90 ± 1</td>
<td>92 ± 1</td>
<td>88 ± 1</td>
</tr>
</tbody>
</table>

Data are means ± SE; HDL, high-density lipoprotein, LDL, low-density lipoprotein.

### Table 2. Vascular characteristics of subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow-mediated dilation, %Δ</td>
<td>6.1 ± 0.2</td>
<td>6.1 ± 0.2</td>
<td>6.3 ± 0.3</td>
</tr>
<tr>
<td>Flow-mediated dilation, mmΔ</td>
<td>0.22 ± 0.01</td>
<td>0.24 ± 0.01</td>
<td>0.19 ± 0.01</td>
</tr>
<tr>
<td>Baseline diameter, mm</td>
<td>3.69 ± 0.04</td>
<td>4.08 ± 0.04</td>
<td>3.12 ± 0.04</td>
</tr>
<tr>
<td>Peak hyperemic blood velocity, cm/s</td>
<td>45 ± 1</td>
<td>46 ± 1</td>
<td>45 ± 2</td>
</tr>
<tr>
<td>Peak shear rate, s⁻¹</td>
<td>438 ± 14</td>
<td>409 ± 15</td>
<td>484 ± 26</td>
</tr>
</tbody>
</table>

Data are means ± SE. Peak hyperemic blood velocity and shear rate assessed in subset of subjects [n (men/women) = 125/56 and 48/30, respectively].
Fig. 2. Relation between FMD and PNE in men (○) and women (●).

-0.20, \( P < 0.001 \); mmΔ: \( r = -0.19, P < 0.001 \) and in men (%Δ: \( r = -0.23, P < 0.01 \); mmΔ: \( r = -0.27, P < 0.001 \) after controlling for PNE. In contrast, the relation between brachial FMD and age no longer was significant in women after controlling for PNE (%Δ: \( r = -0.16, P = 0.06 \); mmΔ: \( r = -0.14, P = 0.10 \)). Consistent with this observation, brachial FMD remained significantly related to PNE when controlling for age in women (%Δ: \( r = -0.24, P < 0.01 \); mmΔ: \( r = -0.25, P < 0.01 \), but not men (\( P > 0.05 \)). Further controlling for menopause status (coded bivariate variable) in women did not affect the FMD-PNE relation (%Δ: \( r = -0.24, P < 0.01 \); mmΔ: \( r = -0.25, P < 0.01 \)). Menopause status was not independently predictive of FMD when controlling for age and PNE in women (\( P > 0.05 \)).

Relation between brachial FMD, age, and PNE when controlling for clinical characteristics. When controlling for clinical characteristics (age, menopause status, systolic blood pressure, diastolic blood pressure, body mass index, waist/hip ratio, physical activity, total cholesterol, HDL cholesterol, LDL cholesterol, and fasting glucose) in a multiple linear regression model, PNE remained a significant independent predictor of FMD in women (%Δ: \( r = -0.22, P = 0.01 \); Table 3; mmΔ: \( r = -0.25, P < 0.01 \)). Indeed, PNE was a stronger independent predictor of FMD in women than any other clinical factor assessed. Accounting for the same clinical characteristics in men did not affect the relation between PNE and FMD (\( P > 0.05 \)), but weakened the association between age and FMD (\( P > 0.05 \); Table 3).

Influence of plasma oxidized LDL on the brachial FMD-PNE relation in women. Because brachial FMD and PNE remained inversely related when controlling for clinical characteristics in women, we sought to determine if the strength of this relation persisted after further accounting for oxidized LDL, a circulating marker of oxidative stress. As in the overall group of women, PNE was an independent predictor of brachial FMD when controlling for all factors shown in Table 3 in the large subset of women on whom plasma oxidized LDL values were available (%Δ: \( r = -0.19, P < 0.05 \); mmΔ: \( r = -0.21, P < 0.05, n = 113 \)). PNE remained an independent correlate of brachial FMD after further accounting for the effect of plasma oxidized LDL in this group (\( P < 0.05 \)).

Brachial artery endothelium-independent dilation. Endothelium-independent dilation, a measure of brachial artery vascular smooth muscle responsiveness to nitric oxide, was not related to age in the overall group or in men or women (\( P > 0.05 \)). Endothelium-independent dilation was positively related to PNE in men (%Δ: \( r = 0.21, P = 0.04 \); mmΔ: \( r = 0.22, P = 0.02 \), but not women (%Δ: \( r = 0.09, P = 0.52 \); mmΔ: \( r = 0.01, P = 0.93 \); Fig. 3). Endothelium-independent dilation did not contribute to the lack of an independent relationship between FMD and PNE when accounting for age in men (data not shown).

**DISCUSSION**

This is the first study to report that vascular endothelial function is related to an index of sympathetic nervous

| Table 3. Multiple linear regression analysis assessing the independent influence of plasma norepinephrine (PNE), age and clinical characteristics on brachial flow-mediated dilation (%Δ) |
|----------------|----------------|----------------|
| Variable       | Women          | Men            |
|                | \( r \)        | \( P \)        | \( r \)        | \( P \)        |
| PNE, pg/ml     | -0.22          | 0.01           | -0.05          | 0.54           |
| Age, yr        | -0.08          | 0.39           | -0.09          | 0.24           |
| Menopause status, pre/post | 0.03  | 0.74           |               |                |
| Systolic blood pressure, mmHg | 0.04  | 0.68           | -0.09          | 0.24           |
| Diastolic blood pressure, mmHg | -0.08 | 0.38           | 0.04           | 0.62           |
| Body mass index, kg/m² | -0.07 | 0.45           | <0.00          | 0.99           |
| Waist/hip ratio | 0.12  | 0.17           | -0.04          | 0.58           |
| Physical activity, MET h/wk | -0.04 | 0.67           | 0.11           | 0.15           |
| Total cholesterol, mg/dl | 0.06  | 0.51           | -0.02          | 0.77           |
| HDL cholesterol, mg/dl | -0.10 | 0.26           | <0.00          | 1.00           |
| LDL cholesterol, mg/dl | -0.06 | 0.48           | 0.02           | 0.82           |
| Fasting blood glucose, mg/dl | -0.05 | 0.53           | -0.10          | 0.19           |

HDL, high-density lipoprotein, LDL, low-density lipoprotein.

Fig. 3. Relation between endothelium-independent dilation (brachial dilation to nitroglycerin [NTG]) and PNE in men (top) and women (bottom).
system activity in individuals free from clinical disease. Specifically, we found brachial artery FMD, a measure of endothelium-dependent dilation (3), was inversely related to PNE, a commonly used marker of sympathetic activity (35, 48), in an overall group of healthy adults aged 18–79 yr. This also was the case in men and women when analyzed separately, with the relation tending to be stronger in women than in men. The inverse relation between brachial FMD and age in women no longer was significant after accounting for the influence of PNE, whereas there was no effect of PNE on the brachial FMD-age relation in men. Importantly, our results indicate that PNE is an independent predictor of brachial FMD across age and menopause status in women and is a stronger correlate of FMD than any clinical characteristic in that group, including conventional risk factors for cardiovascular diseases. Finally, we found that the independent association between brachial FMD and PNE in women was not related to either plasma oxidized LDL, a circulating marker of oxidative stress, or brachial artery dilation to nitroglycerin, a measure of vascular smooth muscle sensitivity to nitric oxide.

**Brachial FMD, PNE, and age.** The relation between baseline brachial FMD and PNE in the present study is consistent with previous findings showing reductions in endothelium-dependent dilation in response to experimental sympathetic activation in young subjects and the fact that endothelium-dependent dilation and sympathetic activity are inversely associated in patients with clinical disorders (2, 5, 11, 15, 18, 25, 27, 41, 42). A recent study also reported an inverse relation between muscle sympathetic activity and nonspecific peripheral vascular function in a small cohort of healthy adults (37) and, in rodents, changes in α-adrenergic vascular tone modulate endothelium-dependent dilation in skeletal muscle arterioles (8, 21). Our results extend these findings by showing for the first time that a well-established measure of vascular endothelial function is inversely related to a commonly used marker of sympathetic activity among individuals free of clinical disease.

The inverse relation between brachial FMD and PNE in the overall group was primarily driven by the strength of this relation in women. As a result, controlling for the influence of PNE in women was sufficiently strong as to render the relation between age (or menopause status) and brachial FMD nonsignificant. Moreover, in contrast to men, PNE was an independent predictor of brachial FMD in women and, in fact, was a stronger independent correlate than conventional cardiovascular disease risk factors. In men, no clinical characteristic was found to be a significant independent predictor of FMD. These findings further support the idea that the factors modulating vascular endothelial function with aging in women may, in some cases, differ from those in men (9, 29). In particular, the present results suggest that increases in sympathetic activity might contribute independently to age-associated endothelial dysfunction in women, but not men.

**Mechanisms.** The mechanisms by which sympathetic activity (PNE) might influence endothelium-dependent dilation more in women than men cannot be completely discerned from the present analysis. That plasma oxidized LDL had no influence on the independent relation between brachial FMD and PNE in women does not support an obvious role for oxidative stress. However, experimental manipulation of reactive oxygen species bioavailability (e.g., via antioxidant administration) would be required to more definitively assess this mechanism. Our data also indicate that brachial artery dilation to nitroglycerin, a nitric oxide donor, is not related to age in either men or women, or to PNE in women. This finding suggests that the inverse relation between brachial FMD and PNE in women is mediated by factors associated with production of dilatory molecules by vascular endothelium per se (e.g., nitric oxide) rather than the responsiveness of vascular smooth muscle to nitric oxide.

It is possible that sympathetic-adrenergic vasoconstrictor mechanisms counteracting endothelium-dependent dilation are greater in women compared with men. For example, sympathetic activity may have been greater in this mixed cohort of pre- and postmenopausal women compared with the men based on their higher mean PNE concentrations. Moreover, the slope of the increase in PNE with age trended toward being greater in women than men. As such, a higher sympathetic “background” may have led to a stronger tonic inhibition of brachial FMD. Another possibility is a greater vasoconstrictor influence in women for a given level of tonic sympathetic stimulation. Although some evidence for this exists in middle-aged and older women (26, 30), we found no differences in vasoconstriction to α-adrenergic stimulation between premenopausal women and men during ganglionic blockade (7). Furthermore, under basal conditions, young women demonstrate less sympathetic vasoconstriction to exogenous norepinephrine than men and this is due, in part, to higher β-adrenergic-mediated dilation (17, 22). Decreases in β-adrenergic receptor expression and/or affinity with age may potentiate sympathetic vasoconstriction in women. Indeed, β2-adrenergic receptor density is modulated by female sex hormones in vivo (44). Finally, because brachial FMD is mediated by endothelium-synthesized dilating molecules (nitric oxide, prostaglandins, and hyperpolarizing factors), it also is possible that the interaction between sympathetic-adrenergic constrictor signaling and these dilating molecules differs in men and women.

**Endothelium-independent dilation and PNE in men.** Although dilation to sublingual nitroglycerin was not related to PNE in women, a modest positive, rather than inverse, relation was observed in men. It is possible that this represents a compensatory response to the suppressive influence of sympathetic activity on brachial artery FMD. If so, it is unclear why a similar response was not observed in women.

**Limitations.** The present study used correlation analysis in a large group of healthy adults as an initial probe to determine if vascular endothelial function might be related to sympathetic activity. Functional studies involving inhibition of sympathetic activity and/or α-adrenergic receptor signaling would be required to more definitively assess sex-specific relationships between brachial FMD, sympathetic activity, and age. However, such studies are not feasible in a large cohort of subjects, and the present findings serve to provide important initial experimental insight upon which to base future work requiring more invasive procedures.

Individual variables assessed in this analysis, including PNE, only explained a relatively small amount of the total variance in brachial FMD. However, it is difficult to find significant relations between vascular function and factors that potentially modulate that function in large, highly

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diverse cohorts of human subjects because of 1) the substantial variability between individuals; and 2) the inherent measurement error associated with physiological assessments in humans. Consequently, the present analysis likely underestimates the true physiological significance of the reported relations.

The present study used brachial artery FMD as a noninvasive measure of conduit artery endothelial function (endothelium-dependent dilatation) and PNE as a minimally invasive marker of sympathetic activity. Invasive methods are available to assess microvascular endothelial function in humans (i.e., forearm blood flow responses to brachial artery infusion of acetylcholine), and the limitations of interpreting PNE as a measure of sympathetic activity compared with more invasive, direct techniques are widely appreciated (13, 35, 39). For example, PNE concentrations are influenced by the rate of metabolic clearance of norepinephrine. Although norepinephrine clearance is reduced with age in both men and women, there is no evidence that these changes differ between sexes (28, 35, 40), suggesting further that our results were most likely due to differences in norepinephrine appearance and sympathetic activity. Moreover, PNE correlates with more invasive measures of sympathetic activity among healthy adults differing in age (31), and we were able to show relations between brachial FMD, PNE, and age despite such limitations.

Finally, circulating estrogen, which exerts a tonic modulatory effect on endothelial vasodilatory responsiveness (1, 14, 45), was not measured in a sufficient number of the women to assess the potential influence of this factor. However, menopause status, as objectively assessed by follicular stimulating hormone levels, did not affect the strong relation between FMD and PNE in women.

Conclusions. Our findings provide the first evidence that endothelium-dependent dilatation is inversely related to sympathetic activity, as assessed by PNE, among healthy adults varying in age, particularly in women. PNE was the strongest independent predictor of brachial FMD in women in the present study, and correction for PNE abolished the relation between brachial FMD and age in this group. Overall, the present results suggest that sympathetic nervous system activity may represent one of several key factors involved in the modulation of vascular endothelial function with primary aging (36), especially in women.

GRANTS
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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES
AGING, ENDOTHELIAL FUNCTION, AND SYMPATHETIC ACTIVITY


