Endothelin-1 Gene LYS198ASN Polymorphism and Blood Pressure Reactivity

Frank A. Treiber, Paule Barbeau, Gregory Harshfield, Hyun-Sik Kang, David M. Pollock, Jennifer S. Pollock, Harold Snieder

Abstract—The Lys198Asn polymorphism of the endothelin-1 gene has been associated with increased blood pressure levels in several studies involving European and Australian adults. The purpose of the present study was to examine the potential moderating influence of ethnicity, obesity, and socioeconomic status on associations between the ET-1/Lys198Asn polymorphism and hemodynamic function at rest and during two laboratory stressors (video game, forehead cold) in a sample of 161 black and 213 white American normotensive young adults (mean age, 18.5±2.7 years). Carrier status of the T allele was not associated with resting blood pressure or total peripheral resistance index. However, carriers of the T allele showed greater diastolic blood pressure increases to the video game (P<0.04), particularly among those who were obese (P<0.02). Carrier status also interacted with socioeconomic status such that T allele carriers who came from lower socioeconomic status backgrounds exhibited the greatest increases in systolic blood pressure to the video game challenge (P<0.05). In conclusion, the findings point out the importance of examining the impact of genetic polymorphisms on blood pressure control phenotypes within the context of potentiating environmental factors.

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Key Words: endothelin ■ genetics ■ blood pressure ■ socioeconomic factors ■ obesity

Endothelin-1 (ET-1) is a potent vasoconstrictor peptide produced by endothelial and vascular smooth muscle cells. It has been implicated in the development of essential hypertension (EH) because of its vasoconstrictive and hypertrophic actions on vascular function. Recent evidence suggests that the role of behavioral stress is pivotal in mediating the adverse effects of ET-1 on vascular function. A 3-minute reaction time task was shown to induce prolonged endothelial dysfunction, which was prevented by a selective endothelin-A receptor antagonist.

Light proposed a gene-by-environment interaction model of stress reactivity for EH development. The model is based on animal studies that found frequent stress exposure resulting in periods of elevated blood pressure (BP) eventuates in EH only in conjunction with a genetic predisposition or with additional potentiating environmental factors. Thus, similar to animal model studies, individuals exposed to frequent environmental stress, such as those from lower socioeconomic status (SES) or black Americans, who also have a genetic susceptibility for EH (eg, family history of EH, EH candidate gene polymorphisms) or are exposed to other potentiating factors (eg, high salt/fat diet) will be most likely to show the greatest BP reactivity to stress and to eventually have EH.

The ET-1 gene is localized on chromosome 6, spans 5.5 kb, and contains 5 exons and 4 introns. It has been identified as a candidate gene for cardiovascular disease, including EH. A G-to-T transversion predicting a lysine-asparagine change at amino acid 198 (Lys198Asn) has been associated with increased resting BP levels in several cohorts of middle-aged adults. In a sample of white 25 to 64 year olds, systolic and diastolic BP were higher in carriers of the T allele compared with the GG homozygotes, but only in those who were overweight (ie, BMI >25 kg/m²). In a second cohort of British 25 to 74 year olds, subjects homozygous for the T allele had higher resting systolic and diastolic BP levels than others, independent of obesity status. Within a subsample that participated in a treadmill exercise task, carriers of the T allele who were obese exhibited the greatest increase in BP. A recent study involving middle-aged Japanese subjects found that among obese individuals (ie, body mass index [BMI] >25 kg/m²), carriers of the T allele exhibited higher diastolic BP compared with noncarriers. Iglarz et al confirmed the impact of the Lys198Asn polymorphism on vascular reactivity. They investigated phenylephrine-induced tone and its amplification by ET-1 and angiotensin II in human mammary artery rings in vitro and found that a subthreshold concentration of ET-1 potentiated a phenylephrine-induced vasoconstriction that was significantly higher in carriers of the T allele.

Associations between the Lys198Asn polymorphism and hemodynamic function at rest and/or in response to acute
stressors have not been examined in black Americans. Such an examination would be informative, since black Americans have a high prevalence of EH and their BP control abnormalities are frequently associated with increased vasoconstrictive tone. Studies involving normotensive youth and young adults found that black Americans compared with white Americans often have higher levels of BP at rest and greater BP increases in response to a variety of physical and psychological stressors. These ethnicity differences in BP were often due to higher levels and/or greater increases in total peripheral resistance (TPR) in the black Americans. Importantly, we recently found that black Americans compared with white Americans have higher basal levels and greater release of plasma ET-1 in response to acute behavioral stressors.

Few studies have examined the functional relations between this polymorphism and plasma ET-1 levels. Barden et al found that T-allele carrier status related to higher levels of both resting SBP and plasma ET-1, controlling for adiposity among women during pregnancy but not after birth. Thus, we evaluated plasma ET-1 and nitrite/nitrate (NOx), metabolites of nitric oxide (NO) in a cohort of young white Americans and black Americans with family history of cardiovascular disease. An index of NO (NOx) was measured because it represents a major counterregulatory vasodilatory agent that may serve to balance the vasoconstrictor actions of ET-1. Therefore, the ratio of ET-1 to NOx would be an indication of vasoconstrictor capacity.

The purpose of this study was to determine whether the ET-1/Lys198Asn polymorphism, particularly in combination with potentiating environmental backgrounds, would be associated with hemodynamic function at rest and in response to acute behavioral stress in a multiethnic sample of normotensive youth free of clinical disease. We hypothesized that carriers of the Asn (or T) allele in combination with being black, overweight, or of lower SES would show the highest levels of BP and TPR index (TPRI) as well as ET-1 and ET-1/NOx at rest and in response to stress.

Methods

Study Population
A total of 374 subjects (213 white Americans, 161 black Americans; average age, 18.6 ± 2.7 years) participated in the laboratory visit. Subjects are among participants in a longitudinal study of the development of biobehavioral risk factors for cardiovascular diseases. All have a verified family history of cardiovascular disease (ie, EH and/or premature myocardial infarction).

Protocol
The study was approved by the institutional review committee. After obtaining informed consent, subjects underwent a battery of anthropometric evaluations including height (cm) and weight (kg), with the use of established protocols. Subjects also completed a brief battery of lifestyle questionnaires assessing stressful life events, physical activity, smoking, drug usage, and anger coping styles. Subjects were prepared for the hemodynamic evaluations through the use of the Dinamap vital signs monitor (model 1864SX; Critikon) and the NCCOM-3 (BoMed Medical Manufacturing, Ltd) continuous thoracic bioimpedance monitor, which measured heart rate and cardiac output. An appropriately sized BP cuff was placed on the right arm. Cardiac output was indexed by body surface area (ie, cardiac index), which was used to calculate TPRI as mean arterial pressure/cardiatic index. The Dinamap BP monitor has been validated for use at rest and during laboratory stressors. The thoracic bioimpedance instrument has been shown to provide accurate measures of relative changes in cardiac output, but absolute levels are less accurate. To help alleviate this drawback, echocardiographic data were collected while the subject was resting, and bioimpedance-derived stroke volumes were adjusted through the use of echo-derived stroke volumes at the same heart rate for each subject. Although the impedance-derived estimates of resting TPRI were comparable to the echo-derived estimates, the echo-derived estimates were used in the analyses of resting levels.

After instrumentation for hemodynamic evaluation was completed, the subjects were placed in supine position on a hospital bed. A 5-mL blood sample was drawn from the left arm and transferred to a 10-mL EDTA Vacutainer and maintained on ice. Blood was centrifuged at 4°C; plasma was collected and stored at −80°C. Buccal cell sampling from cheek cells was conducted through the use of a standard protocol in subjects for whom blood was not obtained.

Hemodynamic Evaluations and Blood Collection
Subjects rested for 20 minutes after the blood draw. During minutes 13, 15, 17, and 19 of this period, hemodynamic measurements (systolic and diastolic BP [SBP, DBP] and TPRI) were recorded. After baseline evaluation, the subjects engaged in the video game challenge and then the forehead cold stimulation in a supine position with the use of standardized protocols. Since the left arm was used for blood drawing, all subjects used their right hand (ie, primarily thumb and index finger) to play the video game. Stressor presentation was not counterbalanced because previous research has indicated significant variability in hemodynamic recovery rates to the cold stressor. Hemodynamic measurements were obtained immediately before each stressor and at minutes 1, 3, 5, 7, and 9 of the video game task and at completion of the 1-minute forehead cold stressor.

A subgroup (n = 215) had ET-1 and NO assays completed by using 5-mL blood samples drawn concurrent with the hemodynamic measurements immediately before and after each stressor. Plasma ET-1 levels were measured by ELISA (Quanti-Glo; R&D Systems), based on manufacturer’s recommendations, except the standard curve had a maximum of 6 pg/mL. Reported cross-reactivity of the antibody was <0.02% for all big ET isoforms, 7.8% for ET-3, and 27.4% for ET-2. All samples and standards were processed in duplicate. Unknown sample data were fitted to a standard curve with commercially available software (Prism 2.0; Graph Pad Software). Intra-assay variability was 4.27%.

Plasma samples for NOx were thawed and protein precipitated by the addition of 2.0N NaOH (0.2 mL) and 40% ZnSO4 (0.2 mL). Samples were vortexed and centrifuged within 15 minutes at 1000g at 4°C. The supernatant was removed for nitrite/nitrate (NOx) analysis. NOx analysis was accomplished with a Sievers NO analyzer (Ionics Instruments). The sensitivity of the assay was ~1 picomole. The coefficient of variation was 5.4%.

Genotyping
Genomic DNA was extracted from plasma buffy coats and buccal cells by using QiaAmp DNA Blood Mini Kits (Qiagen). The extracted DNA was stored at −80°C until analyzed. The Lyn/Asn amino acid change at codon 198 of the ET-1 gene was detected by polymerase chain reaction (PCR) followed by direct sequence analysis, as previously described elsewhere with modifications (Tiret et al, http://genecanvas.idf.inserm.fr/gene.asp-gene=EDN1.htm).

Statistical Analyses
Results are expressed as mean ± SD. Allele and genotype frequencies in black Americans and white Americans were compared by using χ2 analyses. Subjects were classified as overweight versus nonoverweight, based on BMI ≥85th percentile for age and gender. Subjects were classified as lower versus higher SES, based on their mother’s years of education (ie, high school degree or less, lower SES). Mother’s educational level was chosen because 25% of
subjects came from single-parent, mother-head-of-household families. It should be noted that comparable results were observed when the father’s education level was used as the index of SES. Lower SES subjects reported a greater number of stressful life events over the previous year compared with those classified as higher SES (P<0.05). As illustrated in Figure 1, among noncarriers of the T allele, SES status had little impact, whereas among carriers, the individuals from lower SES backgrounds (43% versus 32%, P<0.01). There was not a significant ethnicity difference in height (P>0.77). A slightly greater percentage of black Americans compared with white Americans came from lower SES backgrounds (43% versus 32%, P<0.03).

Genotype frequencies portrayed in Table 2 were in Hardy-Weinberg equilibrium in black Americans and white Americans and were not significantly different between black Americans and white Americans (P>0.50). Allele frequencies for the T allele were 24.9% and 22.0% in white Americans and black Americans, respectively, which was not significantly different (P=0.36).

### Hemodynamic Findings

#### Resting Hemodynamics

Significant ethnicity differences were observed for all three hemodynamic measures at rest (all P<0.01). As depicted in Table 1, black Americans had higher levels than white Americans on each parameter (ie, SBP, DBP, TPRI). Individuals classified as being overweight had, on average, a 2.4-mm Hg lower resting DBP than the nonoverweight individuals (P<0.01). Men had higher resting SBP and DBP than women (both P<0.01). There were no other significant main or interaction effects (all P>0.08).

#### Video Game Reactivity

Men had significantly greater increases in SBP (15.9 versus 10.7 mm Hg, P<0.001), DBP (11.3 versus 9.8 mm Hg, P<0.02), and TPRI (4.5 versus 3.2 mm Hg/L/min/m², P<0.001), compared with women in response to the video game. A significant ET-1 genotype by SES interaction was observed for SBP reactivity (P<0.05). As illustrated in Figure 1, among noncarriers of the T allele, SES status had little impact, whereas among carriers, the individuals from

### Table 1. Descriptive Statistics by Carrier Status and Ethnicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Noncarrier</th>
<th>Carrier</th>
<th>EA</th>
<th>AA</th>
</tr>
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<td>n</td>
<td>213</td>
<td>161</td>
<td>213</td>
<td>161</td>
</tr>
<tr>
<td>Age, y</td>
<td>18.5±2.7</td>
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<td>18.1±2.7</td>
<td>19.0±2.6</td>
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<tr>
<td>Height, cm</td>
<td>170.8±9.5</td>
<td>170.2±9.4</td>
<td>170.7±9.9</td>
<td>170.4±8.7</td>
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<td>Weight, kg</td>
<td>70.6±17.5</td>
<td>72.3±19.7</td>
<td>68.1±15.9†</td>
<td>75.7±20.7</td>
</tr>
<tr>
<td>BMI</td>
<td>24.1±5.4</td>
<td>24.9±6.3</td>
<td>23.3±4.8†</td>
<td>26.0±6.7</td>
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<tr>
<td>Ethnicity, % black</td>
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<td>39.8</td>
<td>0</td>
<td>100</td>
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<td>SES, % upper</td>
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<td>35</td>
<td>32*</td>
<td>43</td>
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<tr>
<td>Obese, %</td>
<td>30</td>
<td>35</td>
<td>26†</td>
<td>39</td>
</tr>
<tr>
<td>Resting SBP, mm Hg</td>
<td>112.9±10.8</td>
<td>112.1±11.1</td>
<td>110.3±9.9†</td>
<td>115.5±11.5</td>
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<tr>
<td>Resting DBP, mm Hg</td>
<td>62.2±7.2</td>
<td>61.0±7.9</td>
<td>59.7±6.4†</td>
<td>64.3±8.1</td>
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<td>Resting TPRI, mm Hg/L/min/m²†</td>
<td>32.1±6.8</td>
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<td>Resting ET-1 level, pg/ml§</td>
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<td>1.06±0.41</td>
<td>1.36±0.53†</td>
<td>1.7±0.68</td>
</tr>
<tr>
<td>Resting NOx level, µL</td>
<td>22.9±7.4</td>
<td>23.6±9.1</td>
<td>23.2±7.6</td>
<td>23.3±9.3</td>
</tr>
<tr>
<td>Resting ET-1/NOx ratio</td>
<td>0.048±0.025</td>
<td>0.051±0.038</td>
<td>0.046±0.023*</td>
<td>0.056±0.044</td>
</tr>
</tbody>
</table>

* Data are expressed as mean±SD.
† Derived using echocardiographic-measured stroke volume; §n=180 for noncarriers, 137 for carriers.

### Table 2. Allele and Genotype Frequencies by Ethnicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alleles</th>
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<th>Frequencies, %</th>
<th>Whites</th>
<th>Frequencies, %</th>
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</thead>
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<td></td>
<td>G</td>
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<td>78.0</td>
<td>320</td>
<td>75.1</td>
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<tr>
<td></td>
<td>T</td>
<td>71</td>
<td>22.0</td>
<td>106</td>
<td>24.9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>322</td>
<td>426</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carriers of T allele</td>
<td>64</td>
<td>39.8</td>
<td>97</td>
<td>45.5</td>
<td></td>
</tr>
<tr>
<td>Noncarriers of T allele</td>
<td>97</td>
<td>60.2</td>
<td>116</td>
<td>54.5</td>
<td></td>
</tr>
</tbody>
</table>
lower SES backgrounds showed greater increases in response to the behavioral challenge. Carriers of the T allele had greater DBP reactivity than noncarriers (P<0.04). Similarly, obese individuals had greater DBP reactivity than nonobese individuals (P<0.04). An ET-1 genotype by obesity interaction was observed (P<0.02). Figure 2 portrays this interaction, which showed that among noncarriers of the T allele, obesity status had little impact on reactivity, whereas among carriers of the T allele, obese individuals had greater increases in DBP. Finally, there was a trend for a similar interaction pattern involving obesity and carrier status (P=0.059) for TPRI reactivity such that among carriers of the T allele, obese individuals showed greater TPRI increases (4.4 versus 3.1 mm Hg·L⁻¹·min⁻¹·m²). There were no other main or interaction effects in response to the video game stressor (all P>0.06).

**Forehead Cold Reactivity**

Men showed greater increases in SBP (19.6 versus 16.2 mm Hg, P<0.02) and TPRI (11.3 versus 9.8 mm Hg/L per minute per m², P<0.02) than women in response to forehead cold. Blacks had greater increases in DBP (6.3 versus 5.6 mm Hg, P<0.05) and TPRI (11.5 versus 9.9 mm Hg/L per minute, P<0.05) than white Americans. No other main or interaction effects were observed (all P>0.07).

**Plasma ET-1 and NOx Findings**

**Resting Levels**

To better examine the balance between the ET and NO systems, we evaluated ET-1/NOx ratios in addition to ET-1 and NOx. As shown in Table 1, black Americans showed higher resting plasma ET-1 concentrations (P<0.01) and ET-1/NO ratio levels (P<0.04) compared with white Americans. No other main or interaction effects were observed (all P>0.08).

**Video Game Reactivity**

Men had greater increases in plasma ET-1 compared with women (0.17 versus 0.06, pg/mL, P<0.01). No other main or interaction effects were observed (all P>0.10).

**Forehead Cold Reactivity**

An ET-1 genotype by obesity status interaction was observed for ET-1 increases to the cold pressor test (P<0.02). As shown in Table 3, among nonobese subjects, carrier status had little impact on ET-1 changes. However, among obese subjects, noncarriers had greater increases in ET-1 compared with carriers of the T allele. Table 3 also notes a similar pattern for the ET-1/NOx ratio results in which an ET-1 genotype effect (P<0.01) was qualified by an interaction involving obesity (P<0.01). That is, among nonobese individuals, carrier status had little impact on ET-1/NOx ratio. However, among obese individuals, noncarriers showed a large increase whereas carriers of the T allele showed a decrease in ET-1/NOx. A gender effect for ET-1/NOx ratio indicated that men produced greater ET-1 per amount of NOx release (0.84 versus 0.35, P<0.01). No other main or interaction effects were observed (all P>0.07).

**Discussion**

This study examined whether the Lys198Asn polymorphism in the ET-1 gene was associated with hemodynamics and plasma ET-1 and NOx levels at rest and changes in response to acute laboratory stressors in a sample of normotensive youth. The potential moderating influences of SES, obesity, and ethnicity on these associations were also examined. The allele frequencies were comparable to those previously reported in Irish, French, and Scottish adults and in a study involving Australian women. There were no ethnic differences in allele frequency, which, to our knowledge, has not been previously examined.

With regard to resting hemodynamic function, ethnicity differences were observed in which black Americans were found to have higher levels of SBP, DBP, and TPRI compared with white Americans. Men had higher resting SBP and
DBP than women. These findings corroborated a number of other studies that have found these patterns of ethnicity and gender differences, which have been noted to first occur in late childhood.12,14 There was no association between carrier status and resting hemodynamic measures nor any interactions involving carrier status. This finding is contrary to that of Tiret et al.,9 who observed that individuals with the T allele who were overweight had higher resting BP. Perhaps environmental factors have not had enough of a potentiating effect by late adolescence for this polymorphism to affect resting BP levels.

With regard to the laboratory stressors, ethnic differences were noted for the predominantly vasoconstrictive mediated stress of forehead cold stimulation in which black Americans had greater increases in DBP and TPRI compared with the white Americans. This finding corroborates previous studies involving the cold pressor in which black Americans have often been found to exhibit greater vasoconstrictive reactivity than white Americans.13,14,16 Consistent with previous pediatric and adult studies,13–15,25 men had greater vasoconstrictive-mediated increases in BP to both stressors.

The Lys198Asn polymorphism was associated with BP reactivity to the behavioral video game challenge, particularly in combination with several potentiating factors. That is, among noncarriers of the T allele, SES status had little impact on BP reactivity. However, carriers of the T allele who came from lower SES backgrounds had greater increases in SBP compared with those from higher SES backgrounds. Similarly, main effects of obesity and carrier status for DBP reactivity were qualified by an interaction such that among noncarriers of the T allele obesity status had little impact on reactivity, whereas among carriers of the T allele, overweight individuals had greater increases in DBP compared with nonobese individuals. These findings are supportive of the gene by environment reactivity hypothesis proposed by Light.5 That is, individuals carrying the T allele who were exposed to chronic environmental stress, as represented by a lower SES background, showed the greatest BP increases to the behavioral task. Obesity cannot be viewed as an entirely environmental potentiating factor but may represent sedentary behavior, a diet characterized by high caloric intake in combination with a genetic susceptibility to become obese. As we have recently proposed in our biobehavioral model of stress-induced hypertension, these findings point to the importance of inclusion of both genetic and environmental factors in stress-related models of EH rather than the typical evaluation of one component or the other.26

Although the findings are intriguing, they must be interpreted cautiously because of several limitations of the study. First, as noted earlier, the mechanistic pathways linking the Lys198Asn polymorphism with BP control have not been delineated. In the present study, the Lys198Asn polymorphism was not associated with plasma ET-1, NOx, or ET-1/NOx levels at rest. With respect to the stressors, changes in plasma ET-1, NOx, or the ET-1/NO ratio did not mirror the changes in hemodynamic variables. For example, although there were no significant effects of genotype and/or obesity status on hemodynamic changes in response to the cold pressor, genotype by obesity status interactions were observed for ET-1 and ET-1/NOx. Among obese individuals, noncarriers showed greater increases compared with carriers. Furthermore, the gene by environmental factor (ie, SES, obesity) interactions observed in BP reactivity to the video game challenge were not mirrored by changes in the vasoactive agents. It should be noted that since endothelin is excreted abuminally, serum levels may not be an accurate indicator of functional levels within the vascular smooth muscle.

As noted above, the underlying mechanism(s) responsible for how obesity in combination with the Lys198Asn polymorphism affected blood pressure reactivity to the behavioral video game challenge is unclear. Insulin resistance is a common problem in obesity, and both obesity and insulin resistance have been associated with increased BP reactivity to behavioral stress.27 One plausible mechanistic pathway noted earlier may be enhanced expression of the ET-1 gene through upregulation by insulin in obese individuals. Recent adult studies found plasma ET-1 concentrations increased in obese individuals compared with nonobese and obesity was a stronger correlate of plasma ET-1 levels than EH status.28,29 Interestingly, Barden et al.7 reported that during pregnancy but not after birth, T-allele carrier status was related to higher levels of both resting BP and plasma ET-1 controlling for adiposity. They speculated that increased insulin resistance, often seen transiently during pregnancy, might have a role since insulin potentiates the release of ET-1 and upregulates endothelin receptors.30,31 Unfortunately, insulin and other neurohormonal factors associated with sympathetic activation to stress and known to promote the release of ET-1 (eg, norepinephrine) were not measured. These factors need to be evaluated in future studies as to their potential mechanistic links with the ET-1 gene Lys198Asn polymorphism and phenotypes related to BP control.

Second, the Lys198Asn is not in the promoter region of the ET-1 gene and is therefore unlikely to affect differential expression of the gene in response to stimulating factors. Although the Lys198Asn polymorphism codes for an amino acid change, the possibility exists that this polymorphism is not functional itself but might be in linkage disequilibrium with a functional polymorphism in the regulatory region of the ET-1 gene.32

Finally, it is unclear what factors associated with SES are responsible for its impact with the ET-1/Lys198Asn polymorphism on BP control. The assumption that frequent psychosocial stress exposure is a contributing factor is supported by our finding that the lower SES group reported a greater number of stressful life events over the previous year. There were no SES group differences in several nonprudent lifestyle behaviors that have been linked to lower SES and found to adversely affect cardiovascular health including smoking, alcohol consumption, and physical inactivity.33 However, other health-damaging behaviors previously linked with lower SES were not evaluated, such as hostility and a nonprudent diet.34,35

**Perspectives**

The primary aim of this study was to evaluate the relation between the ET-1/Lys198Asn polymorphism and hemody-
namic function at rest and in response to acute stress, particularly in combination with SES, obesity, and ethnicity. Our results indicated that carriers of the T allele who were from lower SES backgrounds or who were obese exhibited the greatest BP reactivity to the behavioral stressor. Although these patterns were not reflected in the plasma ET-1 and NOX changes, this is the first report of association between the ET-1/Lys198Asn polymorphism and BP reactivity to behavioral stress. The findings point out the importance of examining the impact of genetic polymorphisms on blood pressure control phenotypes within the context of potentiating environmental factors. Such efforts will provide a better understanding of the cause of EH and have important implications in the primary prevention of EH.

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References
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