Abstract—Experimental evidence indicates that endothelin 1 stimulates the sympathetic nervous system by activation of the subtype A receptor. The aim of the present study was to assess whether this mechanism is active in humans and to investigate its potential role in the pathogenesis of essential hypertension. In 15 hypertensive patients and 12 normotensive subjects, blood pressure, heart rate, and muscle sympathetic nerve activity were evaluated during intravenous 20-minute infusion of BQ123 (0.1 mg/kg per hour), an endothelin A receptor antagonist, and sodium nitroprusside (SNP; 0.4 μg/kg per minute). In hypertensive patients, blood pressure was reduced similarly by BQ123 and SNP. In contrast, the increase in muscle sympathetic nerve activity induced by BQ123 (from 52.0±4.9 to 56.8±5.5 bursts per 100 heartbeats; P<0.05 versus baseline) was significantly lower (P<0.05) than that induced by SNP (from 50.6±4.9 to 61.1±5.1 bursts per 100 heartbeats; P<0.05 versus baseline). In normotensive subjects, SNP reduced blood pressure and increased muscle sympathetic activity, whereas BQ123 was ineffective. Thus, in a subgroup (n=9) of normotensive subjects, we administered BQ123 at a higher dose (0.2 mg/kg per hour), representing an equidepressor dose of SNP, inducing a blunted increase in sympathetic activity (from 44.1±2.4 to 50.1±6.4 bursts per 100 heartbeats; P<0.05 versus baseline). Finally, administration of a different vasodilator (papaverine, 0.5 mg/kg per hour) exerted results superimposable to SNP. Endogenous endothelin 1 appears to have a sympathoexcitatory effect both in normotensive and hypertensive subjects through endothelin A receptors, contributing to basal sympathetic vasomotor tone. Moreover, essential hypertension shows an increased susceptibility to the sympathoexcitatory effect of endogenous endothelin 1. (Hypertension. 2011;57:79-84.)

Key Words: hypertension ■ sympathetic nervous system ■ endothelin ■ microneurography ■ BQ123

Essential hypertension is characterized by increased sympathetic nervous system (SNS) activity, as clearly demonstrated by sensitive techniques, such as the norepinephrine spillover method and microneurographic quantification of nerve traffic. SNS activation, which is already present in normotensive offspring of hypertensive patients, is peculiar to the essential hypertensive state and parallels the degree of blood pressure (BP) increase. In addition, it may exert deleterious metabolic and cardiovascular effects, accelerating progression of the target organ damage associated with hypertension.

Endothelin 1 (ET-1) is a vasoconstrictor and mitogenic peptide produced by endothelial cells. Its important role in regulation of vascular tone and structure is well established. Essential hypertension is characterized by increased ET-1 vasoconstrictor tone, which seems to be a consequence of reduced NO availability. Endothelin receptor antagonists, particularly those acting on endothelin A (ET_A) receptors, are a promising therapeutic option in patients with resistant and renoparechimal hypertension. The role of the endothelin system in cardiovascular homeostasis is not limited to its direct vascular effects but also involves neural regulation of vasomotor tone. Experimental evidence suggests that ET-1 can stimulate central and peripheral SNS activity through ET_A receptors. Although intracerebral administration of ET-1 can increase BP and SNS activity mainly through ET_A receptors in hypertensive as well normotensive animals, administration of an ET_A receptor antagonist induces the opposite effect in hypertensive animals only, suggesting a specific sympathoexcitatory role for the endothelin system in this condition. With regard to the peripheral autonomic nervous system, ET-1 can act in carotid bodies and in cervical superior and nodose ganglia, influencing baroreflex and chemoreflex regulation. It is released by postganglionic sympathetic neurons, possibly modulating catecholamine release and vascular tone, and it stimulates catecholamine...
Table 1. Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypertensive Patients (n=15)</th>
<th>Normotensive Subjects (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45.8±6.8</td>
<td>43.5±5.6</td>
</tr>
<tr>
<td>Male/female sex (n)</td>
<td>11/4</td>
<td>9/3</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>150.9±11.7*</td>
<td>130.1±7.1</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>90.6±6.6*</td>
<td>82.0±7.9</td>
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<tr>
<td>Heart rate, bpm</td>
<td>71.1±8.8</td>
<td>68.7±7.0</td>
</tr>
<tr>
<td>MSNA, bursts per min</td>
<td>34.1±3.9*</td>
<td>29.4±2.4</td>
</tr>
<tr>
<td>MSNA, bursts per 100 heartbeats</td>
<td>50.6±4.9*</td>
<td>43.1±4.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.8±4.1</td>
<td>22.2±3.5</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.1±0.9</td>
<td>5.0±0.6</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.2±0.4</td>
<td>1.3±0.5</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.0±0.6</td>
<td>2.8±0.7</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>5.2±0.2</td>
<td>4.9±0.4</td>
</tr>
<tr>
<td>Plasma creatinine, μmol/L</td>
<td>80.0±13.1</td>
<td>78.3±9.1</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Data are mean±SD unless otherwise specified.

*P<0.05 vs normotensive subjects.

release from adrenal glands. Despite the growing body of evidence arising from experimental studies, few data are available on the systemic interaction between endogenous ET-1 and SNS in humans either in physiological or pathological conditions. Interestingly, local infusion of ET-1 can potentiate SNS-mediated, deep breath–induced vasconstriction. Thus, we speculated that ET-1 could likely modulate sympathetic activity in humans through 

Methods

Population

The present study included 15 essential hypertensive patients (HTs), enrolled from the hypertension outpatient clinic of the University Hospital of Pisa, and 12 healthy subjects (NTs), recruited among the hospital staff.

The patients had never received any antihypertensive treatment and were characterized by mild essential hypertension (systolic BP between 140 and 159 mm Hg and/or diastolic BP between 90 and 99 mm Hg on repeated clinic measurements) and no history or evidence of overt cardiovascular disease, target organ damage, or major noncardiovascular diseases. Current cigarette smoking and daily intake of ≥3 alcoholic beverages were considered as exclusion criteria. Secondary hypertension was excluded by standard testing. The 2 groups were comparable for age, body mass index, glycemic and lipid profile, and renal function (Table 1).

The study protocol was approved by the local ethical committee and was in accordance with institutional guidelines. Patients gave their written informed consent to participation in the study after explanation of its nature and purpose.

Measurements

In each subject, a detailed medical history and physical examination were carried out; office BP (3 measurements in the sitting position by means of the automatic device Omron 705IT), heart rate, and anthropometric parameters were measured; and routine blood sample assays were performed before inclusion in the study.

During the experimental sessions, the following measurements were obtained: (1) noninvasive beat-to-beat BP through a finger photoplethysmographic device (Finapres 2300, Ohmeda or Portapres, FMS); (2) beat-to-beat heart rate, through a transthoracic ECG lead (Biotach, Gould Electronics); (3) plasma norepinephrine and epinephrine (E), both assayed by high-pressure liquid chromatography; and ET-1, by enzyme immunoassay (Biomedica), on venous blood samples taken from an antecubital vein; and (4) multiunit recording of efferent postganglionic muscle sympathetic nerve activity (MSNA). Briefly, a tungsten microelectrode (diameter: 200 μm), with an uninsulated 1- to 5-μm diameter tip (Medical Instruments, University of Iowa) was transcutaneously inserted into the right or left peroneal nerve just posterior to the fibular head. A reference electrode was inserted subcutaneously 1 to 3 cm from the recording site. The signal was integrated with a 0.1-second time constant, amplified with a gain of 50 000 to 80 000, band-pass filtered (700 to 2000 Hz), and acquired with a sampling rate of 1000 Hz through a digital acquisition system (ACQ-16, Gould Electronics). MSNA was identified according to the following criteria outlined in previous studies: (1) electro stimulation through the electrode in the peroneal nerve elicited involuntary leg contractions but no paesthesia; (2) tapping or stretching the innervated muscle region elicited afferent mecanoreceptor discharges, whereas stroking the skin did not; and (3) spontaneous pulse-synchronous bursts, which increase in frequency during voluntary ankle but not after a loud noise, were displayed by the neurogram. The recording was considered acceptable if the signal:noise ratio exceeded the value of 3. Neurograms thereby obtained were recorded together with BP and heart rate by means of dedicated computer software (Protocol LDS). MSNA was quantified as bursts per minute and bursts per 100 heartbeats. MSNA recordings were analyzed by visual inspection by a single investigator blinded to the study protocol and the drug infused. In our laboratory, the coefficient of variation of MSNA at different time intervals in the same individual is 4.4%. During the recording, respiration rate was monitored through a strain-gauge pneumograph (Pneumotrace, Gould Electronics), positioned at the midchest level, to exclude from the data analysis any time interval in which respiratory rhythm alterations were present.

Experimental Protocol

All of the experimental sessions were performed in the morning, and subjects were asked to avoid caffeine- and alcohol-containing beverages and eating for the 12 hours before the study. During the experimental session, subjects were in the supine position in a quiet and comfortable room and were fitted with an intravenous cannula, the microelectrodes for MSNA recording, and the other measuring devices. After a 30-minute interval, BP, heart rate, respiration rate, and MSNA were continuously monitored and recorded in baseline conditions and during infusion of the different drugs. Blood samples for NE, E, and ET-1 were collected at baseline and at the end of each drug infusion. Some patients underwent >1 session, in which case, different sessions were separated by ≥3 weeks and performed in a randomized order.

Session 1: Effect of BQ 123 in Comparison to Sodium Nitroprusside

This session was planned to investigate the hemodynamic and sympathetic effects of BQ-123, a selective antagonist for ET \(_A\) receptors (Clinalfa, Bachem) in comparison with sodium nitroprusside (SNP), a direct vasodilating agent (Malesci). In all of the study participants (12 NTs and 15 HTs), BQ-123 was administered intravenously at the dose of 0.1 mg/kg per hour and SNP at a dose chosen according to preliminary studies to achieve a similar BP reduction in the hypertensive population (0.4 μg/kg per minute). Each drug was infused for 20 minutes and was preceded by 10-minute baseline acquisition. Because of the prolonged pharmacodynamic effect of BQ123, it was not possible to randomize the drug infusions in each experimental session. Thus, SNP, which has a very short half-life, was always infused as the first drug, allowing a 30-minute washout period before the beginning of BQ123 infusion.
Session 2: Effect of BQ123 at a High Dose in NTs
This session was designed to test in NTs the effect of a BQ123 dose capable of inducing significant hemodynamic changes. Given the known lesser vasodilator power of BQ123 in NTs, 9 NTs underwent an adjunctive experimental session, receiving BQ123 at the dose of 0.2 mg/kg per hour for 20 minutes, after a 10-minute baseline recording.

Session 3: Vehicle Session and Comparison Between 2 Different Vasodilators
This session was performed with a 2-fold aim, first, to assess the effect of placebo infusion, and, second, to compare SNP with another vasodilator drug, papaverine, acting through a different mechanism, to exclude specific interactions between the NO donor and the SNS. The papaverine dose was chosen to achieve the equidepressor effect of SNP, in accordance with preliminary studies. Thus, in 4 NTs and 6 HTs, normal saline (NaCl 0.9%) and the vasodilator drug papaverine (0.5 mg/kg per hour IV) were infused following a protocol superimposable to session 1.

Data Analysis
Statistical analysis was performed by NCSS 2007. Results are shown as mean±SD. Differences in baseline characteristics between groups were analyzed by the unpaired t test or χ², as appropriate. BP, heart rate, and MSNA obtained in each subject were averaged for intervals of 10 minutes during the baseline period and of 5 minutes during drug infusion. Within each group, repeated measurements were analyzed by general linear model ANOVA, considering time intervals and drug type as factors, and by Fisher least significant difference multiple comparison post hoc test. A P level <0.05 was used to define statistical significance. Sample size was calculated to reject the null hypothesis with a power of 0.8 and a type I error probability of 0.05.

Results
Baseline Values
Table 1 shows the clinical characteristics and the baseline values of the study population. As expected, BP and MSNA values were higher in HTs as compared with NTs. The other parameters were similar in the 2 groups.

Effect of BQ 123 in Comparison With SNP
In HTs, BP values were significantly reduced both by BQ123 (systolic BP from 149.4±10.0 to 145.5±10.9 mm Hg, P<0.01; diastolic BP from 91.1±7.5 to 87.8±7.6 mm Hg, P<0.05) and by SNP (systolic BP from 150.9±11.7 to 146.1±13.0 mm Hg, P<0.01; diastolic BP from 90.6±8.6 to 87.3±9.6 mm Hg, P<0.05) to a similar extent (Figure 1A). In the control group, on the other hand, SNP and BQ123 infusion gave different results. Although SNP significantly reduced systolic (from 129.2±11.1 to 125.5±11.8 mm Hg; P<0.05) and diastolic BP (from 77.0±9.3 to 73.7±8.8 mm Hg; P<0.05), BQ123 did not modify BP values (systolic BP from 130.3±11.6 to 129.2±12.6 mm Hg, P value not significant [NS]; diastolic BP from 76.9±9.8 to 76.6±9.7 mm Hg, P=NS; Figure 1B).

In NTs, heart rate was significantly increased by BQ123 (from 69.8±10.8 to 78.2±13.1 bpm; P<0.01) and by SNP (from 71.1±8.8 to 80.0±12.4 bpm; P<0.01; Figure 1C). In NTs, heart rate was increased by SNP infusion (from 68.7±7.0 to 81.0±6.8 bpm; P<0.001 versus baseline) to a greater extent as compared with HT (P<0.05 versus HT); despite a similar BP-lowering effect; BQ123 infusion caused a small but significant increase in heart rate (from 69.0±5.8 to 74.9±9.0 bpm; P<0.05) in the absence of any BP change (Figure 1D).

In HTs, MSNA was increased by SNP infusion (from 50.6±4.9 to 61.1±5.1 bursts per 100 heartbeats; P<0.01). But it was noted that the increase in MSNA induced by BQ123 (from 52.0±4.9 to 56.8±5.5 bursts per 100 heartbeats; P<0.05) was significantly lower (P<0.05) as compared with that induced by SNP, even in presence of similar hemodynamic modifications (Figure 2A).

In NTs, the effect of SNP infusion on MSNA (from 43.1±4.2 to 55.3±6.1 bursts per 100 heartbeats; P<0.001) was similar to that observed in HT. In contrast, BQ123 infusion did not significantly modify MSNA (from 43.7±3.9 to 44.4±3.5 bursts per 100 heartbeats; P=NS; Figure 2B).

Effect of BQ123 at High Dose in NTs
The higher dose of BQ123 effectively reduced BP (systolic BP from 130.1±7.1 to 124.6±6.7 mm Hg, P<0.05; diastolic BP from 77.0±7.9 to 73.2±7.7 mm Hg, P<0.05), as shown in Figure 1B. The BP decrease was comparable to that induced by SNP (P=NS), whereas the increase in heart rate (from 67.7±6.0 to 73.5±7.6 bpm; P<0.05) was still significantly smaller as compared with SNP (Figure 1D). High-dose BQ123 also induced an increase in MSNA (from 44.1±2.4 to 50.1±6.4 bursts per 100 heartbeats; P<0.05), which was blunted as compared with SNP (P<0.05; Figure 2B).
Comparison Between 2 Different Vasodilators

Hemodynamic responses to SNP and papaverine infusion were similar both within the hypertensive (systolic BP: -3.3% ± 1.9% versus -3.0% ± 2.1%; diastolic BP: -3.8% ± 1.2% versus -3.2% ± 2.1%; heart rate: +11.3% ± 5.5% versus +11.3% ± 5.5%; P = NS for all) and the control groups (systolic BP: -3.1% ± 2.4% versus -2.9% ± 2.0%; diastolic BP: -4.1% ± 1.7% versus -4.6% ± 1.8%; heart rate: +18.3% ± 6.3% versus +16.6% ± 4.0%; P = NS for all). SNP and papaverine infusion induced a similar MSNA increase within the hypertensive (+21.5% ± 10.5% versus +23.7% ± 9.0%; P = NS) and the control group (+22.4% ± 13.4% versus +25.6% ± 12.8%; P = NS).

Discussion

In this study we tested the hypothesis that inhibition of the endothelin system may modulate SNS activity in humans. Because experimental studies identify ET\textsubscript{A} receptors as mediators of the sympathoexcitatory effect of endothelin,\textsuperscript{11,12} we used BQ123, a well-established selective ET\textsubscript{A}-blocker drug. To distinguish a potential direct effect of BQ123 on sympathetic nerve activity from the aspecific, baroreflex-mediated effect attributed to BP lowering, per se, BQ123 was compared with SNP, a vasodilator acting directly on smooth muscle cells. In patients with essential hypertension, both BQ123 and SNP induced a similar BP reduction, with a parallel increase in heart rate. Nevertheless, despite similar hemodynamic modifications, the increase in MSNA measured by microneurography was significantly smaller during BQ123 infusion than during SNP infusion. In other words, the expected baroreflex-mediated increase in MSNA, induced by any BP-lowering drug, appeared to be blunted by ET\textsubscript{A} blockade. Thus, ET-1 seems to have a stimulating effect on sympathetic nerve activity through activation of the ET\textsubscript{A} receptor subtype.

When the same experimental protocol was applied to NTs, changes in BP and MSNA during SNP infusion were similar to those observed in HTs. In contrast, BP and MSNA were not modified by BQ123 administration. The absence of any hemodynamic effect in response to BQ123 infusion was expected, based on the previous literature,\textsuperscript{9,18,19} indicating a less potent vasoconstrictor effect of endogenous ET-1 in NTs than in patients with essential hypertension.\textsuperscript{6,7} Therefore, in NTs we administered BQ123 at a higher dose, capable of inducing the same BP reduction as that obtained in HTs. In such conditions, we observed a significant increase in MSNA, which, however, was blunted in comparison with that induced by SNP infusion. These results were further confirmed by the fact that another vasodilator, namely papaverine, exerted a BP and MSNA response similar to that induced by SNP, thus highlighting the peculiarity of the ET\textsubscript{A} receptor.

Table 2. Neurohumoral Parameters

<table>
<thead>
<tr>
<th>Time</th>
<th>Hypertensive Patients</th>
<th>Normotensive Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NE, nmol/L</td>
<td>E, pmol/L</td>
</tr>
<tr>
<td>Baseline</td>
<td>2.0 ± 0.8</td>
<td>145 ± 19</td>
</tr>
<tr>
<td>BQ123</td>
<td>2.1 ± 0.7</td>
<td>137 ± 46</td>
</tr>
<tr>
<td>SNP</td>
<td>2.2 ± 0.8</td>
<td>137 ± 24</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.0 ± 0.6</td>
<td>163 ± 51</td>
</tr>
<tr>
<td>Papaverine</td>
<td>2.1 ± 0.5</td>
<td>156 ± 37</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

* P < 0.05 vs normotensive subjects.

† P < 0.05 vs baseline.
blockade effect and excluding a direct effect of exogenous SNP-released NO on sympathetic activity.

Taken together, the present results demonstrate that endogenous ET-1, acting by ET\(_A\) receptor stimulation, contributes to the basal sympathetic tone that controls vascular resistances in humans both in physiological conditions and in essential hypertension. Moreover, in HTs, as compared with NTs, lower doses of BQ123 were sufficient to reveal the vasodilating and sympathoinhibitory effects of ET\(_A\) blockade. Thus, our results confirm that endogenous ET-1 exerts a stronger vasoconstrictor effect in HTs than in NTs\(^{27}\) and demonstrate that essential hypertension is characterized by greater susceptibility to the sympathoexcitatory effect of endogenous ET-1.

Experimental data support the hypothesis of a role of endogenous ET-1 in modulation of central sympathetic drive\(^{10–12}\) particularly in the presence of hypertension.\(^{13,20}\) BQ123 is able to cross the blood-brain barrier, possibly through an active transport system,\(^{21}\) and, thus, to block ET\(_A\)-mediated effects of endogenous ET-1 in several sites within the central nervous system.\(^{13}\) Moreover, BQ123 may act on brain areas characterized by an incomplete blood-brain barrier, such as the area postrema, which could be a key site of ET-1 action within the central nervous system.\(^{22}\) Sympathetic postganglionic neurons could be another possible interaction site.\(^{13}\)

As expected, during SNP infusion, the increase in heart rate was blunted in HTs as compared with NTs, confirming the presence of reduced heart rate-baroreflex gain, which is a well-established feature of essential hypertension.\(^{2}\) During BQ123 administration in NTs, an increase in heart rate was observed even in the absence of any BP modification, in accordance with previous studies\(^{9,18}\) demonstrating that suppressor doses of BQ123 are able to reduce systemic vascular resistances and increase heart rate, possibly via activation of cardiopulmonary reflexes. Interestingly, when higher doses of BQ123 were used in normotensive subjects to induce a significant hemodynamic effect, BP reduction was accompanied by a blunted heart rate response as compared with SNP. Our results are in agreement with experimental observations in which ET-1 increased heart rate-baroreflex gain,\(^{23,24}\) whereas bosentan administration induced the opposite effects.\(^{25}\) These data suggest a specific physiological role for ET\(_A\) receptors in heart rate regulation, which is not evident in essential hypertension and needs to be further investigated.

Plasma NE concentrations were not significantly modified during BQ123 infusion either in HTs or NTs. However, this finding is not necessarily in contradiction with MSNA results, because plasma NE can be considered only a very rough index of the spillover of the neurotransmitter from vascular sympathetic terminations.\(^{26}\) Moreover, the endothelin system modulates NE release from presynaptic sympathetic nerve endings but also from the adrenal glands,\(^{13}\) further limiting the reliability of plasma NE for estimation of sympathetic activity in the setting of the present study.

Plasma ET-1 concentrations, in accordance with the literature, were similar in HTs and NTs\(^{27}\) and remained unchanged by BQ123.\(^{18}\) This finding could be explained by the fact that plasma levels of the peptide do not reflect its biological activity, because ET-1 is released mainly abnormally and removed by plasma, above all by binding with endothelin B receptors.\(^{5}\)

Among the limitations of this study, it is necessary to take into account the absence of any measurement of central venous pressure, a key determinant of sympathetic activity. Although it is well established that SNP-induced sympathoexcitation is attributable both to BP and central venous pressure reductions, little information is available about the effects of ET\(_A\) blockade. Dorsal hand vasoconstriction to ET-1 is greater in HTs than in NTs.\(^{14}\) Thus, it is conceivable that ET-1 inhibition could result in a greater increase in venous capacitance and reduction in central venous pressure in HTs than in NTs, in parallel to what is known from the arterial district. On the other hand, because sympathetically mediated vasoconstriction is potentiated by ET-1 in HTs as compared with NTs,\(^{14}\) we can speculate that ET antagonism could blunt sympathetic responses to central venous pressure changes. Thus, the endothelin/SNS interaction in the venous district could contribute to the blunted MSNA response to BQ123 in HTs in the present study.

**Perspectives**

Our results demonstrate that endogenous ET-1 has a sympathoexcitatory effect both in physiological conditions and in essential hypertension, possibly contributing to the basal sympathetic outflow regulating vasomotor tone. Furthermore, essential hypertension appears to be characterized by increased susceptibility to the sympathoexcitatory effect of endogenous ET-1. The discovery of enhanced biological activity of ET-1 on autonomic cardiovascular regulation, beyond the known effects on vascular tone, further reinforces the fundamental role of the endothelin system in the pathophysiology of essential hypertension and of the related organ damage. Thus, treatment options aimed at counteracting the endothelin system could favorably influence the adrenergic overactivity characterizing essential hypertension.

**Disclosures**

None.

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Interactions Between Sympathetic Nervous System and Endogenous Endothelin in Patients With Essential Hypertension
Rosa Maria Bruno, Isabella Sudano, Lorenzo Ghiadoni, Lorenzo Masi and Stefano Taddei

Hypertension. 2011;57:79-84; originally published online November 8, 2010; doi: 10.1161/HYPERTENSIONAHA.110.163584

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