Uncoupling of the Baroreflex by N\textsubscript{N}-Cholinergic Blockade in Dissecting the Components of Cardiovascular Regulation

John R. Shannon, Jens Jordan, Bonnie K. Black, Fernando Costa, David Robertson

Abstract—Systemic administration of adrenergic agonists and nitric oxide donors is used extensively to determine cardiovascular receptor sensitivity. Conclusions regarding receptor sensitivity in the presence of the baroreflex may be misleading. In 8 normal volunteers, we determined the heart rate and blood pressure changes after incremental bolus doses of isoproterenol, phenylephrine, and sodium nitroprusside before and during neuronal nicotinic cholinergic (N\textsubscript{N}-cholinergic) blockade with trimethaphan. Results are given as median (25th/75th percentile). With trimethaphan, the baroreflex slope (as determined by bolus doses of nitroprusside and phenylephrine) decreased from 24 (22/26) to 0.00 (0.00/0.09) ms/mm Hg (P<0.01). The dose of isoproterenol that decreased systolic blood pressure (SBP) 12.5 mm Hg changed from 0.61 (0.51/5.3) to 0.17 (0.12/0.21) µg (P<0.01); the dose required to increase heart rate 12.5 bpm changed from 0.22 (0.17/0.41) to 0.74 (0.33/2.3) µg (P<0.01). The dose of nitroprusside required to decrease SBP 12.5 mm Hg changed from 2.3 (1.3/3.4) to 0.18 (0.14/0.24) µg/kg (P<0.01). The dose of phenylephrine required to increase SBP 12.5 mm Hg changed from 135 (110/200) to 16 (10/30) µg (P<0.01). We conclude that the efferent arc of the baroreflex can be completely interrupted with N\textsubscript{N}-cholinergic blockade. Estimation of adrenoreceptor sensitivity and sensitivity to nitric oxide donors by systemic administration of agonists is severely confounded by baroreflexes. Uncoupling of the baroreflex by N\textsubscript{N}-cholinergic blockade may be a useful method to obtain an integrated measure of adrenergic receptor sensitivity and sensitivity to nitric oxide donors in humans. This approach would permit the comparison of normal and abnormal physiological states without the “noise” of baroreflex buffering. (Hypertension. 1998;32:101-107.)

Key Words: receptors, adrenergic n phenylephrine n nitroprusside n isoproterenol n trimethaphan

Systemic administration of adrenergic agonists is used extensively to determine adrenoreceptor sensitivity in humans.\textsuperscript{1-7} Similarly, the influence of the distal part of the nitric oxide pathway on cardiovascular responses can be evaluated by systemic administration of nitric oxide donors. A possible role of changes in adrenergic sensitivity or sensitivity to nitric oxide donors in a variety of human conditions has been postulated based on these methods.\textsuperscript{2-7} Results of these studies, however, may be confounded by baroreflex-mediated alterations of sympathetic and parasympathetic tone.\textsuperscript{8,9} In a few studies, an effort was made to block baroreflex-mediated changes of HR and BP with atropine alone\textsuperscript{1-7} or atropine in combination with a centrally acting sympatholytic drug.\textsuperscript{8} The main limitation of these studies is that either the sympathetic outflow was not blocked\textsuperscript{1-7} or was only partially blocked;\textsuperscript{8} or that the completeness of the blockade was not assessed. Therefore, the influence of the baroreflex on the cardiovascular responses cannot be inferred reliably. The efferent arc of the baroreflex (parasympathetic and sympathetic nerves) can be blocked by N\textsubscript{N}-cholinergic antagonists\textsuperscript{10} commonly referred to as ganglionic blockers.\textsuperscript{11} It has been shown recently that N\textsubscript{N}-cholinergic blockade can be used to attenuate the influence of the baroreflex on systemic cardiovascular responses to drugs.\textsuperscript{9}

The purpose of this study was to determine whether or not the efferent arc of the baroreflex could be interrupted completely by N\textsubscript{N}-cholinergic blockade in human subjects. Furthermore, we evaluated the sensitivity to sodium nitroprusside (nitric oxide donor), phenylephrine (\(\alpha\)-adrenoreceptor agonist), and isoproterenol (\(\beta\)-adrenoreceptor agonist) before and after complete blockade of the efferent arc of the baroreflex.

Methods

Subjects

Eight healthy subjects (4 male, 4 female) were recruited from a pool of normal volunteers. Median (25th/75th percentile) age, weight, and height were 30 (25/36) years, 64 (60/88) kg, and 170 (164/180) cm, respectively. All subjects underwent a thorough clinical examination, ECG, and admission urinalysis and blood work. Written informed consent was obtained before study entry. All studies were approved by the institutional review board.

Protocol

Four days before study, volunteers were placed on a 150 mEq Na\textsuperscript{+} and 70 mEq K\textsuperscript{+} diet free of substances that could interfere with catecholamine measurements. All vasoactive medications were discontinued at least 5 half-lives before testing. The volunteers were admitted to the Elliot V. Newman Clinical Research Center at

Received January 16, 1998; first decision January 28, 1998; revision accepted February 19, 1998.
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Baroreflex Uncoupling by \( \text{N}_\text{N} \)-Cholinergic Blockade

Selected Abbreviations and Acronyms

<table>
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<tr>
<th>Abbreviation</th>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>HR</td>
<td>heart rate</td>
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<tr>
<td>MSNA</td>
<td>muscle sympathetic nerve activity</td>
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<td>( \text{N}_\text{N} )-cholinergic</td>
<td>neuronal nicotinic cholinergic</td>
<td></td>
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<tr>
<td>RR</td>
<td>relative risk</td>
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<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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Vanderbilt University Medical Center the day before pharmacological testing was performed. Plasma catecholamines were determined during pharmacological testing, immediately before trimethaphan infusion, and again after the steady state was reached. Blood samples were drawn from a heparin lock placed at least 30 minutes before the first blood draw.

Pharmacological Testing

Pharmacological testing was conducted with subjects in the recumbent position at least 2.5 hours after their last meal. HR was determined with continuous ECG, and BP changes were measured beat to beat by photoplethysmography (Finapres, Ohmeda 2300). Manual brachial BP readings were obtained at baseline and repeatedly during testing. To insure accuracy of beat-to-beat BP measurements, the pulse pressure from the Finapres recording was adjusted for the average of at least 3 consecutive simultaneously determined brachial BPs. Bolus doses of isoproterenol, phenylephrine, and nitroprusside were administered via a heparin lock in an antecubital vein in less than 1 second. For approximately 5 seconds before and 5 seconds after bolus administration, normal saline was flushed through the heparin lock. A catheter in an antecubital vein in the contralateral arm was used for infusion of trimethaphan. Cardiovascular responses to isoproterenol, nitroprusside, and phenylephrine were evaluated before and after \( \text{N}_\text{N} \)-cholinergic blockade.

Incremental bolus doses of isoproterenol starting at 0.025 \( \mu \)g were given to increase HR by at least 25 bpm or to decrease SBP by 25 mm Hg. Incremental bolus doses of sodium nitroprusside starting at 0.05 \( \mu \)g/kg were given up to a dose of nitroprusside sufficient to decrease SBP by 25 mm Hg or increase HR at least 25 bpm. Similarly, incremental bolus doses of phenylephrine sufficient to increase SBP by 25 mm Hg were administered, starting with a dose of 50 \( \mu \)g.

\( \text{N}_\text{N} \)-cholinergic receptors were then blocked by continuous infusion of trimethaphan (Arfonad, Hoffmann La-Roche). In the initial subjects, the infusion was started at 1 mg/min or less and increased at 3-minute intervals until spontaneous fluctuations of BP and HR with respirations were blunted, consistent with complete or near complete blockade of the efferent arc of the baroreflex. (With later subjects, when it was evident that blockade was well tolerated, the infusion was started at 6 mg/min.) The completeness of blockade was assessed by determining the HR response to the SBP increase or decrease resulting from administration of bolus doses of phenylephrine and nitroprusside. We considered blockade to be complete when HR changed less than 1 bpm with a 25-mm Hg increase or decrease in SBP. When this end point was reached, the infusion was continued at a constant rate. Bolus doses of test medications were then administered just as before \( \text{N}_\text{N} \)-cholinergic blockade, but with adjustment in dose ranges to compensate for the disabling of homeostatic adjustment mechanisms.

Changes in SBP induced by phenylephrine or nitroprusside were plotted against corresponding changes in the RR interval to assess baroreflex function before and after \( \text{N}_\text{N} \)-cholinergic blockade. The baroreflex slope was determined at the linear portion of this sigmoidal relation between SBP changes and changes in the RR interval.\(^2\) Log dose-response curves were determined for the change in HR after isoproterenol boluses and the change in SBP after isoproterenol, nitroprusside, and phenylephrine boluses. The doses of each drug that would change HR by 12.5 bpm or SBP by 12.5 mm Hg were determined by interpolation from the regression line plotted from the linear portion of the corresponding log dose-response curve.\(^3\)

Muscle Sympathetic Nerve Activity

To confirm that \( \text{N}_\text{N} \)-cholinergic blockade completely prevented postganglionic sympathetic neurotransmission, MSNA was measured in one volunteer before, during, and after trimethaphan. Bolus doses of phenylephrine and nitroprusside were used to load and unload baroreceptors. MSNA was measured as previously described\(^4\) in the right peroneal nerve at the level of the fibular head. Criteria for an adequate MSNA recording were as follows: (1) electrical stimulation produced muscle twitches but no paresthesias; (2) passive flexion and extension of the toes evoked proprioceptive afferent signals, whereas cutaneous stimulation by slight stroking of the skin did not; (3) the neurogram showed typical morphology; and (4) nerve traffic during phase II of the Valsalva maneuver increased.

Analytic Methods

Plasma was analyzed for catecholamines by a modification of a high-pressure liquid chromatographic method previously described.\(^5\)

Statistics

All data are expressed as median (25th/75th percentile). Intraindividual differences were analyzed by the Wilcoxon matched-pairs test. The relationship between parameters was assessed by linear regression analysis. A value of \( P<0.05 \) was considered to be statistically significant.

Results

The infusion rate of trimethaphan necessary to completely block the efferent arc of the baroreflex in our subjects was 6 (6/7) mg/min [0.1 (0.07/0.1) mg \( \cdot \) min\(^{-1} \cdot kg^{-1} \)]. When the infusion was started at 6 mg/min, complete blockade of the efferent arc of the baroreflex was attained after approximately 10 to 15 minutes. This infusion rate was well tolerated in all subjects, and we did not observe any respiratory complications,\(^6\) although 1 subject reported a sensation of dyspnea at an infusion rate of 6 mg/min. The infusion was stopped for approximately 2 minutes until symptoms resolved and resumed at 5 mg/min, which was well tolerated for the remainder of the study.

SBP was 118 (114/123) mm Hg at baseline and 107 (101/123) mm Hg during trimethaphan infusion (\( P=0.08 \)). Diastolic blood pressure was 77 (67/85) mm Hg at baseline and 70 (67/88) mm Hg during trimethaphan infusion (\( P=NS \)). HR increased from 59 (54/66) to 86 (81/89) (\( P<0.01 \)). The HR and BP variability was markedly attenuated (Figure 1). With \( \text{N}_\text{N} \)-cholinergic blockade, there was a marked decrease in plasma norepinephrine and a concomitant decrease in the plasma dihydroxyphenyl(ethyleneglycol and dihydroxyphenylacetic acid, products of the intraneuronal metabolism of norepinephrine and dopamine, respectively. There was no significant change in plasma epinephrine (Table).

The HR and SBP responses to a bolus dose of phenylephrine before and during trimethaphan infusion in a representative subject are illustrated in Figure 2. There was no compensatory change in HR despite a 23-mm Hg increase in SBP. The baroreflex slope, as determined by administration of phenylephrine and nitroprusside, decreased from 24 (22/26) ms/mm Hg at baseline to 0.00 (0.00/0.09) ms/mm Hg with trimethaphan (\( P<0.01 \)). This effect of trimethaphan was
sustained throughout the study. The combined baroslopes of all subjects before and during \textit{N}α-cholinergic blockade are illustrated in Figure 3.

MSNA was completely eliminated with an infusion of trimethaphan at 6 mg/min (Figure 4). Within 20 minutes after discontinuation of the trimethaphan infusion, bursts of MSNA reappeared. Before trimethaphan infusion, there was a dose-dependent increase and decrease in MSNA with nitroprusside and phenylephrine, respectively. During trimethaphan infusion, there were no changes in MSNA with either nitroprusside or phenylephrine (increase of SBP by 30 mm Hg) or phenylephrine (increase of SBP by 30 mm Hg).

The tachycardic effect of isoproterenol was greatly attenuated with \textit{N}α-cholinergic blockade. During trimethaphan infusion, the dose of isoproterenol required to increase HR 12.5 bpm changed from 0.22 (0.17/0.41) μg to 0.74 (0.33/2.3) μg. In fact, in some subjects, there was almost no change in HR with isoproterenol during \textit{N}α-cholinergic blockade. In contrast, there was a large increase in the sensitivity to the hypotensive effect of isoproterenol (Figure 5). The dose of isoproterenol that decreased SBP 12.5 mm Hg decreased from 0.61 (0.51/5.3) to 0.17 (0.12/0.21) μg (Figure 6) ($P<0.01$).

The dose of nitroprusside required to decrease SBP 12.5 mm Hg decreased about 13-fold, from 2.3 (1.3/3.4) μg/kg before \textit{N}α-cholinergic blockade to 0.18 (0.14/0.24) μg/kg with trimethaphan ($P<0.01$) (Figure 6).

### Plasma Catecholamines Before (Baseline) and During (Trimethaphan) \textit{N}α-Cholinergic Blockade

<table>
<thead>
<tr>
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<th>Baseline, nmol/L</th>
<th>Trimethaphan, nmol/L</th>
<th>$P$</th>
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<tr>
<td>Norepinephrine</td>
<td>0.83 (0.63/1.9)</td>
<td>0.26 (0.18/0.37)</td>
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<tr>
<td>Epinephrine</td>
<td>0.11 (0.076/0.22)</td>
<td>0.076 (0.022/0.131)</td>
<td>NS</td>
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<tr>
<td>DHPG</td>
<td>6.4 (5.2/7.6)</td>
<td>4.3 (3.9/6.3)</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>DOPAC</td>
<td>16 (11/19)</td>
<td>11 (6.3/16)</td>
<td>$&lt;0.05$</td>
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DHPG indicates dihydroxyphenyl(ethylene)glycol; DOPAC, dihydroxyphenylacetic acid.

Plasma catecholamines were obtained at baseline after at least 30 minutes supine and approximately 20 minutes after the trimethaphan infusion was begun (NS = $P>0.05$). Values are median (25th/75th percentile).

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**Figure 1.** Beat-by-beat BP and HR at baseline before trimethaphan infusion (a) and at steady state during trimethaphan infusion (b). In this subject, there was an increase in HR and BP with trimethaphan. HR and BP variability were markedly attenuated with trimethaphan.

**Figure 2.** Changes in BP and HR after a single bolus of phenylephrine (PHE) before (a) and during (b) trimethaphan infusion. With \textit{N}α-cholinergic blockade, there was a marked reduction in the dose of phenylephrine that was needed to achieve a similar increase in BP. During blockade, there was no compensatory decrease in HR with the increased BP caused by phenylephrine.

**Figure 3.** Combined individual data points and baroreflex slope before (pre-blockade) and during (post-blockade) \textit{N}α-cholinergic blockade with trimethaphan. The baroreflex is completely eliminated, as indicated by a median baroslope of 0 ms/mm Hg with \textit{N}α-cholinergic blockade.
phenylephrine required to increase SBP 12.5 mm Hg decreased 8-fold, from 135 (110/200) mg to 16 (9.7/30) mg (P<0.01) (Figure 6).

The sensitivity to nitroprusside, isoproterenol, and phenylephrine with \textit{N},\textit{N'}-cholinergic blockade could not be predicted from plasma norepinephrine levels achieved with \textit{N},\textit{N'}-cholinergic blockade.

**Discussion**

The main finding of this study is that the efferent arc of the baroreflex can be interrupted completely by readily achievable levels of \textit{N},\textit{N'}-cholinergic blockade in human subjects. After interruption of the efferent arc of the baroreflex, there was a dramatic change in the cardiovascular responses to the systemic administration of sodium nitroprusside, phenylephrine, and isoproterenol.

Ganglionic blockers interrupt sympathetic and parasympathetic nerve traffic by competitively binding to postsynaptic \textit{N},\textit{N'}-cholinergic receptors of autonomic ganglia.\textsuperscript{11,16} By contrast, cholinergic agonism increases sympathetic and parasympathetic outflow.\textsuperscript{17} Trimethaphan, a nondepolarizing \textit{N},\textit{N'}-cholinergic antagonist, has been extensively used for the acute treatment of arterial hypertension.\textsuperscript{18–20} In contrast to depolarizing agents, it causes no initial stimulation of the postganglionic neuron. Acetylcholine release from preganglionic neurons is not affected.\textsuperscript{21} Trimethaphan is known to cause histamine release under some experimental conditions. With continuous infusion, plasma histamine levels initially increase but return to baseline after approximately 10 minutes and appear not to contribute to the hypotensive effect in humans.\textsuperscript{22} The concentration of trimethaphan necessary to achieve a direct vasodilatory effect in vitro is approximately 10 to 100 times greater than the concentration necessary to achieve ganglionic blockade.\textsuperscript{23,24}

With interruption of the efferent arc of the baroreflex, homeostatic adjustments normally controlled by the autonomic nervous system (BP, HR, sweating, and other factors) are blunted or abolished. A similar interruption of the efferent arc of the baroreflex occurs in autonomic failure. Thus, \textit{N},\textit{N'}-cholinergic blockade mimics the clinical picture seen in...
human autonomic failure. Patients with pure autonomic failure and multiple system atrophy have been shown to have markedly increased sensitivity to the depressor effect of \( \beta \)-agonists and to the pressor effect of \( \alpha \)-agonists and sympathomimetics. In fact, local administration of \( \alpha \)-agonists (eg, eye drops) can cause marked increases of blood pressure in such patients. Patients with primary autonomic failure also have hypersensitivity to the depressor effect of nitroglycerin.

The afferent arc of the baroreflex can also be interrupted as a complication of extensive neck surgery or irradiation. Patients with bilateral interruption of the afferent baroreflex arc (baroreflex failure) present with paroxysms of severe hypertension and tachycardia resembling the clinical manifestations of pheochromocytoma. In addition, these patients may have episodes of hypotension and bradycardia. The levels of BP and HR depend more on level of arousal rather than on posture. In spite of clinical presentations vastly different from that of primary autonomic failure, patients with baroreflex failure also have a several-fold increase in sensitivity to the pressor response of \( \alpha \)-agonists and to the depressor effects of nitric oxide donors.

Changes of central sympathetic or parasympathetic outflow may also change baroreflex sensitivity. Therefore, with disruption of either the afferent or efferent arc of the baroreflex, or with changes in central sympathetic or parasympathetic outflow, the sensitivity to vasoactive agents is significantly altered. Considering the large changes in response to vasoactive agents with complete disruption of the baroreflex arc, even small changes in the sensitivity of the baroreflex could significantly confound the interpretation of cardiovascular responses. Many disorders that may have changes in adrenoreceptor sensitivity or nitric oxide metabolism have also been shown to have changes in baroreflex function. Even commonly used medications (eg, digoxin) and dietary substances (eg, caffeine) may affect baroreflex function. Furthermore, in normal subjects, the interindividual variability of baroreflex sensitivity appears to be relatively large.

The influence of the baroreflex might limit the usefulness of some commonly employed approaches used to assess adrenoreceptor sensitivity. Local application of vasoactive agents (eg, forearm blood flow model) are sometimes employed to limit baroreflex activation. Theoretically, however, even the small amounts of drug reaching the systemic circulation may influence sympathetic and parasympathetic tone.

One possible approach to address receptor sensitivity in humans is to determine responses to cardiovascular drugs after pharmacological interruption of the efferent arc of the baroreflex. The decrease in sinus arrhythmia with atropine simplifies HR determination. Atropine does not block sympathetic outflow to the vasculature and the heart. Ford and James used atropine and clonidine to block parasympathetic effects and inhibit central sympathetic outflow. Clonidine, however, attenuates rather than eliminates sympathetic outflow. Furthermore, clonidine has peripheral effects that may influence BP regulation. Recently it has been shown that \( N \)-cholinergic blockade can be used to interrupt the baroreflex in human subjects. We and others have shown that complete interruption of the baroreflex arc can be achieved with this method. The lack of HR changes with either increases or decreases in BP strongly suggests complete ganglionic blockade. Theoretically, there could be small changes in sympathetic and parasympathetic nerve traffic not reflected in HR changes. We demonstrated that trimethaphan completely blocked MSNA and that this blockade could not be overcome by activation of the baroreflex (nitroprusside bolus).

With interruption of the baroreflex, cardiovascular responses to drugs can be observed in the absence of compensatory changes of sympathetic and parasympathetic tone. In this study, there was a significant decrease in the chronotropic response to isoproterenol after \( N \)-cholinergic blockade. By contrast, autonomic failure patients have been shown to have an increase in the chronotropic response to isoproterenol. These disparate observations with chronic (autonomic failure) and acute (\( N \)-cholinergic blockade) interruption of the efferent arc of the baroreflex may suggest an increase in \( \beta \)-adrenoreceptor sensitivity or number over time. The depressor effect of isoproterenol was markedly augmented with \( N \)-cholinergic blockade, reaching the sensitivity observed in autonomic failure patients. The changes in cardiovascular responses to isoproterenol during \( N \)-cholinergic blockade suggest that the increase in HR seen with isoproterenol in the absence of blockade is greatly influenced by the indirect or baroreflex-mediated effect on \( \beta \)-adrenoceptors and that direct stimulation of cardiac \( \beta \)-adrenoceptors is less important. The upper end of the dose range of the isoproterenol HR response could not be fully explored during \( N \)-cholinergic blockade. The influence of the baroreflex on cardiovascular responses was assessed using isoproterenol and phenylephrine in conscious, anesthetized or unanesthetized rats. The dose-response curves for BP and HR were extrapolated from the data presented in this study to estimate the dose required to increase BP by 12.5 mm Hg (nitroprusside) or to increase HR by 12.5 bpm (isoproterenol). The dose of isoproterenol needed to increase HR by BP by 12.5 mm Hg (isoproterenol bolus) was increased and the dose to decrease SBP by 12.5 mm Hg (isoproterenol bolus) was markedly decreased with trimethaphan. With trimethaphan, there was a profound decrease in the doses that were needed to decrease SBP with nitroprusside by 12.5 mm Hg (nitroprusside bolus) or to increase SBP with phenylephrine by 12.5 mm Hg (phenylephrine bolus).
ergic blockade given the powerful vasodepressor effect of the drug in the absence of the baroreflex. Paradoxically, there is an increase of BP with continuous infusion of isoproterenol but a decrease of BP with bolus doses of isoproterenol. The increase of BP with continuous infusion of isoproterenol may be due to β₂-mediated renin release or β₂-mediated release of catecholamines from postganglionic adrenergic nerve endings. Therefore, bolus administration of isoproterenol after N₂-cholinergic blockade may be more useful to obtain an integrated measure of vascular β₂ sensitivity than continuous infusion.

After N₂-cholinergic blockade, we observed a 10-fold increase in sensitivity to the pressor effect of phenylephrine. It has previously been observed that the pressor effect of norepinephrine and angiotensin II is augmented with the use of ganglionic blockers. Interruption of the baroreflex arc with N₂-cholinergic blockade seems to be the most likely explanation for the pressor hypersensitivity. We observed the change in the pressor response to phenylephrine immediately after N₂-cholinergic blockade (5 to 10 minutes), and the magnitude of this pressor response remained stable throughout the study (1 to 2 hours). Furthermore, there was no relation between plasma norepinephrine level and the pressor effect of phenylephrine with N₂-cholinergic blockade. Therefore, it appears unlikely that the increase in the pressor response so soon after initiation of N₂-cholinergic blockade would be related to upregulation of adrenoreceptors. The sensitivity to phenylephrine after N₂-cholinergic blockade is comparable to sensitivities observed in severe autonomic failure and baroreflex failure. Much of the hypersensitivity to pressor agents in autonomic failure has been interpreted to be due to upregulation of adrenoreceptors in the setting of low circulating catecholamines. However, debuffering of the baroreflex alone could account for most of the pressor hypersensitivity in autonomic failure. In the complete absence of norepinephrine and epinephrine, one would expect extreme upregulation of α-adrenoreceptors. It has been shown, however, that patients with dopamine β-hydroxylase deficiency, who lack the ability to synthesize norepinephrine and epinephrine but still have an intact baroreflex at least in terms of parasympathetic activation, have less hypersensitivity to α-agonists than patients with primary autonomic failure. Another possible reason for the increase in the sensitivity to adrenergic agonists could be decreased release of norepinephrine from nerve terminals. Decreased release of norepinephrine may leave more postsynaptic receptors uncoupled, which could be available for binding to a systemically administered agonist. This explanation is not supported by the lack of a relation between plasma norepinephrine and sensitivity to phenylephrine (and isoproterenol) observed in this study.

The large increase in the depressor effect of nitroprusside during N₂-cholinergic blockade indicates that the cardiovascular effect of nitric oxide donor is buffered by the baroreflex. In some subjects there was an increase in the HR but only a very small change of BP with nitroprusside before trimethaphan. It has been shown in animals that nitric oxide has central nervous effects and decreases sympathetic outflow. A similar central nervous effect of nitric oxide in humans may be suggested by its bradycardic effect in patients with interruption of low-pressure baroreceptor transmission (cardiac transplant) and in patients with baroreflex failure and integrity of the efferent vagal innervation of the heart (selective baroreflex failure). We did not observe a bradycardia with nitroprusside after interruption of the efferent arc of the baroreflex with N₂-cholinergic blockade. Uncoupling of the baroreflex by N₂-cholinergic blockade may be a useful method for obtaining an integrated measure of adrenergic receptor sensitivity and sensitivity to nitric oxide donors in humans. This approach would permit the comparison of normal and abnormal physiological states without the “noise” of baroreflex buffering.

Acknowledgments
This study was supported in part by National Institutes of Health grants RR00095 and NS33460 and by NASA grants NAS 9–19483 and NAGW3873. Jens Jordan is supported by the Deutsche Forschungsgemeinschaft.

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_Hypertension_. 1998;32:101-107
doi: 10.1161/01.HYP.32.1.101

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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