NN-Nicotinic Blockade as an Acute Human Model of Autonomic Failure

Jens Jordan, John R. Shannon, Bonnie K. Black, Robert H. Lance, Mark D. Squillante, Fernando Costa, David Robertson

Abstract—Pure autonomic failure has been conceptualized as deficient sympathetic and parasympathetic innervation. Several recent observations in chronic autonomic failure, however, cannot be explained simply by loss of autonomic innervation, at least according to our current understanding. To simulate acute autonomic failure, we blocked NN-nicotinic receptors with intravenous trimethaphan (6±0.4 mg/min) in 7 healthy subjects (4 men, 3 women, aged 32±3 years, 68±4 kg, 171±5 cm). NN-Nicotinic receptor blockade resulted in near-complete interruption of sympathetic and parasympathetic efferents as indicated by a battery of autonomic function tests. With trimethaphan, small postural changes from the horizontal were associated with significant blood pressure changes without compensatory changes in heart rate. Gastrointestinal motility, pupillary function, saliva production, and tearing were profoundly suppressed with trimethaphan. Plasma norepinephrine level decreased from 1.1±0.12 nmol/L (180±20 pg/mL) at baseline to 0.23±0.05 nmol/L (39±8 pg/mL) with trimethaphan (P<.001). There was a more than 16-fold increase in plasma vasopressin (P<.01) and no change in plasma renin activity. We conclude that blockade of NN-cholinergic receptors is useful to simulate the hemodynamic alterations of acute autonomic failure in humans. The loss of function with acute NN-cholinergic blockade is more complete than in most cases of chronic autonomic failure. This difference may be exploited to elucidate the contributions of acute denervation and chronic adaptation to the pathophysiology of autonomic failure. NN-Cholinergic blockade may also be applied to study human cardiovascular physiology and pharmacology in the absence of confounding baroreflexes. (Hypertension. 1998;31:1178-1184.)

Key Words: autonomic nervous system ■ hypotension ■ trimethaphan ■ receptors, cholinergic ■ catecholamines ■ vasopressin

Pure autonomic failure in its fullest expression is rarely encountered in clinical practice.1,2 The causes of pure autonomic failure are unknown.1,2 Most of the pathophysiological changes in autonomic failure have been conceptualized as deficient sympathetic and parasympathetic innervation.1,2 In patients with chronic autonomic failure, some autonomic functions appear to be almost completely eliminated (eg, pressor response to pain), whereas other autonomic functions are relatively spared (eg, saliva production, pupillary responses).1,2 Certain findings in patients with autonomic failure cannot yet be explained by a loss of autonomic innervation alone. One surprising finding in autonomic failure is the high incidence of supine hypertension.3 Supine hypertension of autonomic failure is driven by a paradoxically increased total peripheral resistance4 in the face of low plasma norepinephrine levels and PRA.3 These observations suggest that the clinical picture of autonomic failure is determined by a combination of a loss of autonomic function and chronic adaptation to this loss that is imperfectly understood.

The purpose of this study was to develop an acute model for the simulation of autonomic failure in humans. Furthermore, we attempted to use this pharmacological model to contrast consequences of the acute loss of sympathetic and parasympathetic control with observations made in patients with autonomic failure.

Methods

Subjects
Seven healthy subjects (4 men, 3 women, aged 32±3 years, 68±4 kg, 171±5 cm) taking no medications were recruited from a pool of normal volunteers. All subjects underwent a thorough clinical examination, electrocardiography, blood analysis, and urinalysis. Written informed consent was obtained before study entry. All studies were approved by the institutional review board of Vanderbilt University Medical Center.

Protocol
The volunteers were admitted to the Elliot V. Newman Clinical Research Center the day testing was performed. Testing was conducted at least 2.5 hours after breakfast. Patients underwent a thorough autonomic evaluation including a standardized physical examination, autonomic reflex testing, and a modified tilt-table test before and after blockade of NN-cholinergic receptors. Heart rate was determined by electrocardiography and respiration by respiratory bellows; BP was measured with an indwelling catheter in the radial artery.
Autonomic Evaluation

The physical examination consisted of auscultation for bowel sounds for 2 minutes at each abdominal quadrant, a Schirmer test, determination of pupil size, and reaction of the pupils to light and accommodation. Loudness of bowel sounds was quantified as 0, absent; 1, barely audible; 2, immediately audible; and 3, audible with the diaphragm elevated. In addition, we counted bursts of bowel sounds. Pupil size was determined first in a darkened room and then after room light was turned on. The change in pupil size with accommodation was also determined. Saliva production was quantified by measuring the increase in weight of four cotton pads inserted between the teeth and cheeks on both sides over a 10-minute interval.

The degree of sinus arrhythmia was assessed during controlled breathing (5-second inhalation and 5-second exhalation for 90 seconds). The sinus-arrhythmia ratio (SA ratio) was calculated as the ratio of the longest to the shortest RR interval during this 90-second period. The response of BP to rapid (approximately 60 breaths per minute) shallow breathing for 30 seconds was determined. BP and HR responses to isometric handgrip (30% of maximum voluntary contraction for 1 minute) and cold pressor testing were determined. BP and HR responses to the Valsalva maneuver (40 mm Hg pressure for 15 seconds) were also determined.5

Skin temperature was measured with seven thermistors (series 700, Yellow Springs Instruments) at the forehead, upper arm, forearm, index finger, thigh, calf, and the large toe. Three consecutive temperature measurements taken 1 minute apart were averaged at baseline and with complete blockade of N\(_N\)-cholinergic receptors.

Tilt testing was performed on a regular tilt table. First, the subject was tilted head down by \(-10^\circ\) for 3 minutes. Then, the table was tilted head up by \(10^\circ\) every 3 minutes until one of the following end points was reached: a tilt angle of \(60^\circ\), an SBP decrease to 70 mm Hg (or to 50 mm Hg below the baseline), or symptoms prohibiting continuation of the test. Changes in BP and HR reached a plateau after about 5 minutes at steady state.

In six subjects, plasma catecholamine levels were determined just before the first set of physiological tests. Plasma catecholamines were again determined at the end of the first tilt test (without trimethaphan). Similarly, plasma catecholamine, PRA, and vasopressin levels were determined at least 30 minutes after achievement of complete blockade of N\(_N\)-cholinergic receptors as the subjects remained supine. Plasma catecholamines were again determined at the end of the tilt test with blockade of N\(_N\)-cholinergic receptors. In six subjects, plasma catecholamine levels were determined just before trimethaphan infusion and at 3, 6, 10, and 15 minutes after the infusion was begun. Blood samples were drawn from a heparin lock placed at least 30 minutes before testing. Arterial blood gases were determined at baseline and with complete N\(_N\)-nicotinic blockade.

Statistics

All data are expressed as mean±SEM. For statistical analysis, all data were transformed into log values. Intraindividual and interindividual differences were analyzed by paired and unpaired \(t\) tests, respectively. If appropriate, ANOVA testing for repeated measures was used. A value of \(P<.05\) was considered to be statistically significant.

Results

Blockade of N\(_N\)-Nicotinic Receptors

The infusion rate necessary to completely block the efferent arc of the baroreflex with trimethaphan was 6±0.4 mg/min (88 μg·kg\(^{-1}\)·min\(^{-1}\)). Arterial blood gases were unchanged with trimethaphan (Table 1). In one subject, the infusion was discontinued after 2 minutes because of an excessive decrease in BP (60/35 mm Hg). In this subject, the trimethaphan infusion could be resumed after intravenous volume loading with 1000 cc of normal saline over 1 hour and testing was completed. Autonomic results were otherwise like those of the other subjects.

BP and HR Changes

Trimethaphan had a rapid onset of action within 2 minutes. Changes in BP and HR reached a plateau after about 5 minutes (Fig 1). BP decreased from 129±4/65±3 mm Hg at baseline to 90±5/48±2 mm Hg (\(P<.0001\)) at steady state infusion. HR increased from 62±3 to 82±5 bpm (\(P<.0001\)). HR variability was markedly attenuated.

![Graph showing changes in HR and BP with trimethaphan infusion at 6 mg/min. The arrowhead indicates the start of the infusion. There is a marked decrease in SBP and DBP, narrowing of the pulse pressure, and an increase in HR with trimethaphan. BP and HR changes reached a plateau after approximately 5 minutes of continuous infusion.](image-url)
Skin Temperature
Changes in skin temperature with blockade of N<sub>N</sub>-cholinergic receptors are illustrated in Fig 2. With trimethaphan, skin temperature appeared to increase less proximally (forehead, upper arm, thigh) than distally (forearm, finger, calf, toe). A significant part of the variance in skin temperature could be explained by drug administration and the site of temperature determination ($P < .001$ for both). The effect of drug administration on skin temperature was different between sites of temperature determination ($P < .01$ by ANOVA). There was a small increase in room temperature during testing from $24.4 \pm 0.6 ^\circ C$ to $25.0 \pm 0.4 ^\circ C$ ($P < .05$).

Autonomic Reflex Testing
Trimethaphan completely abolished sinus arrhythmia (Fig 3) and the pressor response and increase in HR to cold and handgrip exercise (Table 2). Valsalva tests in a representative subject before and after blockade of N<sub>N</sub>-cholinergic receptors are shown in Fig 4. Before trimethaphan, BP remained stable (2±5 mm Hg change compared with baseline) during phase II of the Valsalva maneuver, and HR increased by 21±5 bpm. In phase IV of the Valsalva maneuver, there was an SBP overshoot by 19±5 mm Hg compared with baseline and a compensatory decrease in HR by 10±7 bpm. With trimethaphan, SBP decreased by 39±8 mm Hg during phase II. The BP overshoot during phase IV was absent. There were no compensatory changes in HR (HR ratio, 1.0±0.01). In four subjects, we observed a delayed pressor response after cold pressor testing (n=3) and/or the Valsalva test (n=4) (Fig 4). The increase in SBP was 14±5 and 22±5 mm Hg after cold pressor testing and Valsalva, respectively. This delayed pressor response started 39±5 seconds after cold pressor testing and 39±3 seconds after the Valsalva maneuver. The increase in BP was sustained for more than 3 minutes in all subjects. The decrease in BP with hyperventilation was not augmented with trimethaphan (Table 2).

Tilt Testing
Before trimethaphan, there was a small decrease in SBP from 124±5 mm Hg at −10° to 116±4 mm Hg at 60° HUT ($P < .001$). There was no significant change in DBP (Fig 5).

![Figure 2](image2.png)

**Figure 2.** Changes in skin temperature with trimethaphan infusion compared with baseline. Temperature increased less proximally (forehead, upper arm, thigh) than distally (forearm, finger, calf, toe).

![Figure 3](image3.png)

**Figure 3.** BP and HR with controlled breathing (12 breaths per minute) before (Pre) and during (Post) trimethaphan. Respiration (Resp) was monitored by respiratory bellows. Sinus arrhythmia is almost completely eliminated with trimethaphan.

![Figure 4](image4.png)

**Figure 4.** Valsalva test before (Pre) and during (Post) trimethaphan. The solid bar indicates duration of the maneuver. With ganglionic blockade, there is a continuous decrease in BP in phase II, and the BP overshoot in phase IV is absent. Compensatory changes in HR are abolished with trimethaphan, and there is a delayed increase in SBP by more than 10 mm Hg after the Valsalva maneuver. The delayed increase in BP was sustained for several minutes (not shown).

<table>
<thead>
<tr>
<th>Test</th>
<th>ΔSBP, mm Hg</th>
<th>ΔHR, bpm</th>
</tr>
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<tbody>
<tr>
<td>Before Cold pressor</td>
<td>34±2*</td>
<td>9±3*</td>
</tr>
<tr>
<td>Handgrip</td>
<td>26±4*</td>
<td>13±2*</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>−1±4†</td>
<td>4±2†</td>
</tr>
<tr>
<td>During Cold pressor</td>
<td>−1±1†</td>
<td>0±1†</td>
</tr>
<tr>
<td>Handgrip</td>
<td>−7±3†</td>
<td>−1±1†</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>−1±2†</td>
<td>0±0.3†</td>
</tr>
</tbody>
</table>

Changes in SBP and HR during cold pressor test, handgrip test, and hyperventilation.

* $P < .001$; † not significant.

**TABLE 2. Autonomic Reflex Testing Before and During Trimethaphan Infusion**
HR increased from 59 \pm 62 \text{ bpm at 210° to 89} \pm 64 \text{ bpm at 60° HUT (} P < .0001\). One subject had a vasovagal reaction at 60° HUT. With trimethaphan, BP decreased from 97 \pm 65/53 \pm 62 \text{ mm Hg at 210° to 79} \pm 54/44 \pm 64 \text{ mm Hg at 20° HUT (} P < .01 \text{ for both) (Fig 5, bottom)}. There was no change in HR. Only one subject tolerated a tilt angle of \text{>20°}.

Salivation and Tearing
Saliva production during a 10-minute period decreased from 3.2 \pm 1.0 \text{ g to 0.3} \pm 0.03 \text{ g (} P < .0001\) with blockade of \text{N}_{\text{cholinergic}} \text{ receptors (Fig 6). Tear production also significantly decreased with trimethaphan (} P < .001\) (Fig 6).

Bowel Sounds
Bowel sounds were clearly audible in all subjects before trimethaphan (grade 2 in three subjects, grade 3 in four subjects), and 21 \pm 1 bursts of bowel sounds per 2-minute period were counted. With trimethaphan, bowel sounds were inaudible in all subjects.

Pupillary Function
At baseline, pupil size in the dark was 6.4 \pm 0.4 \text{ mm and decreased by 2.2} \pm 0.2 \text{ mm in response to light and by 1} \pm 0.1 \text{ mm with accommodation (} P < .001\). With trimethaphan, pupil size in the dark was 6.6 \pm 0.3 \text{ mm and did not change with light or accommodation in any subject.}

Plasma Catecholamine Levels
Plasma norepinephrine level started to decrease approximately 4 minutes after the trimethaphan infusion was begun and approached a plateau after 15 minutes (Fig 7). Supine and upright plasma norepinephrine were decreased with trimethaphan (} P < .001\). Before trimethaphan, plasma norepinephrine was 1.1 \pm 0.12 \text{ nmol/L (180} \pm 20 \text{ pg/mL}) supine and increased to 2.3 \pm 0.3 \text{ nmol/L (390} \pm 50 \text{ pg/mL}) at the end of the tilt table test (} P < .001\) (Fig 8). With trimethaphan, plasma norepinephrine was 0.23 \pm 0.05 \text{ nmol/L (39} \pm 8 \text{ pg/mL}) supine increasing to 0.32 \pm 0.07 \text{ nmol/L (54} \pm 11 \text{ pg/mL}) at the end of the tilt test (} P < .05\). In one subject, plasma norepinephrine decreased to 11 \text{ pg/mL} with trimethaphan. There was no significant change in supine or upright plasma epinephrine concentration with trimethaphan (Fig 8). Upright posture increased plasma epinephrine before (} P < .001\) and during trimethaphan infusion (} P < .05\).

Vasopressin and Renin
Plasma vasopressin levels markedly increased from 1.6 \pm 0.1 \text{ pg/mL before to 27} \pm 14 \text{ pg/mL during infusion of trimethaphan (} P < .01\) (Fig 9). The largest increase in plasma vasopressin level observed was from 1.7 \text{ pg/mL to 111}
pg/mL. PRA was 0.74 ± 0.03 ng · L⁻¹ · h⁻¹ at baseline and did not change with trimethaphan (Fig 9).

**Discussion**

This is the first study to assess systematically the potential of \( \text{N}_\text{C} \)-nicotinic receptor blockade to serve as a model of autonomic failure in humans. \( \text{N}_\text{C} \)-Nicotinic receptor antagonists have been used for many years to achieve ganglionic blockade. Ganglionic blockade results in the interruption of sympathetic and parasympathetic nerve traffic.\(^9\) Trimethaphan can cause histamine release in some circumstances. 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.\(^10\) 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.\(^11\)

In this study, almost complete interruption of sympathetic and parasympathetic efferents was achieved with infusion rates of trimethaphan well within the therapeutic range. Blockade of sympathetic efferents was confirmed by the absence of a BP overshoot in phase IV, the excessive decrease in BP during phase II, and the absence of a HR increase in phase II of the Valsalva maneuver.\(^5,12\) Lack of a pressor response to handgrip testing and the cold pressor test further supports interruption of sympathetic nerve traffic.\(^5,13\) Blockade of parasympathetic efferents was confirmed by the absence of sinus arrhythmia\(^14\) and the absence of a compensatory HR decrease during phase IV of the Valsalva maneuver.\(^5,15\) These changes in autonomic function testing are similar to those observed in the most severe cases of autonomic failure.\(^1,2\) Interruption of sympathetic and parasympathetic efferents with trimethaphan caused an almost complete loss of baroreflex function, indicated by the absence of compensatory changes in HR to changes in BP induced by bolus doses of nitroprusside and phenylephrine or the Valsalva maneuver.\(^16\)

While several cardiovascular responses during \( \text{N}_\text{C} \)-cholinergic blockade resembled the responses observed in chronic autonomic failure, some responses were quite different. The hypotensive response to hyperventilation was not increased with blockade of \( \text{N}_\text{C} \)-cholinergic receptors as it is in autonomic failure patients.\(^17,18\) The depressor effect to hyperventilation may require cardiovascular changes other than just interruption of the sympathetic and parasympathetic efferents. An alternative explanation for this phenomenon is that a mechanism that compensates for hyperventilation-induced vasodilation\(^19\) is present in blockade of \( \text{N}_\text{C} \)-cholinergic receptors but not in chronic autonomic failure.

Another finding that has not been described in autonomic failure is the delayed pressor response after the Valsalva maneuver or the cold pressor test. The timing of this pressor response would be consistent with release of a humoral factor (eg, vasopressin).

Blockade of sympathetic and parasympathetic efferents with trimethaphan decreased BP to a similar degree as described previously.\(^20\) Supine BP with blockade of \( \text{N}_\text{C} \)-cholinergic receptors was much lower than supine BP in patients with chronic autonomic failure. In fact, approximately 50% of the patients with severe autonomic failure have supine hypertension,\(^3\) driven by an increase in total peripheral resistance.\(^4\) Interruption of sympathetic efferents may be more complete with blockade of \( \text{N}_\text{C} \)-cholinergic receptors than in autonomic failure. The upregulation of vascular \( \alpha \)-adrenoreceptors in chronic autonomic failure\(^21,22\) may compensate in part for the decrease in sympathetic nerve
traffic. Another possible explanation for the increase in vascular resistance would be chronic vascular remodeling similar to the consequences of long-standing arterial hypertension.23 While supine BP is different between trimethaphan infusion and autonomic failure, there is a similar decrease in BP with relatively minor postural stress.1,2 The subjects in this study became symptomatic with a small postural decrease in BP. Some patients with autonomic failure are relatively asymptomatic with significant orthostatic hypotension. Nausea, the main orthostatic symptom reported by our subjects, seems to be uncommon in pure autonomic failure.1,2,4

There also seems to be a difference between Nc-nicotinic blockade and chronic autonomic failure in the distribution of cardiac output in the supine position. With trimethaphan, there appeared to be an increase in skin perfusion indicated by an increase in skin temperature, which was more pronounced distally than proximally. Redistribution of blood flow to the skin with blockade of Nc-cholinergic receptors has been previously described. In autonomic failure patients, skin perfusion tends to be decreased.25 Furthermore, after a cold pressor test, hand temperature returns more slowly to baseline in patients with multiple-system atrophy (autonomic failure with motor symptoms) than it does in normal control subjects.25 These observations further support the presence of increased vascular resistance in chronic autonomic failure.4

We observed a dramatic reduction in tear fluid and saliva production with trimethaphan, as severe as in patients with the sicca syndrome. By contrast, even in patients with severe forms of autonomic failure, xerostomia and decreased tearing have not been recognized as major clinical problems. Decreases in salivation could contribute to the potentially life-threatening swallowing difficulties that are particularly common in patients with multiple-system atrophy.26

Pupillary responses to light and accommodation were completely blocked by trimethaphan, consistent with complete sympathetic and parasympathetic denervation.27 A similar loss of pupillary function is not commonly observed in autonomic failure. Hypersensitivity of the pupils to a-adrenergic and muscarinic agonists in these patients is consistent with at least partial sympathetic and parasympathetic denervation.9

Paralysis of the gut appeared to be almost complete with trimethaphan. In the past, a substantial number of patients treated with blockade of Nc-cholinergic receptors were misdiagnosed as having acute abdomen.28 In autonomic failure, constipation is a common symptom; however, bowel sounds are typically present. Gastrointestinal motility appears to be less decreased in autonomic failure than it is with trimethaphan.1,2

This disparity between the effects on secretion, pupillary function, and gastrointestinal motility with acute blockade of Nc-cholinergic receptors and those same functions in chronic autonomic failure suggests that these functions tend to be spared in autonomic failure or that compensatory mechanisms are activated in the long term. It is possible that some organ systems might be able to resume their function over time even in the absence of autonomic innervation.

Plasma norepinephrine levels were strikingly decreased after even a few minutes of trimethaphan infusion. By contrast, Nc-nicotinic agonism increases levels of circulating catecholamines.29 In some subjects, the plasma norepinephrine with blockade of Nc-cholinergic receptors was lower than concentrations observed in patients with quite severe autonomic failure.4 The rapid decrease in plasma norepinephrine with blockade of Nc-cholinergic receptors is most likely due to a decrease of release from adrenergic postganglionic neurons. The smaller plasma norepinephrine levels with Nc-cholinergic blockade compared with levels in autonomic failure may be due to neuronal norepinephrine uptake, which is intact with Nc-cholinergic blockade and at least in part lost in pure autonomic failure.30 Given the completeness of ganglionic blockade achieved in this study, the small increase in plasma norepinephrine with HUT is difficult to attribute to an increase in sympathetic nerve traffic. The postural increase in plasma norepinephrine could be due to decreased clearance.30 As in pure autonomic failure, plasma epinephrine levels were relatively preserved with trimethaphan. With a decrease in BP of the magnitude observed with trimethaphan infusion, the appropriate response would have been a substantial increase in plasma epinephrine.

Profound increases in plasma vasopressin levels with blockade of Nc-cholinergic receptors have been previously described in humans.31 Increases in vasopressin levels have also been observed with upright posture in vasovagal syncope (acute symptomatic withdrawal) and in pure autonomic failure (chronic sympathetic and parasympathetic failure).32,33 The vasopressin release is impaired in multiple-system atrophy patients.34,35 The discrepancy between pure autonomic failure and multiple-system atrophy may be due to interruption of either the afferent arc of the baroreflex or intracerebral connections in multiple-system atrophy.36,35 The physiological significance of vasopressin for BP control in humans is still imperfectly understood.36 It has, however, been recognized that the pressor response to vasopressin at physiological concentrations is greatly enhanced with interruption of either the afferent arc (sinoaortic denervation in dogs)37 or the efferent arc (human autonomic failure)38 of the baroreflex. Vasopressin release with trimethaphan may serve as a compensatory response to prevent excessive decreases in BP with blockade of Nc-cholinergic receptors. In animals, vasopressin receptor antagonists (V1) further decrease BP when added to Nc-cholinergic receptors blockade39,40 or a-adrenergic antagonists.41 Administration of a vasopressin antagonist after blockade of Nc-cholinergic receptors in humans could be dangerous, given the relatively low BP associated with blockade of Nc-cholinergic receptors.

The profound decrease in BP with blockade of Nc-cholinergic receptors was not associated with an increase in PRA. An inadequate response in PRA is also described in patients with autonomic failure.42,43 These observations suggest that intrarenal mechanisms cannot overcome the effect of acute or chronic losses of sympathetic function on renin release. Sympathetic innervation to the kidney appears to be more important for renin release than commonly believed.

Respiratory depression is a possible complication with trimethaphan, and several cases of acute respiratory failure have been reported.44 We did not observe any respiratory complications or changes in arterial blood gases in this study.

In conclusion, blockade of Nc-cholinergic receptors is useful to eliminate the influences of the autonomic nervous system on physiological function. According to our current
understanding of chronic autonomic failure, the physiological and biochemical responses to blockade of N\textsubscript{2}C-cholinergic receptors should be similar to chronic autonomic failure. However, the loss of some physiological functions with blockade of N\textsubscript{2}C-cholinergic receptors is more complete than in most cases of human autonomic failure. These differences may be exploited to elucidate the respective contributions of acute denervation and chronic adaptation to the pathophysiology of human autonomic failure. Furthermore, blockade of N\textsubscript{2}C-cholinergic receptors may profitably be applied to the study of human cardiovascular physiology and pharmacology in the absence of confounding baroreflexes.

Acknowledgments
This study was supported in part by National Institutes of Health grants RR00095 and NS33460 and NASA grants NAGW-3873 and NAS 9-19483. Dr Jordan is supported by the Deutsche Forschungsgemeinschaft.

References
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Hypertension. 1998;31:1178-1184
doi: 10.1161/01.HYP.31.5.1178

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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