Syncope (fainting) is defined by a sudden transient loss of consciousness and postural tone because of cerebral hypoperfusion with spontaneous recovery. The most common form of syncope in the young is simple postural faint, denoted vasovagal syncope (VVS), and is associated with vasodilation and vagal-induced bradycardia causing hypotension and loss of postural tone. VVS is extremely common, with lifetime incidence approaching 50%, and can be induced in most people at different thresholds of orthostatic stress. VVS because of upright positioning is initiated by sub-diaphragmatic gravitational blood pooling primarily within the venous system, thereby excessively reducing central blood volume and cardiac output. In VVS, as in hemorrhage, impaired adrenergic vasoconstriction and venoconstriction result in hypotension. We hypothesized that impaired adrenergic responsiveness because of excess nitric oxide can be reversed by reducing nitric oxide.

Most adults with VVS exhibit excessive pooling in the splanchnic circulation and lower extremities that contributes to increased central hypovolemia, reduced CO, and a sustained increase in TPR. In younger adults and children, however, TPR initially increases but then decreases while upright, producing a fall in BP with or without large changes in CO. This is followed by a rapid decrease in BP and HR with orthostasis.

Key Words: adrenergic regulation • dose–response • L-NMMA • nitric oxide • nitric oxide synthase • phenylephrine • syncope (fainting)
WHAT IS KNOWN

- A common syncopal event in young adults is vasovagal syncope (VVS), which is associated with hypotension and loss of postural tone. Normally, baroreceptors maintain blood pressure (BP) by a compensatory increase in total peripheral resistance (TPR), passive elastic recoil of venous blood, and active splanchnic vasoconstriction. BP is also maintained by an increase in heart rate (HR), which increases venous return and cardiac output (CO).
- During VVS in younger adults and children, TPR initially increases but then decreases while upright, producing a fall in BP followed by a rapid decrease in BP and HR with circulatory collapse. VVS in the young has been associated with impaired adrenergic vasoconstriction of the splanchnic regional vasculature.
- Studies of hemorrhage, a model of syncope, showed that the postsynaptic α1-adrenergic response to norepinephrine and exogenous adrenergic vasoconstrictors was impaired which was reversed by nitric oxide synthase (NOS) inhibition.
- Thus, young adult VVS patients may have an impaired postsynaptic α1-adrenergic response that can be reversed by NOS inhibition.

WHAT THE STUDY SHOWS

- There is impaired postsynaptic α1-adrenergic vasoconstriction in young adult VVS patients compared to healthy volunteers. This is associated with reduced TPR and CO responsiveness to phenylephrine in VVS patients.
- The postsynaptic α1-adrenergic vasoconstrictive impairment was greatest in the splanchnic vasculature; forearm and calf α1-adrenergic vasoconstriction were unimpaired in VVS patients.
- This postsynaptic α1-adrenergic vasoconstrictive impairment in young adults with VVS can be corrected following nitric oxide synthase inhibition using L-NMMA.

circulatory collapse. Impaired adrenergic vasoconstriction has been consistently demonstrated in VVS in the young involving abnormalities of the splanchnic regional vasculature.14,15

VVS likely evolved as a defense against excessive blood loss during hemorrhage.16,17 The time course of hemodynamic impairment during gradual hemorrhage mimics the stages of initial BP stability, with a slow fall in BP associated with tachycardia and a rapid decrease in BP and HR with circulatory collapse. Studies of hemorrhage in animals showed adequate endogenous norepinephrine production, but the postsynaptic α1-adrenergic response to norepinephrine and exogenous adrenergic vasoconstrictors was impaired. This impairment was reversed by nitric oxide (NO) synthase (NOS) inhibition.18–20 We, therefore, hypothesized that young adult patients with recurrent VVS may also have an impaired postsynaptic α1-adrenergic response that can be reversed by NOS inhibition.

Methods

Subjects

to test this hypothesis, we recruited 10 subjects with a history of recurrent fainting (6 female, 21.2±1.2 years) and 12 healthy nonfainting control subjects (8 female, 23.0±1.1 years), all between 15 and 27 years of age. There were no differences in the ages, weight, and body mass index comparing both groups. Fainters were referred to our center for investigation after experiencing at least 3 episodes of fainting within the last 12 months. Fainters gave a medical history and underwent a physical examination, electrocardiography, echocardiography, and prolonged monitoring as needed to exclude cardiac and other medical causes of their fainting. Control subjects were recruited from among age- and body mass index–matched volunteers. Control subjects reported no clinical illness, no orthostatic intolerance, and had never fainted.

The diagnosis of VVS was primarily based on the clinical history. Key diagnostic features encompassed predisposing situations, prodromal symptoms, physical signs, and postdrome recovery and symptoms.21 In all patients, past fainting was induced after prolonged standing, and in 2 patients, it was also triggered by noxious stimuli. Prodromal features included pallor, lightheadedness, nausea with abdominal discomfort, diaphoresis, a feeling of warmth, visual scotomata, or frank loss of vision. After the faint, unconsciousness lasted <30 seconds in all when supine, and most patients felt profoundly fatigued afterward. Exclusion criteria for participation in this study included any infectious or systemic disease (including cardiovascular disease), other forms of orthostatic intolerance, competitive athletic training, recent long-term bed rest, use of nicotine-containing products, or pregnancy within the last year. Prior medication for syncope, if any, was stopped for at least 2 weeks before participation in this study. No subjects were taking neurally active or vasoactive drugs. VVS and healthy control subjects previously underwent an upright head-up tilt test to 70°, in which symptoms and signs of real-world syncope were confirmed in VVS patients, and to ensure absence of orthostatic intolerance in controls under test conditions.

Because prolonged upright tilt may invoke a fainting response in young healthy subjects, we limited the head-up tilt testing to 10 minutes. We10,12 have previously demonstrated that this is a sufficient tilt time for the comparison of orthostatic changes between control and syncopal subjects. All subjects in the syncope group fainted during the 10-minute head-up tilt without any provocation, whereas no subjects in the control group fainted or experienced presyncopal symptoms.

All subjects were required to refrain from caffeine and xanthine-containing products for at least 72 hours before testing. All subjects were instructed to fast for at least 4 hours before testing. This study was approved by the Institutional Review Board of New York Medical College. All subjects aged ≥18 years signed an informed consent; those younger than 18 years assented to participate, and their parent or legal guardian signed an informed consent.

Protocol

All patients and control volunteers were instrumented on 2 separate days. On the first day, they received intravenous administration of the NOS inhibitor, Nω-monomethyl-L-arginine, monooacetate salt (L-NMMA). On another day, they received an equilvolumic intravenous infusion of normal saline as a volume control. An amount of phenylephrine (PE), individualized for each subject, was added to the saline to produce BP and HR changes equivalent to the reflex changes caused by the infusion of the L-NMMA. This is referred to as saline+PE.

Instrumentation

Subjects arrived at our climate-controlled center at 9:30 AM and were instructed about the tests and instrumentation. Subjects were then
instrumented while supine. A left antecubital vein catheter was placed for infusion of L-NMMA or for saline+PE. Beat-to-beat BP was measured by Finometer photoplethysmograph (FMS, Amsterdam, The Netherlands) on the right forefinger or middle finger calibrated to the brachial artery. The Finometer uses the ModelFlow algorithm to estimate beat-to-beat relative CO by pulse wave analysis. Before experiments began, ModelFlow CO was calibrated against an Innocor inert gas breathing CO (Innovision, Denmark). We then placed paired electrodes using anatomic landmarks to estimate thoracic, splanchic, pelvic, and calf segmental blood volumes, blood flows, and vascular resistance by impedance plethysmography. Forearm and calf blood flow was also measured by venous occlusion plethysmography every 5 minutes. Respiratory plethysmography (Respitrace, NIMS Scientific, Miami Beach, FL) and capnography (Smith Medical PM, Waukesha, WI) measured changes in respiration and end-tidal carbon dioxide. An ECG measured HR from the beat-to-beat cardiac electric interval. Signals were acquired at 200 samples/s, multiplexed, and A/D-converted using custom software. These measurements are routine for our usual tilt table studies. After instrumentation, subjects remained awake and supine for 30 minutes to acclimate. Baseline data were acquired. Thereafter, either L-NMMA or saline was given by infusion on different days.

**L-NMMA Infusion**

VVS patients and control subjects received the nonisomeric specific NOS inhibitor L-NMMA delivered as a 500 μg/kg per minute intravenous loading dose for 15 minutes, followed by a 50 μg/kg per minute maintenance infusion. L-NMMA is the only parenteral experimental NOS inhibitor available for human use (Bachem, Switzerland; FDA IND exemption No 76,314, J. Stewart). In all subjects, a steady state for HR, BP, TPR, and CO was reached during the maintenance L-NMMA infusion within 40 minutes. Maintenance L-NMMA continued throughout all subsequent measurements.

**Saline+PE Infusion (Denoted Saline+PE)**

On another day, separated by at least 2 days to allow for the elimination of L-NMMA, VVS patients and control subjects received saline delivered to simulate the fluid volume and timing of a loading dose of L-NMMA. During this maintenance phase, a low dose of PE was slowly titrated until HR and BP were similar to HR and BP in the same subject after loading L-NMMA. This dose of PE was maintained throughout the experiment. The amount of PE required to compensate for HR and BP never exceeded 0.2 μg/kg per minute in any subject.

**PE Dose–Response**

After either L-NMMA or saline+PE was infused and HR and BP stabilized, new post-L-NMMA (or post-saline+PE) baseline hemodynamic data were acquired. A PE dose–response (phenyl DR) was then obtained in each subject by infusing additional PE at 0.5, 1.0, 2.0, 3.0, and 4.0 μg/kg per minute for 10 minutes. At each dose, we measured ModelFlow CO, arm and leg blood flows by venous occlusion plethysmography, cuff BP, and HR at minutes 8 to 10 at each concentration. At each PE dose, data were also obtained using all beat-to-beat measurement modalities (eg, impedance, HR, etc). Stopping criteria for the use of PE included a HR<40 beats per minute, a BP>160/85, or the subject’s request to stop. Not all subjects were able to receive all doses of PE before reaching stopping criteria. However, all patients were able to receive 0.5, 1.0, and 2.0 μg/kg per minute infusions of PE each for 10 minutes in succession, and these doses were, therefore, used for comparison. These data were depicted graphically and used for analysis. Statistics were computed by including postloading data (L-NMMA or saline+PE) and the responses to 0.5, 1.0, and 2.0 μg/kg per minute.

**Data Analysis**

During experiments, mean arterial pressure (MAP) was calculated as (systolic BP +2×diastolic BP)/3, and TPR was calculated as MAP/CO. The primary outcome variables were BP, HR, CO, and TPR; secondary outcome variables were changes in splanchic, forearm, and calf blood flows and related regional resistances calculated as MAP/flow. Thoracic (central) blood flow was measured as the CO. Paired t tests were used to compare the response to drug loading shown in Table 1.

The DR data were analyzed as 2 separate experiments (L-NMMA and saline+PE) using a repeated measures analysis of variance. For each experiment, there was one between factor (group, ie, patient versus control) and one within factor (concentration). Within patient, outcomes were measured at 4 concentrations: prechallenge baseline (0), 0.5, 1, and 2 μg/kg per minute of PE concentration, which constituted the repeated measures. The study was conducted on 2 separate days, with the L-NMMA conducted on the first day and saline+PE on the second (separated by at least 2 days). This was done to ensure that the loading dose of saline+PE matched the patient’s fluid volume and pressor response to L-NMMA.

The primary relationship of interest for both experiments was the group by concentration interaction, which describes how patients and controls differ in their response to the concentration challenge under each experimental setting. For these analyses, we assumed a covariance structure of compound symmetry. Reported P values reflect the interaction term using the Greenhouse–Geisser correction. Further, because we assumed that if there were a response to the concentration challenge for either group, the response would increase or decrease monotonically. Thus, our interest was in the difference in slopes between the study groups, rather than the group difference at any particular concentration level. As such, no post hoc pairwise comparisons of groups at concentration-specific concentration levels were conducted. Values are presented as mean±SEM. Statistical significance was set at P≤0.05. NCSS 2007 (NCSS, LCC, and Kaysville) statistical software was used for statistical analyses.

**Results**

**Baseline and Post-Drug Data**

These data are tabulated in Table 1. There was no significant difference in systolic BP or diastolic BP among control and VVS groups, although these pressures tended to be increased after L-NMMA and saline+PE. MAP, however, was significantly increased (P<0.05). HR was not different at baseline, but was significantly reduced by L-NMMA (P<0.05) for control and VVS compared with baseline. Nevertheless, there was no significant difference in HR between L-NMMA and saline+PE. Neither respiratory rate nor end-tidal carbon dioxide (not shown) was affected by either L-NMMA or saline+PE in both control and VVS subjects. CO (thoracic blood flow) and splanchic blood flow were reduced by L-NMMA for control and VVS (P<0.05) compared with baseline, whereas TPR was increased (P<0.05) compared with baseline. There was no significant difference between L-NMMA and saline+PE CO or TPR for either group. There was no effect of drugs on forearm or calf blood flow for controls and VVS.

**MAP and HR Responses to PE**

MAP (top panels), HR (middle panels), and stroke volume during phenyl DR are shown in Figure 1. MAP monotonically increased for all subjects. MAP increased more in control than in VVS patients (P<0.01) during PE infusion (right panels). Loading with L-NMMA (left panels) increased the MAP phenyl DR for both control and VVS, and their respective response curves became similar. HR decreased after infusion of PE, was similar for both groups, and was shifted significantly and similarly for both groups after L-NMMA (P<0.001). Stroke volume increased significantly in VVS during PE infusions (P<0.01) but remained unchanged in controls. After L-NMMA, stroke volume decreased in a...
similar manner for both control and VVS with higher concentrations of PE ($P=0.56$). Thus, phenyl DR for MAP at each dose tested was decreased in VVS after saline+PE loading but was similar to control after L-NMMA loading. HR response was similar for both groups and decreased with L-NMMA.

**Table 1. Baseline and Post-Drug-Load Characteristics**

<table>
<thead>
<tr>
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<th>Control</th>
<th>VVS</th>
<th>Control</th>
<th>VVS</th>
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<td>Post-Load</td>
<td>Baseline</td>
<td>Post-Load</td>
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<td>Diastolic BP, mmHg</td>
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<td>62±2</td>
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<tr>
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<td>65±3</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>L-NMMA</td>
<td>79±1</td>
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<td>Saline+PE</td>
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<td>81±1</td>
<td>84±2*</td>
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<td>HR, beats per minute</td>
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<tr>
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<td>62±3</td>
<td>62±4</td>
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<td>CO, L/min</td>
<td>L-NMMA</td>
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<td>4.2±0.4*</td>
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<td>5.2±0.4</td>
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<td>4.8±0.4</td>
<td>4.6±0.5</td>
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<td>TPR, mmHg/L per min</td>
<td>L-NMMA</td>
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<td>20.3±2.2*</td>
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<td>Saline+PE</td>
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<td>18.1±1.5</td>
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<td>Splanchnic BF, L/min</td>
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<tr>
<td>Saline+PE</td>
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<td>1.2±0.1</td>
<td>1.2±0.1</td>
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<tr>
<td>Forearm BF, mL%/min</td>
<td>L-NMMA</td>
<td>1.67±0.32</td>
<td>1.65±0.33</td>
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<td>Saline+PE</td>
<td>2.05±0.33</td>
<td>2.10±0.27</td>
<td>2.22±0.25</td>
<td>2.18±0.12</td>
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<tr>
<td>Calf BF, mL%/min</td>
<td>L-NMMA</td>
<td>2.41±0.57</td>
<td>2.33±0.54</td>
<td>1.70±0.60</td>
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<tr>
<td>Saline+PE</td>
<td>1.93±0.59</td>
<td>1.82±0.55</td>
<td>1.57±0.32</td>
<td>1.54±0.58</td>
</tr>
</tbody>
</table>

BF indicates blood flow; BP, blood pressure; CO, cardiac output; HR, heart rate; L-NMMA, N\(^{-1}\)monomethyl-L-arginine, monacetate salt; MAP, mean arterial pressure; PE, phenylephrine; post-load, after L-NMMA or saline+PE; TPR, total peripheral resistance; and VVS, vasovagal syncope. *$P<0.05$ compared with baseline.

The TPR with phenyl DR was the mirror image of CO. After saline+PE loading, TPR increased significantly for control during phenyl DR ($P<0.001$), but was not different from saline+PE for VVS during phenyl DR. The phenyl DR for TPR was similar for both groups in the presence of L-NMMA and was shifted significantly upwards for VVS compared with VVS without L-NMMA ($P<0.001$). Thus, phenyl DR was blunted in VVS after saline+PE but was similar to control after L-NMMA loading.

**Splanchnic Blood Flow ($F_{\text{splanchnic}}$) and Splanchnic Vascular Resistance ($R_{\text{splanchnic}}$) Responses to PE**

Splanchnic blood flow ($F_{\text{splanchnic}}$) and splanchnic vascular resistance ($R_{\text{splanchnic}}$) during phenyl DR are shown in Figure 3. Although there was almost no change in $F_{\text{splanchnic}}$ and $R_{\text{splanchnic}}$ to increasing doses of PE for VVS after saline+PE, these values decreased significantly for controls ($P<0.01$). There was, however, a markedly enhanced response to PE after L-NMMA ($P<0.001$). Thus, for VVS in the presence of L-NMMA, $F_{\text{splanchnic}}$ decreased to a great extent, whereas $R_{\text{splanchnic}}$ increased to a greater extent than control in response to increasing doses of PE. In controls, $F_{\text{splanchnic}}$ and $R_{\text{splanchnic}}$ were unaffected by L-NMMA. However, in VVS after L-NMMA, $F_{\text{splanchnic}}$ was excessively decreased and $R_{\text{splanchnic}}$ was excessively increased.

**Forearm and Calf Vascular Resistance Responses to PE**

In contrast to the splanchnic vasculature, the increase in forearm and calf vascular resistance shown in Figure 4 increased similarly during the phenyl DR for control and VVS subjects, and the presence of L-NMMA did not significantly affect these relationships. These findings are consistent with data presented in Table 2, which show that there were no significant differences in calf and forearm blood flows in control and VVS patients at each concentration of PE tested.

**Discussion**

The results of this study in young adults indicate that there is impaired postsynaptic $\alpha_1$-adrenergic vasoconstrictive impairment in VVS patients compared with healthy volunteers, which results in reduced TPR and CO responsiveness to PE in our subjects with a history of VVS. Interestingly, this postsynaptic $\alpha_1$-adrenergic vasoconstrictive impairment can be corrected after NOS inhibition using L-NMMA.

We show that postsynaptic $\alpha_1$-adrenergic vasoconstrictive impairment is greatest in the splanchnic vasculature, based on our demonstration that splanchnic blood flow in the absence of NOS inhibition by L-NMMA is relatively unaffected by PE. However, after L-NMMA, splanchnic flow decreased in a dose-dependent manner in both control and VVS subjects after PE administration. In contrast, forearm and calf $\alpha_1$-adrenergic vasoconstriction are unimpaired in VVS patients and apparently unaffected by L-NMMA.

In the present investigation, we were only interested in whether PE had an effect on group differences and whether the response slopes differed as concentrations of PE were increased. Thus, we were not interested in differences at each

**CO and TPR Responses to PE**

CO and TPR during phenyl DR are shown in Figure 2. CO monotonically decreased with PE for control subjects ($P<0.001$), but was not different compared with VVS subjects. The presence of L-NMMA resulted in a decrease of CO with PE that was similar for both control and VVS.
Figure 1. Mean arterial pressure (MAP; upper), heart rate (HR; middle), and stroke volume (SV; lower) during phenylephrine (PE) dose–response for control subjects (solid lines) and vasovagal syncope (VVS) subjects (dashed lines). Saline and low-dose PE were infused to simulate the fluid volume and maintained (right) to assure that HR and MAP were similar to HR and MAP in each subject after loading Nω-monomethyl-L-arginine, monoacetate salt (L-NMMA; left). This is depicted as post-saline+PE and is shown for control subjects who received saline and PE (C-PE), control subjects who received L-NMMA (C+LNMMA), patients with VVS subjects who received saline and PE (VVS-PE) and patients with VVS who received L-NMMA (VVS+LNMMA). After that, increasing concentrations of PE were infused each for 10 minutes. P values represent the group by concentration interaction effect.
concentration or in identifying the concentration at which the departure became significant because this was deemed to be relatively unimportant.

These observations are consistent with findings of NO-potentiated splanchnic hyporeactivity,\textsuperscript{24} blunted chemoreflex,\textsuperscript{23} abnormal cerebral autoregulation,\textsuperscript{26} and impaired cardiovagal baroreflex,\textsuperscript{27} which occur during the later presyncopal phase of VVS.

**Evidence From the Literature That Nitric Oxide Blunts Adrenergic Neurotransmission**

NO is a fundamental signaling molecule with pleiotropic effects and ubiquitous distribution. Three separate NOS isoforms are recognized: neuronal NOS (nNOS), inducible NOS, and endothelial NOS. nNOS and endothelial NOS are constitutively expressed and depend on calcium calmodulin.\textsuperscript{28}

nNOS is found in the brain and in peripheral tissues, such as skin, kidney, and splanchnic vasculature, where neuronal NO acts to modulate adrenergic neurotransmission.\textsuperscript{29} nNOS has been localized to nitrergic nerves that proliferate within the gastrointestinal tract and distribute with the parasympathetic nervous system.\textsuperscript{29} Although local endothelial NOS exerts endothelial-mediated vascular effects, which could directly mediate vasodilation in VVS,\textsuperscript{30,31} NO released from nitrergic nerves can act at prejunctional and postjunctional sites to reduce sympathetic transduction.\textsuperscript{32} Effects are largest in the splanchnic vasculature\textsuperscript{33} and in the kidney,\textsuperscript{34} where the density of nitrergic nerves is greatest, and are most potent during sympathetic activation.

Our previous work demonstrated nNOS dependence of the local skin heating response,\textsuperscript{35} whereas corelease of NO from cholinergic nerves in part mediates active cutaneous vasodilation.\textsuperscript{36} Heat-induced NO vasodilation informs on its ability to blunt adrenergic vasoconstriction.\textsuperscript{37} The sympatholytic effect of NO in man may be less potent in skeletal muscle,\textsuperscript{38} although combined prostaglandin and NO inhibition augments adrenergic vasoconstriction during contraction.\textsuperscript{39} Excessive NO may play a role in autonomic failure.\textsuperscript{40}

**Figure 2.** Cardiac output (CO; upper) and total peripheral resistance (TPR; lower) during phenylephrine (PE) dose–response for control subjects (solid lines) and vasovagal syncope (VVS) subjects (dashed lines). Saline and low-dose PE were infused to simulate the fluid volume and maintained (right) to assure that heart rate (HR) and mean arterial pressure (MAP) were similar to HR and MAP in each subject after loading N\textsuperscript{ω}-monomethyl-L-arginine, monoacetate salt (L-NMMA; left). This is depicted as post-saline+PE and is shown for control subjects (C-PE), control subjects who received L-NMMA (C+LNMMA), patients with VVS who received saline and PE (VVS-PE) and patients with VVS who received L-NMMA (VVS+LNMMA). After that, increasing concentrations of PE were infused each for 10 minutes. $P$ values represent the group by concentration interaction effect.
Splanchnic hyperemia occurs in real or simulated microgravity (bedrest in man, hindlimb suspension in rats), where it is associated with orthostatic intolerance, adrenergic hyporeactivity, and enhanced microvascular production of NO through increased transcription of NOS isoforms. Increased NO has been reported in both postural tachycardia syndrome and VVS, but those results are controversial because of measurement methods and lack of subsetting. Nevertheless, nitrergic NO modulation of adrenergic vasoconstriction causes splanchnic hyperemia, and our data indicate that our patients with VVS overproduce NO within the splanchnic circulation by pathways as yet undefined, resulting in a postsynaptic defect in adrenergic vasoconstriction. If present during orthostasis, such a defect could lead to a blunted response to sympathetic stimulation and potentiate VVS in this cohort of subjects.

The effects of NO on the adrenergic system are protean. In this article, we examined only postsynaptic effects, which could include decreased number of adrenergic receptors—unlikely given the fairly rapid normalizing effects of L-NMMA. Postsynaptic effects could also include interference with adrenergic binding and in the transduction process, making them likely candidates for NO-induced vasoconstrictive downregulation. These candidate mechanisms cannot be distinguished based on current data. In addition, other unmeasured NO effects, such as reduction of central sympathetic activation and ganglionic transmission, may be important and are subjects for subsequent investigation.

These results, obtained in young adults, aged 15 to 27 years, may be different than those obtained from older adults. There is an increase in the reporting of VVS with age and in females; there is a first peak of syncopal incidents occurring at 15 to 24 years, with another peak occurring at age 40. The mechanisms of VVS at various ages are unclear, but this increased incidence has been attributed to the increased use of vasoactive and cardioactive medications, decreased vascular compliance, diminished cardiac function, physical deconditioning, and poorer health with age. Therefore, our findings of impaired postsynaptic \( \alpha_1 \)-adrenergic...
vasoconstriction in VVS, which can be corrected by NOS inhibition, may be a finding that is unique to young adults.

**Limitations**

The study may be underpowered with respect to measurements of forearm and calf vascular resistance. Because of this, we were unable to demonstrate changes in resistance after loading L-NMMA, although these noisy data could reflect a trend toward increased limb resistances with L-NMMA. However, the results do show that limb resistance after saline+PE loading is not different for VVS compared with control subjects. In addition, because of the small sample size, significant findings may be products of type I errors given that there are multiple outcomes in addition to multiple testing for each outcome.

Because the incidence of syncope is dramatically higher in older versus younger adults, the findings of this study are likely not applicable across all age groups. Sex differences and menstrual phase were not distinguished. There were insufficient subjects for this purpose. However, no obvious difference in sympathetic nerve activity or vasoconstrictive ability by sex or menstrual phase has been found, although differences in total blood volume reduce BP in women.48,49

**Acknowledgments**

Dr Stewart was responsible for the conception and design of the experiments, interpretation of data, and drafting the article. M. Suggs was responsible for collection, assembly, and interpretation of the data. Dr Merchant was responsible for collection, assembly, and interpretation of the data. Dr Sutton was responsible for interpretation.
of the data and revising the article. C. Terilli was responsible for collection, assembly, and interpretation of the data. Dr Visintainer was responsible for biostatistical analysis and interpretation of the data and critically revising intellectual content of the article. Dr Medow was responsible for the design of the experiments, analysis and interpretation of the data, and critically revising intellectual content of the article.

Sources of Funding
Funding for this project was provided by grants RO1 HL 112736 and RO1 HL 074873 from the National Heart Lung and Blood Institute.

Disclosures
None.

References
Nitrergic Oxidation Blunts Vasodilation in Sympathetic Tone


Postsynaptic $\alpha_1$-Adrenergic Vasoconstriction Is Impaired in Young Patients With Vasovagal Syncope and Is Corrected by Nitric Oxide Synthase Inhibition
Julian M. Stewart, Melissa Suggs, Sana Merchant, Richard Sutton, Courtney Terilli, Paul Visintainer and Marvin S. Medow

*Circ Arrhythm Electrophysiol.* 2016;9:
doi: 10.1161/CIRCEP.115.003828
*Circulation: Arrhythmia and Electrophysiology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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