Sympathetic withdrawal and forearm vasodilation during vasovagal syncope in humans

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Dietz, Niki M., John R. Halliwill, John M. Spielmann, Lori A. Lawler, Bettina G. Papouchado, Tamara J. Eickhoff, and Michael J. Joyner. Sympathetic withdrawal and forearm vasodilation during vasovagal syncope in humans. J. Appl. Physiol. 82(6): 1785–1793, 1997.—Our aim was to determine whether sympathetic withdrawal alone can account for the profound forearm vasodilation that occurs during syncope in humans. We also determined whether either vasodilating $\beta_2$-adrenergic receptors or nitric oxide (NO) contributes to this dilation. Forearm blood flow was measured bilaterally in healthy volunteers (n = 10) by using plethysmography during two bouts of graded lower body negative pressure (LBNP) to syncope. In one forearm, drugs were infused via a brachial artery catheter while the other forearm served as a control. In the control arm, forearm vascular resistance (FVR) increased from 77 ± 7 units at baseline to 191 ± 36 units with −40 mmHg of LBNP (P < 0.05). Mean arterial pressure fell from 94 ± 2 to 47 ± 4 mmHg just before syncope, and all subjects demonstrated sudden bradycardia at the time of syncope. At the onset of syncope, there was sudden vasodilation and FVR fell to 26 ± 6 units (P < 0.05 vs. baseline). When the experimental forearm was treated with bretylium, phentolamine, and propranolol, baseline FVR fell to 26 ± 2 units, the vasoconstriction during LBNP was absent, and FVR fell further to 16 ± 1 units at syncope (P < 0.05 vs. baseline). During the second trial of LBNP, mean arterial pressure again fell to 47 ± 4 mmHg and bradycardia was again observed. Treatment of the experimental forearm with the NO synthase inhibitor N$^G$-monomethyl-L-arginine in addition to bretylium, phentolamine, and propranolol significantly increased baseline FVR to 65 ± 5 units but did not prevent the marked forearm vasodilation during syncope (FVR = 24 ± 4 vs. 29 ± 8 units in the control forearm). These data suggest that the profound vasodilation observed in the human forearm during syncope is not mediated solely by sympathetic withdrawal and also suggest that neither $\beta_2$-adrenergic-receptor-mediated vasodilation nor NO is essential to observe this response.

METHODS

Subjects

Ten healthy subjects (4 women and 6 men) between the ages of 21 and 37 yr were studied. The study was approved by the Institutional Review Board, and each subject gave written informed consent. Female subjects had a negative pregnancy test within 48 h before the study. Before the beginning of the study, we obtained United States Food and Drug Administration permission to administer N$^G$-monomethyl-L-arginine (L-NMMA) to humans.

Subjects were studied in the supine position in a LBNP box with the arms extended and slightly above heart level. Some studies were performed in the morning and others in the afternoon. The subjects were instructed to abstain from caffeine and avoid eating a heavy meal for a period of at least 3 h before the study. Throughout all studies, the laboratory temperature was maintained between 22 and 24°C.
Arterial Catheterization

A 20-gauge, 5-cm brachial artery catheter was placed in the nondominant forearm by using aseptic technique after local anesthesia (1% lidocaine) was administered. The catheter was connected to a pressure transducer and flushed continuously at 3 ml/h with saline containing heparin (2 units/ml). A three-port connector was placed in series with the catheter-transducer system. One port was used to measure arterial pressure, and the two other ports were used for drug infusions (8–10).

Subject Monitoring

Heart rate was obtained by use of a five-lead electrocardiogram. The arterial waveform from the pressure transducer was used to measure arterial pressure.

Forearm Blood Flow (FBF) and Skin Blood Flow

FBF was measured in both forearms by using venous occlusion plethysmography with mercury-in-Silastic strain gauges (15). The venous collecting pressure was set at 50 mmHg and was decreased to 30–40 mmHg during the immediate presyncopal period to ensure that the collecting pressure did not alter arterial pressure. When FBF was measured, flow to the hand was excluded by inflating a wrist cuff to suprasystolic pressure (250 mmHg). FBF was measured four times each minute. Skin blood flow was measured in the experimental forearm with a laser-Doppler blood perfusion monitor (model 403; Vasa Medics, St. Paul, MN) device located in close proximity to the strain gauge with skin blood flow values expressed as arbitrary laser-Doppler units (10). LBNP

The lower body of the subject was sealed in an airtight box at the iliac crests (18). Negative pressure was applied to the box in a graded fashion starting at 20 mmHg and ending at 60–100 mmHg. The end point of LBNP was determined by signs and symptoms of syncope, including a marked decrease in mean arterial blood pressure, bradycardia, and, in some cases, loss of consciousness.

Drug Preparation and Administration

Bretylium (American Regent Laboratories, Shirley, NY) was administered intra-arterially in doses of 2.5 mg/min for 5 min to inhibit the presynaptic release of norepinephrine in the forearm (4). This dose of bretylium is known to abolish forearm vasoconstrictor responses to a variety of physiological stimuli for many hours. A 25-min rest period followed initial administration of this dose of bretylium so that FBF measurements would not be taken during the initial vasoconstriction seen with the administration of bretylium (4). After the 25-min rest period, a second dose of the same amount was given. At this time the forearm was also treated with phentolamine (Regtine, CIBA Pharmaceutical, Summit, NJ) in a dose of 100 µg/min for 5 min intra-arterially to inhibit α-adrenergic receptors (11). In pilot studies these drugs selectively inhibited the vasoconstrictor response to venous pooling with moderate (<40 mmHg) LBNP. Finger temperature was also measured to evaluate the adequacy of forearm α-adrenergic-receptor inhibition. During the bouts of LBNP, low-dose intra-arterial infusions of both drugs (bretylium and phentolamine) were continued to control for potential drug washout. Propranolol (SoloPak Laboratories, Elk Grove Vil-lage, IL) was infused intra-arterially at 200 µg/min for 5 min (11, 19) to block α-adrenergic receptors in the forearm and thus inhibit the action of any circulating catecholamines. This dose has been shown previously to block the forearm vasodilator response to the α-adrenergic-receptor agonist isoproterenol (19). During initial infusions of bretylium, phentolamine, and propranolol, the subject was instructed to perform gentle hand contractions with the arm receiving the drugs to facilitate more uniform drug distribution throughout the forearm muscles.

Our overall rationale was that local infusion of these drugs allowed us to inhibit the release and/or actions of catecholamines on the forearm circulation but permitted the normal changes in sympathetic nerve traffic to the forearm to continue during orthostatic stress. This would allow any potential vasodilating factors dependent on intact sympathetic innervation to continue to act on the experimental forearm during orthostatic stress and syncope. In contrast, previous studies in humans have used either peripheral nerve blocks or patients who have undergone surgical sympathectomy to address these issues (2, 3). Our experimental approach also differed from experiments in conscious animals that have used systemic administration of drugs that can alter arterial blood pressure to study the mechanism of syncope caused by experimental hemorrhage (20).

The NO synthase inhibitor l-NMMA (Calbiochem, La Jolla, CA) was given intra-arterially (8–10, 37). A total of 50 mg was given in divided doses over 15 min (4 mg/min for 5 min, 1 min of rest, 4 mg/min for 5 min, and 2 mg/min for 5 min after an acetylcholine test). This dose of l-NMMA has been shown to cause a marked reduction in baseline FBF, a variable blunting of the vasodilator responses to intra-arterial acetylcholine, and a reduction of the rise in FBF during mental stress by ~70% (9). l-NMMA was infused with the wrist cuff inflated to saturate the forearm, and the subject was instructed to perform gentle contractions during the infusion to ensure distribution throughout the forearm. In three additional subjects, atropine sulfate (American Regent Laboratories) was administered intra-arterially in doses of 0.2 mg to selectively inhibit cholinergic-muscarinic receptors (27). This dose has been shown previously to attenuate the forearm vasodilator response to acetylcholine.

Acetylcholine (Miochol, IOLAB, Claremont, CA) was administered in doses of 32 µg/min given intra-arterially to stimulate the release of NO from the vascular endothelium (8, 9). A blunting of the vasodilator response to acetylcholine was consistent with inhibition of NO synthase in the vascular endothelium (8, 9, 37). Sodium nitroprusside (Eikins-Sinn, Cherry Hill, NJ) was administered intra-arterially in doses of 10 µg/min to test the continued ability of the forearm vasculature to dilate after l-NMMA administration (8, 9, 37).

Protocol

Forearm vascular responses to orthostatic stress and syncope after pharmacological sympathectomy and NO synthase inhibition. After subject instrumentation, resting values were obtained for arterial blood pressure, heart rate, FBF, skin blood flow, and fingertip temperature. Bretylium, phentolamine, and propranolol were then administered as described in Drug Preparation and Administration.

After additional blood flow measures were taken to establish a post-drug administration baseline, acetylcholine was administered and changes in FBF were measured. After a break (5–10 min) to allow FBF to return to baseline, sodium nitroprusside was administered and changes in blood flow were measured.
When blood flows had returned to baseline after acetylcholine and sodium nitroprusside, FBF was measured for 2 min and LBNP was then initiated at 20 mmHg. After 2 min the LBNP was increased to 40 mmHg and subsequently increased in increments of 10 mmHg, with a duration of 2 min at each level of LBNP. This pattern of LBNP was continued until the subject displayed signs or symptoms of syncope, including marked hypotension, bradycardia, and/or loss of consciousness. At syncope, the LBNP was discontinued. Blood flow was measured in both forearms during the entire period of LBNP and for 2 min after the LBNP was stopped.

After the subjects had recovered and FBF returned to baseline, L-NMMA was infused. An acetylcholine trial was then conducted to test the NO synthase inhibition. The supplemental dose of L-NMMA was then infused along with supplemental doses (one-half of the initial dose) of the other drugs to replace any drugs that may have washed out or been metabolized.

Baseline measurements were then taken, followed by a second bout of LBNP. Again, low-dose infusions of bretylium, phentolamine, and propranolol were administered throughout the entire period of LBNP. After a 10-min rest period, a sodium nitroprusside trial was conducted to demonstrate that the forearm vasodilatory capacity was not altered in the presence of L-NMMA. It should be noted that it was not possible to counterbalance the order of testing in this study because of the prolonged effects of the drug treatments of bretylium, propranolol, phentolamine, and L-NMMA.

RESULTS

Effects of Various Drugs on Baseline Values and Dilator Responses to Acetylcholine and Sodium Nitroprusside

Baseline FBF was initially the same in both arms and rose in the experimental arm after bretylium, phentolamine, and propranolol in a manner consistent with forearm sympathectomy (4.0 ± 0.3 vs. 1.3 ± 0.2 ml·100 ml⁻¹·min⁻¹ in the control arm; P < 0.05). Finger temperature also rose in the treated arm from 30.3 ± 1.5 to 35.9 ± 0.2°C after bretylium, phentolamine, and propranolol (P < 0.05). These responses indicate that there was a marked reduction of local adrenergic constrictor tone in the treated forearm.

Baseline FBF after L-NMMA, bretylium, phentolamine, and propranolol fell to 1.6 ± 0.2 ml·100 ml⁻¹·min⁻¹ (P < 0.05 vs. pre-L-NMMA value). FBF during acetylcholine rose to 11.4 ± 1.6 ml·100 ml⁻¹·min⁻¹ after bretylium, phentolamine, and propranolol (P < 0.05 vs. baseline). L-NMMA caused a ~65% reduction in the blood flow response to acetylcholine (5.1 ± 1.3 ml·100 ml⁻¹·min⁻¹; P < 0.05 vs. pre-L-NMMA). The FBF responses to sodium nitroprusside were unaffected by any of the drugs (10.1 ± 1.1 vs. 10.3 ± 1.2 ml·100 ml⁻¹·min⁻¹; P > 0.05). These data indicate that L-NMMA reduced both the basal and stimulated release of NO but did not alter the ability of the forearm vessels to dilate.

Effects of Orthostatic Stress on Heart Rate and Arterial Blood Pressure

Syncope was achieved during trial 1 at a mean LBNP of 70 ± 3 mmHg (range 60–100 mmHg) and during trial 2 at a mean LBNP of 70 ± 4 mmHg (range 60–100 mmHg) (P > 0.05 trial 1 vs. trial 2). Table 1 displays heart rate and mean arterial pressure data during the protocol as well as FBF. Heart rate increased progressively with increasing orthostatic stress and decreased suddenly at syncope while mean arterial pressure progressively decreased to a minimum value seen at syncope.

Figure 1 is an original tracing of arterial pressure responses along with the blood flow record from one subject. It shows the characteristic reductions in FBF in the control forearm during LBNP, with a large increase in flow at syncope. Similar responses were seen in the control arm during both trials. There were also marked increases in FBF during syncope in the arm treated with bretylium, phentolamine, and propranolol and then again in the second trial after L-NMMA. In the three subjects who received selective intra-arterial atropine before the second bout of LBNP, similar vasodilator responses were observed in both forearms. After observing this negative result for three consecutive subjects, we chose not to address this issue further.

Vasoconstrictor and vasodilator responses to orthostatic stress. Figure 2A shows forearm vascular resistance during the two bouts of syncope. Figure 2B displays forearm vascular conductance for the same
At syncopal there was a decrease in resistance to a value creased with increasing LBNP, whereas forearm vascular study period. In the control arm, forearm vascular responses during LBNP.

### Table 1. Mean arterial pressure and heart rate responses during LBNP

<table>
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<tr>
<th></th>
<th>Heart Rate, beats/min</th>
<th>Mean Arterial Pressure, mmHg</th>
<th>FBF, ml·100 ml⁻¹·min⁻¹</th>
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<tbody>
<tr>
<td><strong>Trial 1 LBNP</strong></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>61 ± 3</td>
<td>94 ± 2</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>20 mmHg</td>
<td>64 ± 3†</td>
<td>92 ± 1†</td>
<td>0.9 ± 0.1†</td>
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<td>40 mmHg</td>
<td>78 ± 3†</td>
<td>91 ± 2†</td>
<td>0.9 ± 0.2†</td>
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<tr>
<td>Maximum heart rate*</td>
<td>103 ± 4†</td>
<td>84 ± 3†</td>
<td>4.0 ± 0.7†</td>
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<tr>
<td>Syncope</td>
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<td>47 ± 4†</td>
<td>5.2 ± 0.4†</td>
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<tr>
<td><strong>Trial 2 LBNP</strong></td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>56 ± 3</td>
<td>94 ± 2</td>
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<tr>
<td>20 mmHg</td>
<td>60 ± 3†</td>
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<td>80 ± 3†</td>
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Values are means ± SE. LBNP, lower body negative pressure; FBF, forearm blood flow. *Actual time point associated with maximum heart rate varies from subject to subject, and blood pressure values corresponding to this point were selected for each subject. FBF data are not included for this time point because it was difficult to obtain 3 consecutive consistent blood flow measurements because of rapidly changing hemodynamic variables. †P < 0.05 vs. baseline value (same trial). ‡P < 0.05 vs. maximum value (same trial).

Table 1. Mean arterial pressure and heart rate responses during LBNP

study period. In the control arm, forearm vascular resistance was 77 ± 7 units and progressively increased with increasing LBNP, whereas forearm vascular conductance decreased (both P < 0.05 vs. baseline). At syncopal there was a decrease in resistance to a value significantly less than baseline (26 ± 6 vs. 77 ± 7 units; P < 0.05). This corresponded with a significant increase in forearm vascular conductance above baseline. In the forearm that received pharmacological sympathetic inhibition, baseline vascular resistance was less than baseline (26 ± 2 vs. 77 ± 7 units; P < 0.05 vs. control forearm), and the progressive increase in resistance seen with increasing LBNP was nearly eliminated (P < 0.05 vs. control). Similarly, almost no change in conductance was observed. However, at syncope, forearm vascular resistance in the sympathectomized arm suddenly decreased below baseline to 16 ± 1 units (P < 0.05), and forearm vascular conductance was increased to greater than the postsympathectomy baseline. This peak vasodilator response was slightly greater than that seen in the control forearm (P < 0.05 for forearm vascular resistance, and P < 0.10 for forearm vascular conductance).

During the second bout of LBNP, the changes in forearm vascular resistance and forearm vascular conductance in the control arm were similar but with greater subject-to-subject variability than those seen in the control arm in the first bout. In the experimental forearm that received L-NMMA in addition to the pharmacological sympathetic inhibition, baseline forearm vascular resistance was increased significantly compared with with the pre-L-NMMA baseline (65 ± 5 vs. 26 ± 2 units; P < 0.05), and the progressive increase in resistance seen with increasing LBNP was again eliminated. At syncope, as in the first bout, there was a large sudden decrease in forearm vascular resistance and a large increase in conductance (both P < 0.05).

The minimum resistance values during syncpe were similar in the experimental (L-NMMA-treated) and control forearms (24 ± 4 vs. 29 ± 8 units; P > 0.05) and was also similar to the values observed during the first bout of LBNP. The peak dilator responses in the control forearm were almost identical during the two trials when expressed as either resistance or conductance. Of note was that the peak dilator responses were somewhat lower during the second trial after the experimental forearm was treated with L-NMMA when expressed as resistance (P < 0.05 for forearm vascular resistance) but not as conductance. However, because the baseline resistance was higher, the total fall in resistance was actually greater. It is likely that this represents an artifact associated with the curvilinear relationship of resistance to flow and arterial pressure, which can become evident when resistance values are compared over a wide range.

**Contribution of Skin to Forearm Dilator Responses During Syncope**

Baseline skin blood flow measured by laser Doppler was 1.5 ± 0.3 units after bretylium, phentolamine, and propranolol administration and decreased to 0.8 ± 0.2 laser-Doppler unit at syncope (P < 0.05). Baseline skin blood flow after L-NMMA administration was 1.0 ± 0.2 laser-Doppler units (P < 0.05 vs. pre-L-NMMA baseline) and again fell at syncpe to 0.4 ± 0.1 laser-Doppler units (P < 0.05).

**DISCUSSION**

The major finding of this study is that the marked vasodilation seen in human limbs during syncpe is still observed after local inhibition of sympathetic adrenergic neurotransmission and blockade of both α- and β₂-adrenergic receptors. Additionally, this vasodilation was only minimally affected by inhibition of NO synthesis. When these findings are viewed in the context of prior research, they support the concepts that 1) intact autonomic innervation of the upper extremity is required for the marked forearm vasodilation seen during syncpe and 2) neither β₂-adrenergic-receptor-mediated vasodilation nor NO is essential to observe this dilation (2, 20, 28, 29). The limitations associated with these observations along with physiological relevance of these observations will be discussed.

**Use of Plethysmography to Study FBF During Syncpe**

There may be limitations inherent with the use of venous occlusion plethysmography to measure FBF in this particular situation that warrant comment. In this context, the resting flows measured in this study were lower than usually observed in our laboratory (i.e., ~2 ml·100 ml⁻¹·min⁻¹) with use of identical techniques at a similar ambient temperature (8–10, 12). We offer several explanations for this observation. First, knowledge of impending syncpe may have contributed to a higher baseline level of sympathetic activity in our subjects. This mechanism is supported by our observa-
tions that the FBF values after bretylium and phentolamine administration were similar to those observed previously (8). Second, almost one-half of our subjects were women, with a slighter build and less forearm muscle mass than the male subjects. This resulted in mean FBF values that were lower than those of the typical male study populations from which most blood flow data have traditionally been collected. Finally, absolute values of flow are difficult to compare from study to study and between individuals when plethysmography is used to measure flow. This is due to a variety of issues related to the technique and its application. However, venous occlusion plethysmography remains a reliable index of relative changes in flow when cardinal rules related to its use are followed (15, 26).

It should also be noted that baseline blood flows between the two arms were different after pharmacological inhibition of sympathetic vasoconstrictor tone. However, we were interested primarily in the peak dilation seen during syncope. Thus the marked dilation seen during syncope in both forearms makes this concern less pressing. Further, our conclusions are similar when vasomotor tone is considered by using either calculated forearm conductance or resistance (6, 21).

Another potential problem with the use of plethysmography during LBNP is posed by the rapidly changing systemic hemodynamics and arterial blood pressure. To address this issue we followed the cardinal principles of venous occlusion plethysmography when arterial pressure was changing (15). Care was taken to ensure that the collecting pressure did not interfere with the arterial waveform. Additionally, only linear plethysmographic slopes (Fig. 1) were used in interpretation of data and for calculation of conductance and resistance values. However, our strict adherence to these guidelines often prevented assessment of FBF during the nadir of the vasovagal response because

Fig. 1. Forearm blood flow (FBF) changes during lower body negative pressure (LBNP). Actual record from 1 subject of arterial blood pressure (AP) and plethysmographic slopes obtained from strain gauges on both forearms during 2 trials of LBNP. Actual FBF values in mL·100 ml⁻¹·min⁻¹ are shown corresponding to each individual plethysmographic slope. Recordings at baseline are represented in panels at left, during 40 mmHg of LBNP in panels in middle, and at syncope in panels at right. A: during trial 1 of LBNP, baseline flows were higher in experimental forearm that had received pharmacological sympathetic inhibition with bretylium, phentolamine, and propranolol. During LBNP (middle), marked vasoconstriction was seen in control forearm, with little change in slope seen in experimental forearm. At syncope (right), there was a marked increase in FBF (increased slopes) and vasodilation in both forearms. B: during trial 2 of LBNP, baseline flows (left) in experimental forearm were lower than in trial 1 after nitric oxide synthase inhibition with N⁷-monomethyl-L-arginine was added to bretylium, phentolamine, and propranolol. During LBNP (middle), marked vasoconstriction was seen in control forearm, with no change in flow seen in experimental forearm. At syncope (right), there was again a marked increase in FBF (increased slopes) and vasodilation in both forearms. This observation suggests that an active vasodilator mechanism contributes to skeletal muscle vasodilation during syncope. It also suggests that neither β₂-adrenergic-receptor-mediated vasodilation nor nitric oxide is essential to observe this dilator response.
perfusion pressure was often too low to allow valid measurements. Thus the actual vasodilation may have been even greater before the time our peak vasodilation was recorded.

It is unlikely that marked changes in skin vasomotor tone can explain these responses because skin blood flow responses fell by 50% at syncope. These responses are consistent with the general concept that marked skin vasodilation does not occur during syncope (2, 22, 38).

NO Synthase Inhibition in Humans

Assessment of the level of NO synthase inhibition after L-NMMA is difficult. Administration of L-NMMA significantly decreased FBF below the baseline value observed after bretylium, phentolamine, and propranolol. This suggests that basal release of NO was reduced. A blunting of the vasodilator response to acetylcholine is also consistent with blockade of NO synthase in the vascular endothelium. However, the vasodilator responses to acetylcholine were blunted in a variable manner by L-NMMA administration. In prior studies from our laboratory (8, 9, 12), when variable FBF responses to acetylcholine after L-NMMA have also been seen, consistent changes in the blood flow or vasodilator responses to other physiological stimuli such as mental stress have been evident. Additionally, several lines of evidence favor the concept that pharmacological doses of acetylcholine might also evoke release of a second vasodilator substance not subject to inhibition by L-NMMA (25, 30). When these limitations are considered in the context of the maintained vasodilator responses to sodium nitroprusside after L-NMMA, the reductions in basal FBF after L-NMMA, and the consistent blocking by L-NMMA of the vasodilator responses to various other physiological stimuli, our contention that the doses of L-NMMA we used were sufficient to markedly inhibit NO synthase seems reasonable.

Normal Sequence of Responses During Orthostatic Stress

LBNP causes venous pooling in the lower extremities similar to the upright posture, resulting in cardiopulmonary and arterial baroreceptor unloading. This leads to reduced vagal tone and increased sympathetic traffic,

Fig. 2. Forearm vascular resistance (A) and forearm vascular conductance (B) responses to LBNP. A: forearm vascular resistance responses for both forearms during the 2 trials of LBNP (n = 10 subjects). Values are means ± SE. For each trial of LBNP, forearm vascular resistance is displayed at baseline, 20 mmHg of LBNP (LBNP-20), 40 mmHg of LBNP (LBNP-40), and syncope. During trial 1 (left), resistance in control arm progressively increased with increasing LBNP, and at syncope there was a significant decrease in resistance to below baseline. In experimental arm that had received bretylium, phentolamine, and propranolol (BT + PT + PROP), baseline forearm vascular resistance was decreased from control, showed only a modest increase at higher levels of LBNP (40 mmHg), and suddenly decreased below baseline at syncope. During trial 2 of LBNP (right), control arm displayed similar changes in forearm vascular resistance but with greater subject-to-subject variability. In experimental forearm that received N^G-monomethyl-L-arginine (L-NMMA) in addition to bretylium, phentolamine, and propranolol (BT + PT + PROP + L-NMMA), baseline forearm vascular resistance was increased (P < 0.05) compared with pre-L-NMMA baseline. Progressive increase in forearm vascular resistance seen with increasing LBNP was eliminated, and at syncope there was a sudden large decrease in resistance. Minimum resistance seen in experimental forearm with syncope was not affected by treatment with L-NMMA. B: forearm vascular conductance changes for same 2 trials of LBNP. Values are means ± SE. During trial 1 (left), forearm vascular conductance in control arm decreased with increasing LBNP, and there was a significant increase in conductance above baseline at syncope. Forearm vascular conductance in experimental arm was significantly higher at baseline, did not change with increasing LBNP, but showed a large increase at syncope. During trial 2 (right), forearm vascular conductance changes in control arm were similar to those in trial 1. In experimental arm that had now received L-NMMA in addition to pharmacological sympathetic inhibition, baseline forearm vascular conductance was decreased compared with pre-L-NMMA value. Forearm vascular conductance did not change with increasing LBNP but showed large increase at syncope. Maximum conductance seen in experimental forearm was not affected by treatment with L-NMMA. *P < 0.05, progressive vasococontractor response during LBNP seen in control but not experimental forearm (same trial). †P < 0.05 vs. control forearm.
which cause increases in heart rate and peripheral resistance to maintain arterial blood pressure (18). If the orthostatic stress is sufficiently potent, vasovagal syncope can result (2, 33, 38). While there are a variety of syncope syndromes, classic vasovagal syncope is characterized by both a sudden precipitous fall in blood pressure, caused by marked vasodilation, and by bradycardia (22, 38). Direct measurements of sympathetic nerve traffic to skeletal muscle vascular beds in humans have shown that sympathetic outflow ceases immediately before syncope (34, 35, 39). In animal models of hemorrhage, renal sympathetic nerve activity also falls before syncope (16). Thus the currently accepted concept is that sympathetic withdrawal and passive vasodilation account for much of the hypotension that is associated with fainting.

Evidence for Active Vasodilation During Syncope

Barcroft and Edholm in 1945 (2) conducted a study in humans in whom syncope was induced by venous congestion in the subject’s legs and withdrawal of blood. In their study the rise in FBF accompanying vasovagal syncope was prevented by use of local anesthetics to block sympathetic nerves to the forearm. Additionally, the vasodilation during syncope in the unblocked arm exceeded that in the nerve-blocked arm, suggesting that an active process was operating. Finally, they also studied several subjects who had undergone unilateral surgical sympathetomy of the upper extremity, and they failed to observe the expected rise in flow during syncope in the chronically sympathetomized arms. They interpreted these observations as evidence for “active” vasodilation during syncope.

Our study differs from that of Barcroft and Edholm but supports their conclusions because we allowed normal changes in sympathetic traffic to occur in both forearms while inhibiting the action of classic sympathetic neurotransmitters in one. Our results demonstrate that there is forearm vasodilation at syncope even when sympathetic constrictor tone has already been in essence “lysed” by a combination of bretylium and α-adrenergic-receptor inhibition.

Therefore, our data, in combination with those of Barcroft and Edholm, suggest that first, normal innervation of upper extremity blood vessels is required to see forearm vasodilation during syncope; second, sympathetic withdrawal does not explain all of the dilation; and third, the dilation can occur despite β2-adrenergic receptors being antagonized.

Active vasodilation exists in animals and humans. Previous studies have shown that there can be sympathetic vasodilation in skeletal muscle vascular beds in a number of species (7, 13, 23, 36). This dilation is particularly pronounced when sympathoexcitatory maneuvers are performed after either pharmacological interventions that reduce catecholamine release from sympathetic nerves or blockade of α-adrenergic receptors (13, 36). In general, sympathetic vasodilation in skeletal muscle can be reduced or eliminated by selective intra-arterial infusion of cholinergic-blocking drugs (e.g., atropine) to the vascular bed under study (13, 36).

There is also histological evidence of cholinergic nerves in skeletal muscle blood vessels in many species (36). Recently, sympathetic vasodilation has been shown to be blunted by arginine analogs that inhibit NO synthase (7, 23, 24). This suggests that acetylcholine from sympathetic cholinergic nerves is reaching the vascular endothelium and evokes NO release, or “nitroxidergic” nerves are releasing NO directly, or both (5).

A number of observations suggest that there can be neurally mediated skeletal muscle vasodilation in humans. First, during mental or emotional stress, there can be profound forearm vasodilation that is confined to muscle and not skin and is probably active in nature (3). This dilator response is also attenuated by intra-arterial infusions of atropine or the NO synthase inhibitor L-NMMA (3, 9). Additionally, sympathoexcitatory maneuvers that normally cause forearm vasoconstriction due to an increase in sympathetic outflow can, after α-adrenergic-receptor inhibition of the forearm, evoke marked forearm vasodilation that is blunted by intra-arterial atropine and/or L-NMMA (1, 8). In both humans and animals, the peripheral neural pathways and fiber types responsible for this response are poorly understood (9, 14, 36).

With this information as a background, we attempted to block the forearm dilator responses during syncope with the NO synthase inhibitor L-NMMA. Surprisingly, this approach had little impact on this response (Fig. 2) even though we used doses of L-NMMA that normally blunt the dilation seen during a variety of maneuvers (8, 9). Along similar lines, Koch and colleagues (20) demonstrated that systemic NO synthase inhibition did not have a major effect on the hemodynamic responses to severe (syncopal) hemorrhage in rabbits. Finally, we also selectively treated the forearms of several subjects with atropine and did not notice any major impact on the dilator responses during syncope, confirming that cholinergic mechanisms are not involved in this dilator response (22).

Potential Contribution of Circulating Factors

Prior observations of sudden increases in plasma epinephrine levels at the time of syncope have led some investigators to suggest that the forearm vasodilation observed at syncope is due to β2-adrenergic-receptor vasodilator effects on the skeletal muscle vasculature (28, 29). However, we observed forearm vasodilation at syncope despite local β2-adrenergic-receptor inhibition of the forearm. There are a large number of other circulating factors that have been suggested to play a role in vasovagal syncope. These include the renin-angiotensin-aldosterone system, vasopressin, and endogenous opioids (16, 17, 31, 32). However, there are no consistent data to support any of these as a major contributor to vasodilation during syncope in humans (33, 38).

Summary

In summary, our results suggest that sympathetic withdrawal alone cannot account for all of the forearm...
vasodilation that occurs during syncope and are consistent with the possible existence of active vasodilation in human forearm muscle vessels during syncope. They also suggest that neither \( \beta_2 \)-adrenergic-receptor-mediated vasodilation nor NO is needed for this phenomenon to occur. In addition to active vasodilation, what mechanism might explain this vasodilator response? One speculative explanation is that increases in sympathetic nerve activity during orthostatic stress suppress the release of some poorly understood dilating factor and that this factor is then released in a relatively large quantity when sympathetic nerve activity is suddenly withdrawn. It may also be possible that there are mechanical interactions induced by the rapid changes in arterial pressure and sympathetic tone that along with local factors combine to cause the marked vasodilation seen with syncope. Whatever the mechanism(s) responsible for the vasodilation above that which can be explained by sympathetic withdrawal alone, the mediator(s) of this response remains elusive.

The authors express their gratitude to the subjects. Expert secretarial help was provided by K. D. Sankey.

This work was supported by National Institutes of Health (NIH) Grants HL-46493, NS-32352, and RR-00585; the Glen L. and Lyra Ebling Cardiology Research Endowment; and the Mayo Foundation.

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Received 15 August 1996; accepted in final form 5 February 1997.

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Ebling Cardiology Research Endowment; and the Mayo Foundation.

Grants HL-46493, NS-32352, and RR-00585; the Glen L. and Lyra Ebling Cardiology Research Endowment; and the Mayo Foundation.


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