Hemodynamic and Autonomic Nervous System Responses to Mixed Meal Ingestion in Healthy Young and Old Subjects and Dysautonomic Patients With Postprandial Hypotension

Lewis A. Lipsitz, MD; Sheila M. Ryan, MD; J. Anthony Parker, MD, PhD; Roy Freeman, MD; Jeanne Y. Wei, MD, PhD; and Ary L. Goldberger, MD

Background. Although postprandial hypotension is a common cause of falls and syncope in elderly persons and in patients with autonomic insufficiency, the pathophysiology of this disorder remains unknown.

Methods and Results. We examined the hemodynamic, splanchnic blood pool, plasma norepinephrine (NE), and heart rate (HR) power spectra responses to a standardized 400-kcal mixed meal in 11 healthy young (age, 26±5 years) and nine healthy elderly (age, 80±5 years) subjects and 10 dysautonomic patients with symptomatic postprandial hypotension (age, 65±16 years). Cardiac and splanchnic blood pools were determined noninvasively by radionuclide scans, and forearm vascular resistance was determined using venous occlusion plethysmography. In healthy young and old subjects, splanchnic blood volume increased, but supine blood pressure remained unchanged after the meal. In both groups, HR increased and systemic vascular resistance remained stable. Forearm vascular resistance and cardiac index increased after the meal in elderly subjects, whereas these responses were highly variable and of smaller magnitude in the young. Young subjects demonstrated postprandial increases in low-frequency HR spectral power, representing cardiac sympathoexcitation, but plasma NE remained unchanged. In elderly subjects, plasma NE increased after the meal but without changes in the HR power spectrum. Patients with dysautonomia had a large postprandial decline in blood pressure associated with no change in forearm vascular resistance, a fall in systemic vascular resistance, and reduction in left ventricular end diastolic volume index. HR increased in these patients but without changes in plasma NE or the HR power spectrum.

Conclusions. 1) In healthy elderly subjects, the maintenance of blood pressure homeostasis after food ingestion is associated with an increase in HR, forearm vascular resistance, cardiac index, and plasma NE. In both young and old, systemic vascular resistance is maintained. 2) Dysautonomic patients with postprandial hypotension fail to maintain systemic vascular resistance after a meal. This impairment in vascular response to meal ingestion may underlie the development of postprandial hypotension. 3) The measurement of mean HR or plasma NE does not adequately characterize autonomic cardiac control. Power spectral analysis suggests an impairment in the postprandial autonomic modulation of HR in healthy elderly and dysautonomic subjects, possibly predisposing to hypotension when vascular compensation is inadequate. (Circulation 1993;87:391–400)

Key Words • syncope • autonomic failure • elderly • blood pressure • power spectral analysis

Food ingestion and oral glucose loading have been shown to reduce systemic blood pressure (BP) in elderly healthy subjects,1–6 elderly institutionalized subjects,7,8 hypertensive elderly subjects,9 elderly patients with meal-related syncope,10 patients with Parkinson’s disease,11,12 and patients of all ages with autonomic insufficiency.13–15 In some elderly people with multiple illnesses and in patients with autonomic insufficiency, postprandial hypotension is of sufficient magnitude to result in falls and syncope.8,16,17

Several previous studies have investigated possible contributors to postprandial hypotension.18,19 Proposed from the Hebrew Rehabilitation Center for Aged; the Department of Medicine, Neurology, and Radiology of Beth Israel Hospital; the Division of Neurology of New England Deaconess Hospital, and Harvard Medical School, Boston.

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mechanisms include 1) age- or hypertension-related impairments in baroreflex function,27,20 2) insulin-induced vasodilatation19,21,22 or baroreflex impairment,3,6,7 3) release of vasodilatory gastrointestinal peptides,9,15,23-26 4) excessive splanchnic blood pooling during digestion,27,28 and 5) inadequate sympathetic nervous system compensation for meal ingestion.10,29 The observation that somatostatin or its analogue octreotide prevents postprandial BP reduction in normotensive and hypertensive elderly subjects9,23,25 and in patients with autonomic failure26,30,31 suggests that vasoactive gastrointestinal hormones may be involved in the pathophysiology of this phenomenon. However, studies investigating the possible role of insulin, gastrin, motilin, cholecystokinin, vasoactive intestinal peptide, somatostatin, or substance P have failed to demonstrate a relation between levels of these gastrointestinal hormones and the degree of postprandial hypotension in healthy elderly subjects3,6,23,25 or patients with autonomic failure.24

A role for adenosine-induced splanchnic vasodilatation also has been suggested by recent investigations showing that the adenosine receptor antagonist caffeine ameliorates declines in postprandial BP in healthy elderly subjects52 and patients with autonomic failure.53 However, no studies have measured postprandial splanchnic blood pooling directly. Although duplex Doppler measurements of postprandial changes in superior mesenteric artery blood flow show no difference between normal subjects and autonomic failure patients with postprandial hypotension,27 measurements of mesenteric blood flow may not represent changes in splanchnic blood volume.

Other studies focusing on autonomic nervous system responses to meal ingestion have shown blunted heart rate (HR) or plasma norepinephrine (NE) responses to meal ingestion in elderly and autonomic failure patients with postprandial hypotension.4,7,10,15,27,20 These studies suggest that sympathetic nervous system compensation for splanchnic blood pooling may be impaired. Two previous investigations using power spectral analysis of continuous HR time series to quantify cardiac autonomic responses have demonstrated in young persons that there is an increase in low-frequency HR power after a meal17,18 that is consistent with cardiac sympathoexcitation. In contrast, we demonstrated that chronically ill elderly persons with postprandial hypotension do not increase their low-frequency HR power.34 This suggests an impairment of sympathetic nervous system function either in the production of NE or in cardiac response. To our knowledge, no studies have simultaneously analyzed HR dynamics and plasma NE responses to meals in healthy subjects and those with overt autonomic failure.

The comparison and interpretation of these previous studies is limited by differences in subject characteristics, meals, timing and position of measurements, and the lack of simultaneous postprandial measurements of splanchnic blood pooling, hemodynamics, and autonomic nervous system responses to the meal. Furthermore, potential mechanisms of postprandial hypotension have been examined primarily in asymptomatic subjects given oral glucose. The current study was designed to clarify the pathophysiology of postprandial hypotension by comparing the hemodynamic, splanchnic blood pool, plasma NE, and HR power spectrum responses to a standardized mixed meal in three groups of subjects: healthy young subjects, healthy old subjects, and dysautonomic patients with symptomatic postprandial hypotension. We addressed the following three questions: 1) Does postprandial hypotension occur in response to mixed meal ingestion in very healthy elderly individuals? 2) Do postprandial hemodynamic and autonomic responses differ between healthy young and old subjects? 3) What is the pathophysiology of postprandial hypotension in symptomatic patients with autonomic insufficiency?

Methods

Subjects

Eleven healthy young subjects (age range, 20–38 years; seven men, four women) and nine healthy elderly subjects (age range, 74–91 years; two men, seven women) with no history of medical illness, smoking, or medication use were recruited from the local Boston community through newspaper advertisements. Ten patients with autonomic dysfunction and orthostatic hypotension (age range, 28–83 years; seven men, three women) were referred to us by their primary care physicians.

Each of the autonomic failure patients had marked orthostatic hypotension and postprandial symptoms of profound weakness, dizziness, or syncope. Five of these subjects had a probable diagnosis of Shy-Drager syndrome with parkinsonian features and normal basal supine plasma NE levels, three had progressive autonomic failure with low basal plasma NE concentrations, and two had unknown causes of chronic orthostatic hypotension associated with normal circulating NE levels. Five autonomic failure patients were taking fludrocortisone, two were taking sinemet, two were taking sedatives, and one was taking clonidine.

All subjects were evaluated no more than 7 days before the meal study with a routine history, postural vital signs, physical examination, blood studies, ECG, Doppler echocardiogram, and autonomic function tests that included HR response to deep breathing and to the Valsalva maneuver.

HR response to deep breathing was conducted in the supine position by recording the ECG continuously for 3 minutes while subjects took slow deep breaths at a rate of five per minute in response to verbal and visual cues from one of the investigators. The ratio of the maximum RR interval during expiration to the minimum RR during inspiration (E/I ratio) was calculated for each breath. The mean E/I during the second minute was calculated as the average of the five E/I ratios recorded during this minute, and the maximum E/I was defined as the single largest ratio during the second minute.

The Valsalva maneuver was conducted in the supine position during continuous ECG recording by having subjects blow into a mercury manometer to maintain a pressure of 30 mm Hg for 10 seconds.35 Practice sessions were conducted to teach subjects how to exert pressure from their chest. Measurements were taken after a 2-minute rest period between trials. The Valsalva ratio was calculated as the ratio of the longest RR interval after release of the Valsalva (phase IV) to the shortest RR interval during the procedure (phase II). The highest ratio of three trials is reported.
The study was approved by the Institutional Review Boards of the Beth Israel Hospital and Hebrew Rehabilitation Center for Aged. All subjects provided written informed consent.

**Meal Study Protocol**

All subjects were studied between 7:30 and 11:00 AM after an overnight fast from midnight the night before. If subjects were taking chronic medications, these were withheld for as long as it was safe to do so: a minimum of 12 hours before the study for medications routinely given two to four times daily and 24 hours before the study for those given once daily.

At 7:30 AM on the day of their meal study, each subject had an echocardiogram and cardiac Doppler study to exclude the presence of myocardial or valvular heart disease or left ventricular outflow tract obstruction. Each subject then reported to the nuclear medicine laboratory where a 21-gauge angiocatheter and heparin lock was placed in one antecubital vein for blood sampling throughout the study. This intravenous catheter was also used to withdraw a 3-ml blood sample during each radionuclide ventriculogram to determine biological clearance of the tracer. A second temporary angiocatheter was placed in the opposite antecubital vein for collection and reinjection of autologous red blood cells (RBC) that were labeled with 740 MBq (20 mCi) of ⁹⁹ᵐTc. This line was removed after labeled RBC injection.

The cuff from a Dynamap automated oscillometric BP device (Critikon, Tampa, Fla.) was attached to one arm for BP and HR recordings at 5-minute intervals throughout the study. Upper arm and wrist cuffs and a mercury-in-silastic strain gauge were attached to the other arm for venous occlusion plethysmographic measurements of forearm blood flow.²⁶ Finally, a Holter monitor (Del Mar Avionics, Irvine, Calif.) and standard ECG chest leads were attached to monitor cardiac rhythm. After each study, the continuous Holter monitor ECG recordings were used for power spectral analysis (see below) and to identify possible ischemic ST segment and T wave changes that could account for postprandial BP declines.

After ⁹⁹ᵐTc-labeled RBC injection and a minimum of 30 minutes of supine rest, 10 minutes of baseline measurements were performed. Subjects then sat for 10 minutes to ingest a liquid 400-kcal meal, after which they resumed a supine position for the duration of the study. BP and HR were recorded at 5-minute intervals throughout the study. Plasma NE samples were collected as described below, twice before the meal (−5 and 0 minutes), then at 30, 45, 60, and 90 minutes after the meal. Forearm blood flow was determined by repeated venous occlusion plethysmography measurements over 3-minute periods. Measurements were taken before the meal, then at 15-minute intervals beginning at +15 minutes after the meal. Five-minute acquisitions for gated cardiac blood pool³⁵,³⁶ and 2-minute splanchnic blood pool determinations³⁹ were obtained sequentially before the meal and at 30-minute intervals after the meal. Except for a 10-minute period with the subject sitting for meal ingestion, all studies were performed with the subject in the supine position to eliminate the possible effect of orthostatic hypotension. Room temperature remained constant (23 ± 1°C) throughout the study.

The meal was a 400-kcal drink (Carnation Instant Breakfast in lactose-free whole milk) containing 40% carbohydrate, 45% fat, 15% protein, 12 meq sodium, and no caffeine. It was served at a temperature of 22°C to avoid potential temperature effects on BP²⁴ and was ingested within 10 minutes. This meal composition represents that of a mixed breakfast and has been shown to evoke a hypotensive response in institutionalized subjects during previous studies.⁷

**Water Control Studies**

Two healthy elderly subjects agreed to undergo a second study conducted in identical fashion at least 1 week later, during which an equal volume of water was given instead of a meal. The water was served at a temperature of 22°C and was consumed over the same time interval as the meal. Based on the negative results of these two control studies, we could not justify exposing other subjects to the potential risks of additional radionuclide exposure.

**Radionuclide Ventriculogram**

The left ventricular ejection fraction (EF) was calculated with a fixed region of interest method. The area and longest axis of the region of interest was used to calculate absolute left ventricular end-diastolic volume (EDV). Peak filling rate (PFR) was calculated from a third-order polynomial fit to the rapid filling portion of diastole. As the absolute value of EDV was known, we were able to express PFR as milliliters per second.

Cardiac index (CI), stroke volume index (SVI), and EDV index were calculated by dividing the cardiac output (SV×HR), SV (EDV×EF), or EDV by body surface area, which was estimated according to the equation of DuBois and DuBois⁶⁰ from the measured height and weight.

**Splanchnic Blood Volume Determination**

Relative changes in radionuclide activity from a region of interest overlying the bowel were used as an index of changes in splanchnic blood volume.²⁹ A Co-57 marker was attached to the lower abdomen to aid in repositioning the patient and to align the images during analysis. Two sequential 2-minute images of the abdomen were obtained during the baseline period to establish that equilibrium had been adequately achieved. Images were obtained at 15, 30, 60, and 90 minutes after the meal. Images were obtained in the anterior position to decrease the contribution from excreted activity. An attempt was made to exclude the urinary system from the region of interest when it could be identified. The counts were corrected for background, biological clearance, and physical decay. The changes in splanchnic blood volume are reported as a percentage of the baseline activity.

**Norepinephrine Assay**

Blood for catecholamine determinations was collected from the antecubital intravenous catheter without the use of a tourniquet in vacutainer tubes containing ethyleneglycol-tetraacetic acid and reduced glutathione. The tubes were placed immediately on ice. Plasma was separated by refrigerated centrifugation, then fast-frozen in dry ice and acetone and stored at −70°C until assayed. Plasma NE concentrations were
TABLE 1. Autonomic Function Characteristics of Subjects

<table>
<thead>
<tr>
<th></th>
<th>Healthy young</th>
<th>Healthy old</th>
<th>Autonomic insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Postural MABP change* (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine-standing 1 minute</td>
<td>5±1</td>
<td>4±3</td>
<td>27±8‡</td>
</tr>
<tr>
<td>Supine-standing 3 minutes</td>
<td>5±1</td>
<td>2±3</td>
<td>34±10‡</td>
</tr>
<tr>
<td>Postural HR change (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine-standing 1 minute</td>
<td>10±3</td>
<td>11±3</td>
<td>11±4</td>
</tr>
<tr>
<td>Supine-standing 3 minutes</td>
<td>11±3</td>
<td>7±2</td>
<td>11±4</td>
</tr>
<tr>
<td>Mean E/I</td>
<td>1.29±0.03</td>
<td>1.18±0.03§</td>
<td>1.04±0.01‡</td>
</tr>
<tr>
<td>Maximum E/I</td>
<td>1.41±0.04</td>
<td>1.23±0.05§</td>
<td>1.06±0.02‡</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>1.50±0.11</td>
<td>1.46±0.09</td>
<td>1.13±0.05‡</td>
</tr>
<tr>
<td>Basal plasma norepinephrine level (pg/ml)</td>
<td>154±20</td>
<td>269±24‡</td>
<td>209±65†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. MABP, mean arterial blood pressure; HR, heart rate; bpm, beats per minute; E/I, expiration/inspiration.
*Only seven dysautonomic subjects were able to stand for these measurements.
†p<0.05 compared with other groups.
‡p<0.05 compared with healthy young.

Dysautonomic dysfunction was excluded because of technical problems with the ECG recordings.

Heart Rate Power Spectral Analysis

Three subjects were excluded before this analysis. One healthy elderly subject was excluded because of excessive atrial ectopy, and two individuals with autonomic dysfunction were excluded because of technical problems with the ECG recordings.

Tape-recorded ECG signals were digitized at 128 Hz using a Marquette Series 8000 Holter analysis system. The digitized data were then annotated using an automated arrhythmia detection algorithm, and the beat annotations were verified by visual inspection. Eight-minute sections were selected during the initial baseline period at -30, -20, and -10 minutes and then during consecutive 10-minute time periods from 10 to 90 minutes after the meal. Instantaneous HRs during these 8-minute segments were obtained by resampling the reciprocal of the RR interval time series at 2 Hz. Each 8-minute HR time series was analyzed with a fast Fourier transform algorithm yielding a 512-point power spectrum. Total HR spectral power was computed (in arbitrary units) for the 0.01–0.40-Hz band, relatively low-frequency HR power for the 0.01–0.15-Hz band (predominantly sympathetic activity), and high-frequency HR power for the 0.15–0.40-Hz band (parasympathetic activity) at each time segment. The ratio of high- to low-frequency HR power was also calculated during the baseline and postprandial time periods.

Data Analysis

Basal values for physiological variables (mean arterial BP [MABP], systolic BP, diastolic BP, HR, NE) that were measured more than once during the 10-minute baseline period before the meal were calculated by averaging all premeal measurements. For all other variables, the single premeal measurement was used as the baseline value. Fifteen minutes after the start of the meal, mean values for BP and HR were calculated at 15-minute intervals. Each mean value is the average of three measurements 5 minutes apart before, during, and after each time point of interest. MABP was calculated as the sum of the diastolic BP and one-third the pulse pressure. Forearm vascular resistance was calculated as MABP divided by the forearm blood flow, and systemic vascular resistance was calculated as MABP divided by cardiac output (in liters per minute).

Baseline subject characteristics were compared using a one-way ANOVA when the variance was similar between groups or a Kruskal-Wallis test when the within-group variances between groups differed. Within-group changes over time for each variable were evaluated by repeated-measures ANOVA. When the results indicated an overall significant effect of time, the postmeal measures were each individually compared with baseline using the Bonferroni method to adjust for multiple comparisons.

Changes for each variable over time were compared among the three groups of subjects (two groups at a time) using a two-factor (group and time) repeated-measures ANOVA. Data summaries and analyses were performed using the SAS (v6.06.01) system on a MicroVAX computer. An α-level of 0.05 was used as the criterion for determining statistical significance. Data are presented as mean±SEM.

Results

Baseline Subject Characteristics

Basal autonomic function and cardiovascular characteristics of the subjects are shown in Tables 1 and 2. Dysautonomic patients had marked orthostatic hypotension and impaired HR responses to deep breathing and the Valsalva maneuver. In comparison with the young subjects, healthy elderly subjects also had impaired HR responses to deep breathing. Basal supine plasma NE levels were higher in the elderly than in the two other groups of subjects.

Resting supine MABP was highest in dysautonomic patients and higher in the healthy elderly than in the
TABLE 2. Basal Supine Cardiovascular Characteristics of Subjects

<table>
<thead>
<tr>
<th></th>
<th>Healthy young</th>
<th>Healthy old</th>
<th>Autonomic insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>26±1</td>
<td>80±2</td>
<td>65±5</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.86±0.05</td>
<td>1.66±0.06</td>
<td>1.86±0.08</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.3±0.7</td>
<td>23.9±2.0</td>
<td>24.4±1.2</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>85±2†</td>
<td>98±3</td>
<td>117±7*</td>
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<tr>
<td>SBP (mm Hg)</td>
<td>120±3*</td>
<td>146±4</td>
<td>165±10</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>67±2</td>
<td>74±3</td>
<td>94±5*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>60±3</td>
<td>57±3</td>
<td>69±4</td>
</tr>
<tr>
<td>FVR (units)</td>
<td>72±11</td>
<td>62±5</td>
<td>96±31</td>
</tr>
<tr>
<td>FBF (ml/100 ml tissue/min)</td>
<td>1.5±0.2</td>
<td>1.7±0.2</td>
<td>2.0±0.3</td>
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<tr>
<td>SVR (units)</td>
<td>20±1†</td>
<td>30±3</td>
<td>24±2</td>
</tr>
<tr>
<td>EDV index (ml/m²)</td>
<td>64±3</td>
<td>57±4</td>
<td>67±4</td>
</tr>
<tr>
<td>SV index (ml/m²)</td>
<td>41±3</td>
<td>36±4</td>
<td>42±3</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m²)</td>
<td>2,486±217</td>
<td>2,019±169</td>
<td>2,844±221†</td>
</tr>
<tr>
<td>FPR (ml/sec)</td>
<td>435±38*</td>
<td>182±24</td>
<td>277±31</td>
</tr>
<tr>
<td>EF (%)</td>
<td>64±2</td>
<td>62±3</td>
<td>63±3</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
MABP, SBP, DBP, mean arterial, systolic, and diastolic blood pressure, respectively; HR, heart rate; bpm, beats per minute; FVR, forearm vascular resistance; FBF, forearm blood flow; SVR, systemic vascular resistance; EDV, end-diastolic volume; SV, stroke volume; FPR, peak filling rate; EF, ejection fraction.

* p<0.05 compared with all other groups; † p<0.05 compared with healthy old.

Plasma NE levels (Figure 2D) increased by 30 minutes after the meal in healthy elderly subjects but not in the young. Plasma NE remained elevated in the elderly group throughout the 90-minute postprandial period. Left ventricular SVI, PFR, and EF were unchanged after the meal.

Hemodynamic Responses in Autonomic Failure Patients

MABP, systolic BP, and diastolic BP fell significantly at all time points between 15 and 90 minutes in the group of patients with autonomic dysfunction. HR increased at all time points after the meal and to a significantly greater extent in autonomic failure patients than in healthy young subjects. In contrast to the healthy young and old, autonomic failure patients had no significant change in forearm vascular resistance. Bowel blood volume and CI were highly variable and tended to increase, although this change was not statistically significant (p<0.15 and p<0.09, respectively). However, systemic vascular resistance and EDV index both fell to a significant extent by 30 minutes after the meal. There was no statistically significant change in plasma NE level in these patients, although individual responses were also quite variable.

ECG and Heart Rate Spectral Responses to the Meal

There was no significant difference in spectral power for the three premeal time periods at −30, −20, and −10 minutes within each group of subjects. The middle value (−20 minutes) time period was chosen as the basal period for comparison to postprandial values because this represents the time during which the subjects were most likely to be in a physiological steady state.

Young subjects had significantly higher HR spectral power than the other two groups for all bands: total, low, and high. In addition, the patients with autonomic failure had significantly lower power in all bands compared with the healthy young and old subjects (Table 3). However, the baseline ratio of high to low power was not significantly different among the groups.

The young subjects demonstrated a significant increase in spectral HR power 80 minutes after the meal. The change was most prominent in the total power, which increased progressively from a baseline value of 30.4±25.5 units to 63.0±48.5 units at 80 minutes. The low-frequency band increased significantly from a baseline of 24.7±19.7 units to 55.8±44.1 units at 80 minutes. The healthy elderly subjects and those with autonomic dysfunction did not exhibit any changes in spectral power after the meal in either low- or high-frequency bands (Figure 3).

No subject had evidence of cardiac ischemia or clinically important arrhythmias on cardiac monitoring during the study. Among all subjects of the study, there were no relations between individual postprandial changes in plasma NE and forearm vascular resistance or HR dynamics.

Water Control Studies

Two healthy elderly subjects underwent water control studies to determine the effect of an equivalent-volume, noncaloric liquid feeding on postprandial hemodynamic and NE responses. There were no directional changes in
BP, HR, forearm vascular resistance, bowel blood volume, CI, EDV index, or plasma NE levels during the water control studies.

**Discussion**

The results of this study suggest that 1) postprandial BP reduction is not observed in healthy elderly subjects resting in the supine position after a mixed (40% carbohydrate) meal; 2) postprandial BP homeostasis in the healthy elderly is associated with an increase in HR, forearm vascular resistance, CI, and plasma NE; and 3) an impairment in vascular response to mixed meal ingestion may play a role in the pathogenesis of postprandial hypotension in patients with autonomic dysfunction. In association with pooling of blood in the splanchic circulation, healthy young and old subjects either maintain or increase peripheral vascular resistance and CI. These hemodynamic responses may result in redistribution of blood from the periphery to the splanchic circulation, leaving total systemic vascular resistance and BP unchanged. In patients with autonomic failure and postprandial hypotension, systemic vascular resistance and EDV index fall to such an extent that BP cannot be maintained.

In addition, our data show a striking dissociation between HR, BP, peripheral plasma NE responses, and HR spectral power measures in healthy young and old subjects and dysautonomic subjects. The differing profiles of hemodynamic and autonomic responses to meal ingestion for these three groups of subjects are summarized in Table 4.

**Postprandial Hemodynamics in the Healthy Young**

In healthy young human subjects, food intake has been reported to be accompanied by an increase in mesenteric blood flow,27,42,43 increase in HR and cardiac output,15,44–51 decrease in systemic vascular resistance,47,50 and a rise in forearm vascular resistance.15,27 Plasma NE levels have been reported to increase3,10,15,52 or remain unchanged.50,51,53 Spectral analysis of HR variability after a meal shows increased low-frequency HR fluctuations, suggesting heightened sympathetic nervous system control of HR.15,27,44,45 Mean arterial BP and systolic BP remain stable or increase, presumably as a result of sympathetically mediated increases in HR, cardiac output, and peripheral vascular resistance.

Our data in healthy young subjects show very modest cardiovascular responses. This group demonstrated an
increase in bowel blood volume, which was associated with cardioacceleration and the preservation of CI and systemic vascular resistance. Consequently, BP remained unchanged. There was no demonstrable increase in plasma NE despite spectral evidence of sympathetic effects on HR. This may be due to reuptake and clearance of NE at sympathetic nerve terminals, thus reducing spillover into plasma. There was no increase in stroke volume, consistent with the lack of change in EDV and EF. Previous studies showing postprandial increases in stroke volume are at variance with our data. Imprecision in the impedance cardiographic, acetylene, or “Exerdop” techniques used to measure stroke volume in some of these studies might partially explain the discrepant findings.

Healthy Elderly Subjects

Healthy elderly subjects demonstrated postprandial increases in HR, CI, and forearm vascular resistance in association with a stable BP. These hemodynamic responses were surprisingly more pronounced in healthy elderly subjects than in the young. The increase in plasma NE observed after the meal in healthy elderly subjects has been observed previously and is consistent with the known age-related increase in NE spillover at sympathetic nerve terminals. However, the associated increase in HR was not expected. The well-described age-related decline in β-adrenergic responsiveness would be expected to blunt the HR response to meal-induced sympathetic activation in elderly subjects. The absence of a postprandial increase in the

<table>
<thead>
<tr>
<th>Table 3. Premeal Spectral Heart Rate Power</th>
</tr>
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<tbody>
<tr>
<td>Healthy young</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Total power*</td>
</tr>
<tr>
<td>Low-frequency power*</td>
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<tr>
<td>High-frequency power*</td>
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<tr>
<td>High/low-frequency ratio*</td>
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<tr>
<td>Maximum spectral power increase after the meal</td>
</tr>
<tr>
<td>Total heart rate power*</td>
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<tr>
<td>Low-frequency power*</td>
</tr>
</tbody>
</table>

*Power is expressed as mean units (SEM).
†p<0.05 compared with healthy young.
‡p<0.05 compared with healthy old and young.
low-frequency (predominantly sympathetic) component of the HR power spectrum suggests that the β-adrenergic response was indeed impaired. It is notable that also there was no evidence of parasympathetic withdrawal in the HR power spectrum (a reduction in high-frequency power), suggesting that cardioacceleration was due to other unknown mediators of HR (see below). Despite their advanced age, the healthy elderly subjects of our study did demonstrate intact vascular responsiveness to sympathoexcitation.

The relatively small postprandial cardiovascular response in healthy young subjects compared with the healthy old suggests that the meal stimulus alone, without superimposed orthostasis, may represent a relatively greater physiological stress to healthy elderly subjects than to young subjects. This is consistent with previous investigations that have demonstrated an enhanced plasma NE response to oral glucose ingestion in healthy elderly subjects compared with young subjects,28,59 independent of circulating levels of glucose or insulin.59 The mechanism of this heightened plasma NE response to meal ingestion in old age is currently unknown.

**Autonomic Failure Patients**

In contrast to the above findings in healthy young and old subjects, autonomic failure patients with postprandial hypotension demonstrated inappropriate vascular responses to the meal. This finding is supported by the work of Kooner et al.32 and Hoeldtke et al.33 who showed no postprandial changes in skin or forearm forearm blood flow and a profound fall in BP in patients with autonomic failure. In our study, the behavior of resistance vessels in the forearm has direct relevance to BP measured in the brachial artery and may represent peripheral vascular adjustments in all extremities during meal ingestion. An impairment in peripheral vasoconstriction in autonomic failure patients may account for the observed postprandial reduction in systemic vascular resistance and EDV index.

The postprandial increase in plasma NE observed in many autonomic failure patients is difficult to explain in light of previous observations by Lipsitz et al.10 and others26,29,60 suggesting impaired sympathetic nervous system activity after a meal in subjects with postprandial hypotension. It is well recognized that plasma NE may not always be a reliable indicator of synaptic release of NE.61 Decreased BP in these subjects may have reduced clearance of NE from plasma, thus artificially elevating circulating levels. In patients with postprandial hypotension, sympathetic nerve firing and/or synaptic release of NE may not have been sufficient to maintain adequate vascular tone. Alternatively, the vascular response to NE may be impaired. Unfortunately, we were not able to examine sympathetic nerve and adrenoreceptor responses directly.
HR also increased unexpectedly in patients with postprandial hypotension, although it, too, may not have been sufficient to offset the fall in BP. Data from previous studies indicate similar postprandial increases in HR in patients with autonomic failure, although this finding was not discussed by the investigators.\textsuperscript{13,26} Although postprandial cardioacceleration could be due to sympathetic activation and/or parasympathetic withdrawal, there was no evidence of either in the HR power spectra for these subjects. Furthermore, patients with postprandial hypotension had abnormal HR responses to deep breathing and the Valsalva maneuver, suggesting that parasympathetic control of cardiovascular function was impaired.

The mechanism of paradoxic cardioacceleration in our elderly and dysautonomic subjects is currently unexplained. Despite autonomic blockade with atropine and propranolol, young individuals show an increase in HR after a meal.\textsuperscript{62} Our findings raise the possibility that factors other than parasympathetic withdrawal or sympathetic nervous system activation may mediate postprandial HR changes. Frase et al\textsuperscript{63} demonstrated that the gastrointestinal hormone vasoactive intestinal polypeptide has potent direct cardioacceleratory effects. Rigel\textsuperscript{64} reported that in anesthetized dogs, vasoactive intestinal polypeptide and peptide histidine leucine exerted prominent chonotropic effects after vagotomy in the presence of β-blockade. Histamine also has been shown to have chonotropic effects in animals and humans.\textsuperscript{65} These effects are inhibited by H-1 receptor antagonists and are independent of baroreflex stimulation. Increases in HR, therefore, may be mediated in part through neuropeptide hormones secreted in response to meal ingestion.

Limitations

The current investigation is limited to some extent by its reliance on noninvasive cardiovascular measurement techniques that lack sensitivity to small, transient, hemodynamic changes and do not permit the simultaneous determination of multiple interacting physiological variables that influence BP. More invasive techniques, however, were not feasible in our subjects.

The heterogeneity of autonomic failure patients and the relatively small number of subjects in this study limit the power to detect small differences in postprandial hemodynamic responses. Furthermore, it is possible that some of our findings may be due to the effects of chronic diseases or long-acting medications in patients with autonomic insufficiency.

In contrast to a previous report by Lipsitz and Fullerton,\textsuperscript{2} the elderly subjects in the present study did not exhibit postprandial hypotension. This may be due to at least two factors. First, our subjects were supine before and after the meal. It is possible that the orthostatic stress of sitting combined with the stress of eating would have resulted in BP reduction. Second, the meal contained only 40% carbohydrate. Meals with a higher carbohydrate content appear to provoke a greater hypertensive reaction in susceptible individuals.\textsuperscript{6} The components of the mixed meal that we used may be more representative of meals actually consumed during normal physiological conditions.

Conclusions

The current study provides new information about potentially important circulatory and neurohumoral mechanisms of postprandial BP regulation in healthy young and old subjects and elucidates abnormalities associated with postprandial hypotension in symptomatic patients with autonomic insufficiency. The finding that healthy elderly patients can maintain postprandial BP by increasing peripheral vascular resistance, whereas patients with autonomic insufficiency cannot, suggests that elderly patients with postprandial hypotension may have disease- or medication-related abnormalities in autonomic function that affect vascular responsiveness. Future studies of vascular smooth muscle function and clinical trials of vasoconstrictor agents are warranted. Furthermore, clinicians should be cautioned to avoid the use of vasodilatory medications in patients at risk of postprandial hypotension.

The postprandial cardioacceleration that was observed in all subjects despite evidence of impaired sympathetic and parasympathetic modulation of HR in elderly and dysautonomic subjects raises the possibility that nonautonomic mechanisms may control HR in the postprandial period. This important finding also deserves further investigation.

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