Acarbose, an α-Glucosidase Inhibitor, Attenuates Postprandial Hypotension in Autonomic Failure

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Abstract—Postprandial hypotension is an important clinical condition that predisposes to syncope, falls, angina, and cerebrovascular events. The magnitude of the fall in blood pressure after meals depends on enteric glucose availability. We hypothesized that acarbose, an α-glucosidase inhibitor that decreases glucose absorption in the small intestine, would attenuate postprandial hypotension. Acarbose or placebo was given 20 minutes before a standardized meal in 13 patients with postprandial hypotension in the setting of autonomic failure (age: 65±2.6 years; body mass index: 25±1.08 kg/m²; supine plasma norepinephrine: 110±26.6 pg/mL). Four patients were studied in a single-blind protocol and 9 patients in a double-blind, randomized, crossover fashion. Patients were studied supine, and blood pressure, heart rate, and neuroendocrine parameters were obtained at baseline and for 90 minutes after meal intake. After adjusting for potential confounders, acarbose significantly attenuated the postprandial fall in systolic and diastolic blood pressures by 17 mm Hg (95% CI: 7 to 28; P=0.003) and 9 mm Hg (95% CI: 5 to 14; P=0.001), respectively. Furthermore, acarbose effectively reduced plasma levels of insulin, a known vasodilator, by 11 μU/mL (95% CI: 5 to 18; P=0.001) compared with placebo. After adjusting for insulin levels, the attenuation of postprandial hypotension by acarbose remained significant, indicating that additional mechanisms contribute to this effect. In conclusion, 100 mg of acarbose successfully improved postprandial hypotension in patients with severe autonomic failure. This effect is not explained solely by a reduction in insulin levels. (Hypertension. 2007;50:54-61.)

Key Words: postprandial □ hypotension □ acarbose □ α-glucosidase inhibitor □ autonomic nervous system diseases □ autonomic failure

Postprandial hypotension (PPH), defined as a fall in systolic blood pressure (SBP) of >20 mm Hg occurring within 2 hours after a meal,1,2 is an important clinical problem that predisposes to syncope, falls, angina pectoris, and cerebrovascular events.3,4 The clinical presentation is characterized by symptoms of lightheadedness with an onset within 30 minutes after food ingestion.5 The magnitude of the decrease in blood pressure depends on the size of the meal6 and its carbohydrate content.8 Those most affected are patients with some degree of autonomic impairment, suggesting that, in healthy subjects, the hypertensive effect of meals is buffered by the autonomic nervous system. PPH has been reported in healthy elderly persons,9,10 elderly patients with hypertension,11–13 those with diabetes mellitus,19 PPH is particularly severe in patients suffering from primary forms of autonomic failure.1

The pathogenesis of PPH is likely multifactorial. Gastrointestinal and pancreatic hormones with vasodilatory properties seem to play a key role. These are released into the bloodstream in response to food intake and are responsible for pooling of blood in the splanchnic circulation.20 Notably, drugs that blunt the release of these hormones, for example, octreotide,21 or that antagonize their action, for example, caffeine,22 attenuate PPH and are integral components of the treatment strategy for this condition.

Recently, it has been proposed that acarbose, commonly used to control postprandial hyperglycemia in type 2 diabetes mellitus,23 could potentially improve PPH. Acarbose inhibits α-glucosidase in the brush border of the small intestine, delaying glucose absorption by decreasing the breakdown of complex carbohydrates. These actions have been shown to decrease the release of gastrointestinal hormones including insulin, a known vasodilator.

Two case reports found improvement of PPH in patients with type 124 and type 225 diabetes mellitus. Furthermore, Maruta et al26 showed that voglibose, another α-glucosidase inhibitor, also attenuates PPH in patients with neurologic...
disorders, such as multiple system atrophy and Parkinson disease. Although these findings are promising, further studies are needed to support the use of acarbose for the treatment of PPH because of the lack of randomization and placebo control in previous reports. Thus, the aim of our study was to evaluate the effectiveness of acarbose for the treatment of PPH in patients with severe autonomic failure.

Methods

Study Population
A total of 13 patients with severe autonomic failure secondary to postganglionic neuronal denervation (12 with pure autonomic failure and 1 with Parkinson disease) were recruited from referrals to the Autonomic Dysfunction Center at Vanderbilt University. PPH was defined as a fall of \( \geq 20 \) mm Hg in SBP within 2 hours after meal intake.\(^27\) Patients were excluded if they had secondary causes of autonomic failure (e.g., diabetes mellitus or amyloidosis) or if acarbose was contraindicated (e.g., abnormal liver function or Crohn disease). The criteria of the American Autonomic Society was used to ascertain the diagnosis of pure autonomic failure.\(^28\) The study was approved by the institution review board at Vanderbilt University, and all of the subjects gave informed consent.

Experimental Protocol
All of the subjects were admitted to Vanderbilt University General Clinical Research Center. Subjects were fed a low monoamine, caffeine-free diet containing 150 mEq of sodium and 60 to 80 mEq of potassium per day for \( \geq 3 \) days before evaluation. Medications affecting the autonomic nervous system were withheld for \( \geq 7 \) half-lives before admission. Patients were studied in 3 different days, a screening day and 2 study days (day 1 and day 2), for the medication trials.

Screening
All of the participants underwent an initial screening phase. Autonomic function tests were performed to evaluate the integrity of autonomic reflex arcs. These included the Valsalva maneuver, cold pressor test, isometric handgrip, and sinus arrhythmia (change in heart rate [HR] in response to controlled breathing).\(^29\) All of the tests were standardized previously in our laboratory.\(^30\)

To diagnose PPH, a hypertensive breakfast test with a standardized meal (414 calories, 14 g of protein, 51.7 g of carbohydrates, and 16.8 g fat) was performed. Brachial blood pressure and HR were measured using an automated sphygmomanometer (Dinamap, GE Medical Systems Information Technologies) for 30 minutes at baseline while seated and for 120 minutes after meal intake.\(^31\)

An orthostatic test was performed to evaluate hemodynamic and hormonal changes on standing. An indwelling catheter was placed in an antecubital vein to obtain blood samples while patients remained supine after an overnight rest. Subjects were asked to stand as long as possible or for \( \geq 10 \) minutes. During this period, they were allowed to sit at intervals if presyncopal symptoms developed. Brachial blood pressure and HR were measured, and blood samples for catecholamine determinations were obtained while supine and standing.

Medication Trial
The study was conducted in the morning after an overnight fast and in the postvoid state. To assess the tolerability of acarbose in our patients, the effect of 100 mg of acarbose (Bayer Pharmaceuticals Corporation) was first studied on a single-blind, nonrandomized, crossover design (day 1, placebo; day 2, 100 mg of acarbose) in 4 patients (3 patients with pure autonomic failure and 1 patient with idiopathic Parkinson disease and autonomic dysfunction). After acarbose was found to be well tolerated during this initial phase, the remainder of the patients were studied in a double-blind, randomized fashion. The hospital investigational pharmacy was responsible for the randomization sequence and kept the blind code. Two identically colored capsules were dispensed each day to maintain the double-blind nature of the study. All attempts were made to replicate the experimental conditions between study days.

A 21-gauge catheter was inserted into an antecubital vein for blood sampling. Blood pressure and HR measurements were obtained with an automated sphygmomanometer attached to the same arm. Heart rhythm was monitored through ECG leads. Forearm blood flow was measured using a mercury-in-silastic strain gauge connected to a plethysmograph (Hokanson EC4, DE; Hokanson Inc) as described previously.\(^32\) A thoracic bioimpedance measurement device (KIM4; Heinemann and Gregory) was used to calculate relative changes in cardiac output (CO) and total peripheral resistance (TPR). All of the signals were digitized at a sampling rate of 500 Hz using DI-720USB and Windaq Pro software (DATAQ Instruments) and processed with custom software written in PV-Wave (Visual Numerics Inc).

Subjects remained in the supine position throughout the study to control for the effect of orthostasis on blood pressure. Premeal baseline measurements were taken every 5 minutes for 30 minutes. After this period, the blinded medication was administered by mouth with 50 mL of plain water. Twenty minutes later, subjects were asked to ingest a standard solid meal of 423 Kcal (19.9 g of fat, 42.3 g of carbohydrates, and 19.5 proteins) prepared by a certified nutritionist. The meal was consumed over a 20-minute period. Blood pressure and HR were monitored every 5 minutes for 90 minutes after food ingestion.

TPR and Forearm Vascular Resistance
TPR and forearm blood flow were measured at baseline and at 30, 45, 60, and 90 minutes after meal intake. TPR was calculated by dividing mean arterial pressure (millimeters of mercury) by cardiac output (milliliters per second) and expressed in peripheral resistance units. Mean arterial pressure was calculated from the formula (DBP) +1/3(SBP − DBP). Forearm vascular resistance (FVR) was calculated as mean arterial pressure divided by forearm blood flow and expressed in units of millimeters of mercury milliliters^-1 deciliter (tissue) ^-1 minutes^-1.

Hormone Determinations
Catecholamines (norepinephrine and epinephrine), insulin, and glucose levels, were determined at baseline and at 30, 45, 60, and 90 minutes after meal intake through an intravenous catheter placed \( \geq 30 \) minutes before sampling using assays described previously.\(^33\)

Statistical Analysis
All of the data are presented as mean \( \pm \) SEM. The SBP, DBP, and HR measurements taken every 5 minutes for 90 minutes after the intervention (acarbose or placebo) were the primary end points. Random-effects models were used to examine the difference in time course between interventions while taking into account the correlation among repeated measurements obtained from individual subjects over time. We also used robust SEs to calculate 95% CIs in consideration of the small sample size. The baseline SBP and DBP measurements (the mean of 7 baseline measurements), body mass index (BMI), linear and quadratic time trend, period, and sequence were adjusted for as potential confounders.

Secondary end points included a comparison between interventions (acarbose versus placebo) in the following parameters: glucose and insulin taken at premeal baseline and at 30, 45, 60, and 90 minutes postmeal. Random-effect models were used, and BMI, period, and sequence were adjusted for as potential confounders.

Tertiary end points included changes in plasma catecholamine levels, CO, TPR, and FVR. Percentage changes were calculated for CO and TPR using 4 time points (30, 45, 60, and 90 minutes postmeal). Differences between interventions at specific time points were determined using Wilcoxon signed rank test.

All of the tests were 2-tailed, and a \( P<0.05 \) was considered significant. Analyses were performed with the SPSS statistical software (SPSS 14.0; SPSS Inc) or Stata 9.2 (Stata Corp). The authors had full access to the data and take responsibility for its
integrity. All of the authors have read and agree to the article as written.

Results

Basal Cardiovascular and Autonomic Function

Subjects’ demographic characteristics are presented in Table 1. All of the subjects fulfilled the diagnostic criteria for PPH; the average postprandial fall in SBP and DBP was 34 ± 2.6/17 ± 2.2 mm Hg. The postprandial increase in HR was 5 ± 1.7 bpm, which is inappropriately low, considering the magnitude of the postprandial blood pressure fall.

The results of the autonomic function tests are presented in Table 2. All of the patients had a profound decrease in blood pressure on standing without an adequate increase in HR. As expected, supine plasma norepinephrine was low and did not increase appropriately on standing, consistent with postganglionic loss of sympathetic fibers. The decrease in SBP during phase II of the Valsalva maneuver was exaggerated, and the SBP overshoot during phase IV was absent. The Valsalva ratio was low, indicating inadequate compensatory changes in HR. The pressor responses to isometric handgrip exercise or pain stimulus (cold pressor test) were impaired. Sinus arrhythmia was markedly reduced. Hence, autonomic testing indicated severe sympathetic and parasympathetic involvement.

Effect of Acarbose on Hemodynamic and Neuroendocrine Parameters

Blood Pressure and HR

After adjusting for baseline measurements, BMI, period, and sequence effect, acarbose reduced the postprandial fall in SBP and DBP by 17 mm Hg (95% CI: 7 to 28; P = 0.003) and 9 mm Hg (95% CI: 5 to 14; P = 0.001), respectively, compared with placebo (Figure 1). HR tended to increase more during placebo as compared with acarbose, but this effect did not reach statistical significance; the difference between placebo and acarbose was −2 bpm (95% CI: −4 to −0.2; P = 0.079; Figure 2). No patients reported any adverse events with acarbose.

Plasma Catecholamines, Glucose, and Insulin

There were no differences in plasma norepinephrine and epinephrine postmeal compared with at baseline or between interventions. As expected, acarbose significantly reduced the absorption of glucose by 10 mg/dL (95% CI: 2 to 18; P = 0.02) as compared with placebo. Hence, acarbose reduced insulin secretion by 11 μU/mL (95% CI: 5 to 18; P = 0.001; Figure 3) compared with placebo.

Because insulin is a known vasodilator, we applied a statistical model to determine the effect of acarbose on blood pressure after adjusting for plasma insulin levels and other confounders (baseline measurements, BMI, period, and se-
sequence). We found that the total effect of acarbose in reducing the postprandial fall in SBP decreased from 17 to 14 mm Hg (95% CI: 4 to 25 mm Hg) when the changes in insulin levels were considered, and the effect of acarbose remained significant ($P<0.005$). Similarly, the effect on DBP decreased from 9 to 7 mm Hg (95% CI: 2 to 11 mm Hg; $P<0.005$). These results indicate that, though insulin may play a role, there are other factors involved in the attenuation of PPH by acarbose.

**CO, TPR, and FVR**

Because of technical difficulties, we were able to obtain measurements of forearm blood flow and FVR in only 6 patients. CO and TPR were measured in 11 patients. There were no significant differences in CO between interventions, whereas TPR tended to decrease more with placebo as compared with acarbose. We found statistical significant differences at 90 minutes postmeal intake (Figure 4). Furthermore, acarbose significantly attenuated the postprandial decrease in FVR compared with placebo. The maximum effect was observed at 30 minutes postmeal (Figure 5).

**Discussion**

We found that acarbose effectively attenuates the fall in blood pressure after meals in patients with severe autonomic failure, suggesting a potential therapeutic use in the treatment of PPH. There results are consistent with the hypothesis that PPH is mediated at least in part by the secretion of vasodilatory hormones in response to glucose absorption.

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Change in SBP (circles) and DBP (squares) measurements during placebo (open) and acarbose (filled) at baseline and for 90 minutes postmeal challenge. Postprandial hypotension was significantly attenuated with acarbose. $^*P<0.01$.

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Change in HR measurements during placebo (△) and acarbose (▲) days at baseline and for 90 minutes postmeal challenge. The differences observed between interventions did not reach statistical significance ($P=0.08$).
The pathophysiology of PPH is complex and likely multifactorial. In normal subjects, food ingestion promotes biochemical and hormonal changes, including the secretion of gastric acid and gut peptides, that result in blood pooling within the splanchnic circulation. To maintain blood pressure, a variety of hemodynamic changes are necessary, including an increase in HR, stroke volume, and CO. These responses are partially mediated by a compensatory sympathetic activation as shown by the increase in plasma norepinephrine and muscle sympathetic nerve activity after food intake in normal subjects. Failure of these compensatory mechanisms seems pivotal in the development of PPH, explaining the greater prevalence of this condition in subjects with autonomic impairment.

On this background, a few nonpharmacological and pharmacological interventions have been advocated to prevent the development of PPH. In mild cases, a reduction in the meal size or its carbohydrate content may be useful. However, the latter approach is difficult to adhere to, considering that carbohydrates represent 45% to 65% of the normal Western diet. Severe cases are challenging to treat, and these patients can be symptomatic even while supine and have a higher risk of syncope if they stand up after meals. Hence, a pharmacological intervention is often necessary.

Three different pharmacological approaches have been used to improve PPH. One approach has been to increase the baseline sympathetic nervous system with 3,4-DL-threo-dihydroxyphenylserine before meal ingestion. Another has been to block the release of gastrointestinal and pancreatic hormones with octreotide. A third approach has been to antagonize the effect of vasodilators, such as adenosine with caffeine. Although these drugs seem to ameliorate PPH, their use is limited by aspects of their clinical pharmacology, their mode of application, and adverse effects. For instance, 3,4-DL-threo-dihydroxyphenylserine and other sympathomimetics should be taken ≥1 hour before meals and may induce hypertension. Octreotide is expensive, must be administered subcutaneously, and may induce abdominal cramps or diarr-
rhea after fatty meals, limiting its use, particularly among patients with diabetes mellitus. Caffeine has not been found to be universally effective. Thus, it would be advantageous to develop novel pharmacological interventions for the treatment of PPH.

For this purpose, we studied PPH in patients with severe peripheral autonomic failure. These subjects suffer from a neurodegenerative process that affects postganglionic autonomic fibers resulting in low levels of plasma catecholamines and interruption of the baroreflex arc. By using this pathophysiological model, we sought to unmask any beneficial effect of acarbose in PPH.

Considering that, among dietary components, carbohydrate exerts the greatest hypotensive effects, any slowing of the rate of carbohydrate absorption could potentially improve PPH. We used acarbose, a potent competitive inhibitor of intestinal α-glucosidase, to delay the absorption of glucose and to determine its effect on blood pressure after meals. We found an average improvement of 17 mm Hg after a standard mixed-meal ingestion in patients with peripheral autonomic failure. As expected, our patients did not show any sympathetic response to the meal challenge. Plasma norepinephrine and epinephrine were similar during placebo or acarbose, indicating that the improvement in blood pressure in our patients was not explained by sympathetic activation. Conversely, acarbose prevented the decrease in TPR and FVR, supporting the hypothesis that a circulating vasodilator partially suppressed by this drug was mostly responsible for the fall in blood pressure after meals.

In this context, we argued that insulin could play a role as a possible mediator of this vascular response. Insulin acts as a vasodilator via generation of NO, is normally released during the postprandial state, and has been shown to decrease blood pressure when infused intravenously at physiological levels in patients with autonomic failure. In our study, the attenuation in glucose absorption produced by acarbose blunted the postprandial peak of insulin, and this coincided with a reduction in PPH. However, our statistical model showed that acarbose still had a significant effect in reducing PPH after adjusting for changes in insulin levels, indicating
that blockade of other vasodilators may contribute to PPH. These findings are consistent with previous observations that patients with type 1 diabetes mellitus who, by definition, are insulin deficient, also develop PPH.24 The action of acarbose on glucose absorption affects a common pathway that influences the secretion of other gut hormones with known vasodilatory actions, such as neurotensin.26,41 It is likely that more than one vasodilator is involved in the pathophysiology of PPH.

In conclusion, 100 mg of acarbose taken with meals effectively attenuates the postprandial decrease in blood pressure in patients with autonomic failure. Our results provide a novel therapy for the treatment of this condition.

Perspectives

PPH is commonly associated with syncope, falls, angina, and cerebrovascular events. Those at most risk are subjects with varying degrees of autonomic impairment. Effective treatment strategies for this condition are limited. Our study provides a novel pharmacological approach to treat this condition; 100 mg of acarbose taken 20 minutes before meals effectively attenuates the fall in blood pressure induced by meals in patients with severe autonomic failure. We speculate that these results can be extrapolated to other patients with milder forms of autonomic impairment such as the elderly, but formal studies are needed to evaluate this postulate.

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Disclosures

None.

References


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