Gastric distension attenuates the hypotensive effect of intraduodenal glucose in healthy older subjects

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Submitted 13 February 2008; accepted in final form 21 May 2008

Gentilcore D, Meyer JH, Rayner CK, Horowitz M, Jones KL. Gastric distension attenuates the hypotensive effect of intraduodenal glucose in healthy older subjects. Am J Physiol Regul Integr Comp Physiol 295: R472–R477, 2008. First published May 21, 2008; doi:10.1152/ajpregu.00108.2008.—Postprandial hypotension occurs frequently, and current management is suboptimal. Recent studies suggest that the magnitude of the fall in postprandial blood pressure (BP) may be attenuated by gastric distension. The aim of this study was to determine the effect of gastric distension on the hypotensive response to intraduodenal (ID) glucose. Eight healthy subjects (5 males, 3 females, aged 65–76 years) received an ID infusion of either 1) 50 g glucose in 300 ml saline (ID glucose) over 60 min (t = 0–60 min), 2) 50 g glucose in 300 ml saline over 60 min and intragastric (4) infusion of 500 ml water between t = 7–10 min (IG water and ID glucose), or 3) ID saline (0.9%) infusion over 60 min and IG infusion of 500 ml water (IG water and ID saline) all followed by ID saline infusion for another 60 min (t = 60–120 min) on three separate days. BP and heart rate (HR) were measured. Gastric emptying (GE) of the IG water was quantified by two-dimensional ultrasonography. Between t = 0–60 min, systolic and diastolic BP was greater (P < 0.05 for both) with IG water and ID saline compared with IG water and ID glucose, and less (P < 0.05 for both) with ID glucose compared with IG water and ID glucose. These effects were evident at relatively low IG volumes (~300 ml). GE was faster with IG water and ID saline when compared with IG water and ID glucose. We conclude that, in healthy older subjects, IG administration of water markedly attenuates the hypotensive response to ID glucose, presumably as a result of gastric distension.

POSTPRANDIAL HYPOTENSION, defined as a decrease in systolic blood pressure ≥20 mmHg, occurring within 2 h of the end of a meal (18, 19, 27, 28), is now recognized as an important clinical problem, as it can lead to syncope and falls (19) and in some cases, stroke and angina (1, 19, 39). Those at greatest risk include the elderly and patients with autonomic dysfunction, and most often the latter, secondary to diabetes (18, 19, 27, 28). The mechanisms responsible for postprandial hypotension are unclear, but impaired regulation of splanchnic blood flow, the release of gastrointestinal hormones, and sympathetic nerve activity appear important (18, 19, 27, 28). The magnitude of the postprandial fall in blood pressure is dependent on meal composition; carbohydrates like glucose, have a highly suppressive effect on blood pressure (1, 34). In contrast to oral glucose, intravenous glucose has little, if any, effect on blood pressure (19), indicating that postprandial hypotension is, at least in the broadest sense, triggered by gastrointestinal mechanisms.

It is now apparent that the hypotensive response to a meal is modulated by gastric distension (4, 22, 24, 25, 38) and the interaction of nutrients with the small intestine; of the latter, glucose has been the most widely studied (21, 23, 31, 36). The rate of glucose delivery from the stomach to the small intestine has been shown to be a major determinant of the hypotensive response to enterally administered glucose (21, 23, 31, 36). For example, in healthy older subjects, when glucose is infused intraduodenally at a rate of 3 kcal/min, the magnitude of the maximum fall in systolic blood pressure (mean ~24 mmHg), is substantially greater compared with infusion at a rate of 1 kcal/min (mean ~9 mmHg) (31). Even healthy young subjects exhibit a fall in blood pressure in response to intraduodenal glucose at 3 kcal/min, although the magnitude of this decrease is less than in healthy elderly (41). Studies conducted by both ourselves (22) and others (4, 24, 25, 35, 38, 40) indicate that gastric distension has the capacity to attenuate the postprandial fall in blood pressure. In healthy young and older subjects, an increase in intragastric pressure induced by a gastric balloon linked to a “barostat” device increases systolic blood pressure and muscle sympathetic nerve activity in a “pressure-dependent” fashion—the so-called “gastrovascular reflex” (35, 40). Intragastric volume was not measured in these experiments. In patients with postprandial hypotension associated with autonomic neuropathy, Shannon et al. (38) observed that 480 ml of water, drunk immediately before a 414-calorie meal (52% of calories as carbohydrate), prevented a postprandial fall in blood pressure for 40 min, after which systolic blood pressure fell below baseline. Subsequently, Deguchi et al. (5) reported similar effects in patients with multiple-system atrophy, who consumed 350 ml of water before a standardized breakfast—the beneficial effect of the drink on blood pressure was sustained for ~30 min. Ingestion of water has also been shown to increase blood pressure in the fasted state (25). A limitation of all these studies (35, 38, 40) was that changes in intragastric volumes during gastric emptying after meals were not quantified. Hence, there is no information as to the minimum intragastric volume needed to modulate blood pressure in the fasted state or eliminate the hypotensive response to a meal.

The primary aim of this study was to determine in healthy older subjects whether a volume of 500 ml water has the capacity to counteract the “maximum” hypotensive effect of glucose infused into the duodenum at 3 kcal/min and to determine the minimum intragastric volume required to elicit a blood pressure response in the fasting state.

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Materials and Methods

Subjects

Eight healthy older subjects, (five male and three female) with a median age of 71 years (range: 65–76 years) and body mass index (BMI) of 24.1 kg/m² (range: 21.1–28.2 kg/m²), recruited by advertisement, were studied. All subjects were nonsmokers. None had a history of gastrointestinal disease or surgery, diabetes, significant respiratory, renal, hepatic or cardiac disease, chronic alcohol abuse or epilepsy, or was taking medication known to influence blood pressure or gastrointestinal function.

Protocol

The protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital, and each subject provided written, informed consent prior to their involvement. All experiments were carried out in accordance with the Declaration of Helsinki.

Each subject was studied on three occasions, each separated by a minimum of 7 days, in single-blind, randomized order. On each day, the subject attended the University of Adelaide, Discipline of Medicine, Royal Adelaide Hospital, at 0830 following a fast (10.5 h for solids; 8.5 h for liquids) (9–11). At that time, a silicone-rubber catheter (external diameter ~4 mm) (Dentsleeve International, Mui Scientific, Ontario, Canada), was introduced into the stomach via an anesthetized nostril (10, 31). The assembly included an infusion channel (internal diameter ~1 mm) and was positioned so that the infusion port was located ~10 cm distal to the pylorus (i.e., in the duodenum), as well as two other channels that were positioned in the antrum (2.5 cm proximal to the pylorus) and duodenum (2.5 cm distal to the pylorus), respectively, and were perfused with 0.9% saline. The correct positioning of the catheter was maintained by continuous measurement of the transmucosal potential difference between the antral (~40 mV) and the duodenal (0 mV), channel (13). For this purpose, an intravenous cannula filled with sterile saline was placed subcutaneously in the left forearm and used as a reference electrode (13). A smaller-diameter (~0.2 mm internal) silicone tube was attached to the catheter with its outlet located ~10 cm proximal to the pylorus, to allow intragastric (4) infusion. The tip of the catheter passed into the duodenum by peristalsis, which took between 40 and 205 min. An automated blood pressure cuff was placed around the left arm (10, 31). Once intubated, the subject initially rested in the recumbent position. Approximately 30 min after the tube was positioned correctly (at t = 0 min), the subject was seated in a chair and received either 1) an intraduodenal (ID) infusion of 50 g of glucose dissolved in 300 ml 0.9% saline (ID glucose group) at a rate of 5 ml/min (3.3 kcal/min) between t = 0–60 min, 2) an identical ID infusion between t = 0–60 min, and an intragastric (IG) infusion of 500 ml water between t = 7–10 min (IG water and ID glucose group), or 3) an ID saline (0.9%) infusion at 5 ml/min between t = 0–60 min and an IG infusion of 500 ml water between t = 7–10 min (IG water and ID saline group). On all three days, normal saline was infused intraduodenally at 5 ml/min between t = 60–120 min (31). The osmotic pressure of the intraduodenal glucose solution was 22.4 atmospheres. Intraduodenal infusions were performed using a volumetric infusion pump (Imed Gemini PC-1; San Diego, CA). For the intragastric infusions, water was pressurized (170 kPa) with oxygen and delivered at a rate of ~166 ml/min. Gastric emptying of the water was measured using ultrasound (17); in the ID glucose group (between t = 0–120 min), sham ultrasonography measurements were performed to ensure that the subject remained blinded to the study conditions. At t = 120 min, the catheter was removed, the subject was given a light meal and then allowed to leave the laboratory. On one day, cardiovascular autonomic nerve function was evaluated immediately after the completion of the study (7, 33).

Measurements

Blood pressure and heart rate. Blood pressure (systolic and diastolic) and heart rate were measured using an automated oscillometric blood pressure monitor (DINAMAP ProCare 100, GE Medical Systems, Milwaukee, WI) at t = −9, −6, and −3 min before commencement of the intraduodenal infusions and then every 3 min between t = 0–120 min (10, 31). Baseline blood pressure and heart rate, that is, t = 0 min, were calculated as the mean of measurements taken at t = −9, −6, and −3 min. Postprandial hypotension was defined as a fall in systolic blood pressure of ≥20 mmHg that was sustained for at least 30 min (19).

Gastric emptying. Antral area was measured by real-time two-dimensional ultrasonography using a Logiq 9 ultrasonography system (GE Healthcare Technologies, Sydney, Australia). The subject was scanned using a 3.5C broad-spectrum 2.5–4 MHz convex transducer (20) before (t = −2 min) the commencement of the intraduodenal infusion, at t = 15 min, i.e., 5 min after the completion of the intragastric infusion and then every 15 min until t = 120 min. With the subject seated, the transducer was positioned vertically, in the region of the umbilicus, to visualize the antrum in cross section with the superior mesenteric vein and the abdominal aorta as landmarks (17). Antral area (cm²) was measured using manually operated on-screen calipers. The circumference of the antrum was outlined and the area recorded during the fasting state (t = −2 min) was subtracted from subsequent measurements. At all time points, gastric emptying was expressed as retention (%) = [AA(t) − AA(−2)}/AA(max) − AA(−2)] × 100, where AA(t) = antral area measured at a specific time point, AA(−2) = antral area at t = −2 min and AA(max) = maximum antral area (17). The 50% emptying time (T50) was also determined, as previously described (12). This method has been well validated to calculate total intragastric volumes (17).

Autonomic function. Autonomic nerve function was assessed using standardized cardiovascular reflex tests (7, 33). Parasympathetic function was evaluated by the variation (R-R interval) of the heart rate during deep breathing and the response to standing (30:15 ratio). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. Each of the test results was scored according to age-adjusted predefined criteria as 0 = normal, 1 = borderline, and 2 = abnormal for a total maximum score of 6. A score ≥3 was considered to indicate autonomic dysfunction (7, 33).

Statistical Analysis

Data were evaluated using mixed-model repeated-measures two-way ANOVA, with “treatment” and “time” as within-subject factors. Systolic and diastolic blood pressure and heart rate were analyzed as changes from baseline. Data were analyzed separately from t = 0–60 min and t = 60–120 min to evaluate the effects of “treatment” and “time” on the effects of intraduodenal glucose. Gastric emptying was analyzed as absolute values. One-way ANOVA was used to analyze the effects of “time” on systolic and diastolic blood pressure, heart rate, and gastric emptying. The maximum fall in blood pressure was defined as the greatest mean change from baseline in each subject at any given time point for each treatment. In all analyses, post hoc comparisons of adjusted means were performed using Student’s t-tests. All analyses were performed using Statview (ver. 5.0; Abacus Concepts, Berkeley, CA) and SuperANOVA (ver. 1.11, Abacus Concepts). Data are shown as the change from baseline and mean values ± SE. A P value <0.05 was considered significant in all analyses.

Results

The studies were well tolerated, and there were no untoward events. The median score for autonomic nerve dysfunction was 0.88 (range: 0–3). One of the eight subjects had definite autonomic dysfunction. While no subject experienced post-
or IG water and ID saline (P < 0.01), and a trend for a rise in diastolic (P = 0.09), blood pressure during IG water and ID saline (Fig. 1, A and B). In contrast, there was a fall in systolic (P < 0.01) and diastolic (P < 0.0001) blood pressure with ID glucose and no change in systolic (P = 0.98) or diastolic (P = 0.17) blood pressure during IG water and ID glucose. There were significant treatment × time effects for systolic (P < 0.001) and diastolic (P < 0.0001) blood pressure between t = 0–60 min, so that systolic and diastolic blood pressure were greater (P < 0.05 for both) during IG water and ID saline when compared with IG water and ID glucose, and less (P < 0.05 for both) between IG glucose when compared with IG water and ID glucose. Between t = 60–120 min, systolic blood pressure was higher (P < 0.05) after IG water and ID saline when compared with IG water and ID glucose. However, there was no difference (P = 0.70) in systolic blood pressure after ID glucose compared with IG water and ID glucose. There was also a rise (P < 0.01) in diastolic blood pressure after ID glucose, but not following IG water and ID glucose (P = 0.48) or IG water and ID saline (P = 0.97) and a trend (P = 0.09) for a difference in diastolic blood pressure between the three study days.

Heart rate. Between t = 0–60 min, there was no effect of IG water and ID saline on heart rate (Fig. 1C; P = 0.23). In contrast, there was a progressive rise in heart rate (P < 0.0001 for all) during ID glucose with, or without, IG water. There was a significant treatment × time effect (P < 0.0001) for heart rate between t = 0–60 min. Heart rate was higher (P < 0.05) with IG water and ID glucose when compared with IG water and ID saline, with no difference between the ID glucose and IG water and ID glucose groups. Between t = 60–120 min, there was no change (P = 0.23) in heart rate, during IG water and ID saline and a progressive fall (P < 0.0001 for both) with ID glucose both with, and without, IG water. There was a significant treatment × time effect (P < 0.05); heart rate was greater (P < 0.05) following IG water and ID glucose when compared with IG water and ID saline.

Gastric Emptying

Gastric emptying of water following IG water and ID saline approximated a monoexponential pattern, so that emptying of water was rapid from instillation to t = 45 min and then reached a plateau so that by t = 45–60 min only ~100 ml of water remained in the stomach (Fig. 2). Following IG water and ID glucose, there was no statistically significant emptying of water until t = 75 min (P = 0.04), and intragastric volumes remained stable after that time. Gastric emptying was much faster (P < 0.01) during IG water and ID saline when compared with IG water and ID glucose. Similarly, the T50 was less during IG water and ID saline (41.0 ± 4.0 min) compared with IG water and ID glucose (77.7 ± 8.3 min; P = 0.006). At t = 120 min, the intragastric retention of water was 187.9 ± 81.8 ml after IG water and ID glucose and 47.9 ± 28.6 ml after IG water and ID saline.

**DISCUSSION**

We have demonstrated that gastric distension produced by intragastric instillation of water, prevents the falls in systolic
have decreased to a greater extent with the 200-ml drinks, had this study, we cannot predict whether blood pressure would were ingested at a higher volume (600 ml vs. 200 ml), but from less when glucose drinks of the same concentration (12.5%) of healthy older subjects (22), the fall in blood pressure was volume required for this effect is uncertain. In our recent study intensive response to a meal (4, 5, 22, 24, 25, 38, 42, 43), the relationship between the magnitude of the fall in systolic blood pressure induced by intraduodenal glucose was substantial (maximum 14.3 ± 2.7 mmHg), consistent with previous studies (10, 31, 32). Hence, our observations, which establish that the hypotensive response to small intestinal nutrients is attenuated by nonnutrient gastric distension, have substantial implications for the management of postprandial hypotension.

Our previous studies have established that there is a direct relationship between the magnitude of the fall in systolic blood pressure and the rise in heart rate with the rate of gastric emptying of glucose drinks (23) and the exposure of glucose to the small intestinal mucosa (21, 32, 36) and that the response to small intestinal glucose is load, rather than concentration, dependent (10). In healthy subjects, gastric emptying of glucose solutions approximates an overall rate of 1.5–3 kcal/min, after an initial emptying phase that may be somewhat faster (14, 16), as a result of inhibitory feedback arising from the small intestine (15, 26). This formed the basis for the use of a 3 kcal/min infusion in the current study, which can be considered to be a maximum stimulus.

Gastric distension has the capacity to influence blood pressure (4, 22, 24, 25, 35, 38, 40). While there is no doubt that rapid ingestion of water has the ability to attenuate the hypotensive response to a meal (4, 5, 22, 24, 25, 38, 42, 43), the volume required for this effect is uncertain. In our recent study of healthy older subjects (22), the fall in blood pressure was less when glucose drinks of the same concentration (12.5%) were ingested at a higher volume (600 ml vs. 200 ml), but from this study, we cannot predict whether blood pressure would have decreased to a greater extent with the 200-ml drinks, had there been no intragastric volume, while glucose was entering the small intestine. This is, however, supported by observations that 1) oral glucose (75 g in 350 ml water), which emptied from the stomach at 1.3–1.7 kcal/min decreases blood pressure significantly in healthy older, but not young subjects (23) and 2) intraduodenal glucose at 3 kcal/min decreases blood pressure in healthy young, as well as older subjects, albeit to a lesser extent (41). In the current study, gastric emptying of water was predictably much slower during intraduodenal glucose infusion, so that the intragastric volume remained at around 300 ml throughout the entire 60-min glucose perfusion, as a result of small intestinal feedback stimulated by the presence of glucose (2). Given that during this period, the 300 ml of intragastric volume significantly elevated blood pressure to baseline to levels much above those observed when glucose was perfused in the absence of intragastric water, it is clear that as little as 300 ml of intragastric water suffices to correct the hypotensive effects of high loads of intraduodenal glucose. By contrast, emptying of intragastric water commenced immediately during intraduodenal saline infusion so that only ~100 ml remained by 45–60 min. During this period of rapid decay of intragastric volume, systolic blood pressure remained elevated by 6–8 mmHg over baseline. Although we found no effect of volume in the range of ~100–500 ml on blood pressure, van Orshoven et al. (40) reported that proximal gastric balloon stepwise distension using a “barostat” device increased blood pressure (mean ~12 mmHg) in healthy older subjects (40). It remains to be determined whether these effects are dependent on the region of the stomach distended (22). Furthermore, Shannon et al. (38) reported that a 480-ml drink of water elevated blood pressure for up to 40 min after a meal but did not observe or relate intragastric volume to the time course of the hypotensive effects of the drink.

The mechanisms mediating the blood pressure responses to acute ingestion of water and small intestinal glucose/gastric distension remain unclear. It has been suggested that the increase in blood pressure induced by water ingestion may reflect resetting of the baroreflex (35), diminished compliance of the splanchnic arteries (40), reflex sympathetic activation (24), the hypooosmotic properties of water (3), and individual fluid balance (30). Plasma noradrenaline levels have been reported to be increased after water ingestion in normal healthy young (37) and elderly (24) subjects, despite a pressor effect evident only in the older group. The release of vasoactive peptides, including insulin (18), neurotensin (28), vasoactive intestinal polypeptide (29), CGRP (6), and glucagon-like peptide-1 (GLP-1) (9) by enteral glucose may potentially modulate blood pressure. It has been reported that the magnitude of the increase in muscle sympathetic nerve activity (MSNA) induced by intraduodenal glucose infusion is comparable in healthy young and older subjects (41), while the response to gastric distension is attenuated in the elderly (40). Hence, the blunted response to oral glucose in the elderly (8) is likely to reflect an impaired gastrovascular reflex.

**Perspectives and Significance**

Our observations establish that, in healthy older subjects, intragastric administration of water markedly attenuates the hypotensive response to intraduodenal glucose infusion, presumably as a result of gastric distension, and suggest that low volumes of water (<300 ml and, possibly ≤100 ml) would prove effective. While further studies are required to formally evaluate the effects of volumes of water <500 ml and the effects of chronic gastric distension, our observations add to the rationale for patients with postprandial hypotension to drink water before eating.
ACKNOWLEDGMENTS

Data from this manuscript have been presented in abstract form at Digestive Diseases Week at the 108th Annual Meeting of the American Gastroenterology Association, Washington DC, USA, May 20, 2007 (Gentilcore D, Meyer JH, Horowitz M, Jones KL. Gastroenterology 132: A324, 2007).

GRANTS

This study was supported by the National Health and Medical Research Council (NHMRC) of Australia. Dr. Gentilcore is supported by a postdoctoral fellowship (PR 07A 3309) from the National Heart Foundation of Australia. Associate Professor Jones’ salary is funded jointly by Diabetes Australia and the NHMRC of Australia. The purchase of the Logiq 9 ultrasonography system was supported by an Equipment Grant from the NHMRC of Australia, funds from the University of Adelaide, and GE Medical Systems Australia.

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