

## Effects of drink volume and glucose load on gastric emptying and postprandial blood pressure in healthy older subjects

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**Jones, Karen L., Deirdre O'Donovan, Antonietta Russo, James H. Meyer, Julie E. Stevens, Yong Lei, Jennifer Keogh, Anne Tonkin, and Michael Horowitz.** Effects of drink volume and glucose load on gastric emptying and postprandial blood pressure in healthy older subjects. *Am J Physiol Gastrointest Liver Physiol* 289: G240–G248, 2005. First published March 17, 2005; doi:10.1152/ajpgi.00030.2005.— Postprandial hypotension (PPH) occurs frequently in the elderly; the magnitude of the fall in blood pressure (BP) is related to the rate of glucose entry into the duodenum during intraduodenal glucose infusion and spontaneous gastric emptying (GE). It is unclear if glucose concentration affects the hypotensive response. Gastric distension may attenuate PPH; therefore, meal volume could influence the BP response. We aimed to determine the effects of 1) drink volume, 2) glucose concentration, and 3) glucose content on the BP and heart rate (HR) responses to oral glucose. Ten subjects ( $73.9 \pm 1.2$  yr) had measurements of BP, GE, and blood glucose on 4 days after 1) 25 g glucose in 200 ml (12.5%), 2) 75 g glucose in 200 ml (37.5%), 3) 25 g glucose in 600 ml (4%), and 4) 75 g glucose in 600 ml (12.5%). GE, BP, HR, and blood glucose were measured for 180 min. After all drinks, duodenal glucose loads were similar in the first 60 min. Regardless of concentration, 600-ml (but not 200-ml) drinks initially increased BP, and in the first 30 min, systolic BP correlated ( $P < 0.01$ ) with volume in both the proximal and total stomach. At the same concentration (12.5%), systolic BP fell more ( $P = 0.02$ ) at the smaller volume; at the same volumes, there were no effects of concentration on BP. There was no difference in the glycemic response to drinks of identical glucose content. We conclude that 1) ingestion of glucose at a higher volume attenuates and 2) under constant duodenal load, glucose concentration (4–37%) does not affect the fall in BP.

postprandial hypotension; gastric emptying; elderly

POSTPRANDIAL HYPOTENSION, leading to syncope and falls, is an important clinical problem, particularly in the elderly and patients with autonomic dysfunction (7, 12, 14, 19). The mechanisms responsible for postprandial hypotension are poorly defined, and current treatments are less than optimal (7, 12, 14, 19). The magnitude of the postprandial fall in blood pressure is known to be dependent on meal composition—ingestion of carbohydrate, particularly glucose, has the greatest effect on blood pressure (27), whereas the effects of fat and protein appear to be much less (10).

Changes in splanchnic blood flow, sympathetic nerve activity, and release of gastrointestinal peptides are all thought to play a role in postprandial hypotension (7, 12, 14, 19). Onset of the fall in blood pressure is evident soon after a meal, with a maximum response at 30–60 min (14). While oral ingestion of

glucose leads to a fall in blood pressure, intravenous infusion of glucose has little, if any, effect (13) indicating that the response is mediated from the gastrointestinal tract. We have reported that in both healthy older subjects and patients with type 2 diabetes managed by diet alone, the hypotensive and heart rate responses to oral glucose vary with the rate (g/min) at which glucose enters the small intestine (i.e., the glucose load) (16, 17, 24, 30). If it is assumed that after a standard glucose-containing meal the glucose concentrations of the gastric content would in most individuals be similar, one might conclude from these observations that the hypotensive responses are dependent on proximal small intestinal glucose loads, rather than concentration. However, in two of these studies (16, 30), gastric emptying was varied by adding (vs. not adding) guar to slow the emptying of a glucose drink. Since the guar was shown to have much more profound effects on intestinal glucose absorption than gastric emptying, it was unclear which effect of guar ameliorated postprandial hypotension. In another study (24) in which two different loads of glucose (1 and 3 kcal/min) were infused directly into the duodenum, hypotensive and heart rate responses were greater at the higher load. But since the loads were achieved by infusing either 8.3 or 25% glucose at 3 ml/min, this experiment could not distinguish between a concentration effect independent of load or a load effect independent of concentration. Vloet et al. (35) reported in older subjects with postprandial hypotension that the magnitude and duration of the hypotensive response to 200 ml glucose drinks are both progressively greater with increased carbohydrate concentration (25 vs. 65 vs. 125 g, in 200 ml). In this study (35), gastric emptying was not measured, and it is again impossible to distinguish between the potential effects of glucose concentration vs. load.

It should also be recognized that gastric emptying may affect postprandial blood pressure by influencing the duration and site of gastric distension. In patients with autonomic failure, consumption of water (480 ml) immediately before a meal attenuates the postprandial fall in blood pressure (31). Furthermore, in healthy young subjects, proximal gastric distension, using a barostat device, increases muscular sympathetic nerve activity and systolic blood pressure (the so-called “gastrovascular reflex”) (29). Accordingly, the magnitude of the postprandial fall in blood pressure induced by oral glucose may be less when intragastric volume is relatively higher as a result of increased gastric distension, and this effect could be dependent on the site of gastric distension as determined by distribution of the meal within the stomach.

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Gastric emptying is recognized as a major determinant of postprandial glycemia in both healthy subjects (8) and patients with type 2 diabetes (15, 28). It has been suggested that a lack of standardization of the volume of water ingested in an oral glucose tolerance test accounts for some of its documented variability (4, 6, 32–34). Whereas increases in volume have been associated with higher peak blood glucose concentrations, reports are inconsistent and interpretation has been limited by the lack of concurrent measurement of gastric emptying (33, 34).

The primary aims of the present study were, therefore, to determine in healthy older subjects 1) whether postprandial hypotensive responses vary with glucose concentration, at constant duodenal load and 2) the effect of drink volume on the postprandial blood pressure response to oral glucose. On the basis of prior experiments in monkeys, dogs, and humans (9, 18, 20), we predicted that normal regulation of gastric emptying would ensure virtually constant duodenal loads of glucose so that meal volumes and glucose concentrations could be manipulated to determine how different concentrations of glucose entering the duodenum might also affect postprandial hypotension. A secondary aim was to examine the effects of drink volume on the glycemic response to oral glucose.

## MATERIALS AND METHODS

### Subjects

Ten healthy older subjects (6 men and 4 women) with a mean age of  $73.9 \pm 1.2$  yr (range, 66–80 years) and a body mass index of  $25.0 \pm 0.8$  kg/m<sup>2</sup> (range, 20.6–29.2 kg/m<sup>2</sup>) were recruited by advertisement. All subjects were nonsmokers, and none had a history of gastrointestinal disease or surgery, diabetes mellitus, significant respiratory or cardiac disease, chronic alcohol abuse, or epilepsy. No subject was known to be hypertensive, and none was taking medication known to influence either blood pressure or gastrointestinal function.

### Protocol

Each subject had concurrent measurements of blood pressure, heart rate, gastric emptying, and blood glucose concentrations on four separate days before and after ingestion of the following drinks: 1) 200 ml water containing 25 g glucose (12.5% glucose), 2) 200 ml water containing 75 g glucose (37.5% glucose), 3) 600 ml water containing 25 g glucose (4% glucose), and 4) 600 ml water containing 75 g glucose (12.5% glucose). Subjects could not be blinded to the test drinks because of differences in volume. All of the drinks were labeled with 20 MBq <sup>99m</sup>Tc-sulfur colloid and consumed at room temperature within 5 min. The order of the four studies was randomized and each study was separated by at least 3 days. On each study day, subjects attended the Department of Nuclear Medicine, PET, and Bone Densitometry at ~0900 h following an overnight fast (14 h for solids; 12 h for liquids). A cannula was placed in a right antecubital vein for blood sampling and the subject was seated with his or her back against a gamma camera, with a blood pressure cuff around the left arm. Venous blood samples were obtained immediately before ( $t = -2$  min) ingestion of the drink and then at  $t = 15, 30, 45, 60, 90, 120, 150,$  and 180 min. Cardiovascular autonomic nerve function was evaluated on one of the study days. Each subject gave written, informed consent before the commencement of the study. The study was carried out in accordance with the Declaration of Helsinki and the protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

### Measurements

**Gastric emptying.** Radioisotopic data were acquired for 180 min (30-s frames for the first 30 min, 3-min frames thereafter) (2, 17).

**Time 0 ( $t = 0$  min)** was defined as the time of completion of the drink. A region of interest was drawn around the total stomach, which was subsequently divided into proximal and distal stomach regions (2). Data were corrected for subject movement, radionuclide decay, and  $\gamma$ -ray attenuation (3). The retention of the drink in the total, proximal, and distal stomach at  $t = 0, 15, 30, 45, 60, 90, 120, 150,$  and 180 min was derived (2, 17) and expressed as a percentage of the counts in the total stomach, where 100% immediately followed ingestion of the drink. It has been established that measurement of the <sup>99m</sup>Tc marker provides accurate indications of gastric emptying and intragastric distribution of the glucose (9). We did not measure intragastric volumes, but assumed that increases in aqueous volumes in which <sup>99m</sup>Tc was distributed would be small in the first 30 min, relative to the initial volumes of the meal.

**Blood pressure and heart rate.** Blood pressure (systolic and diastolic) and heart rate were measured using an automated oscillometric blood pressure monitor (Dinamap; Johnson & Johnson) immediately before ( $t = -2$  min) ingestion of the drink, at 3-min intervals for the first 60 min, and then at 15-min intervals for a further 120 min (16, 17, 24). Postprandial hypotension was defined as a fall in systolic blood pressure of  $\geq 20$  mmHg after the drink that was sustained for at least 30 min (11, 14).

**Blood glucose concentrations.** Blood glucose concentrations were determined immediately using a portable blood glucose meter (Companion 2 Meter; Medisense, Waltham, MA) (16). Peak blood glucose and the time to peak blood glucose were calculated.

**Cardiovascular autonomic function.** Autonomic nerve function was evaluated using standardized cardiovascular reflex tests (5). Parasympathetic function was evaluated by the variation (R-R interval) of the heart rate during deep breathing and the response to standing (30:15). 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 of  $\geq 3$  was considered to indicate autonomic dysfunction (5).

### Statistical Analysis

Data were evaluated using repeated-measures ANOVA and are presented as means  $\pm$  SE, unless stated otherwise. Mean contrasts were used to analyze individual point-by-point comparisons to test preplanned hypotheses in the case of a “treatment by time” interaction. Changes in blood pressure were calculated separately for the first 60 min because the maximum postprandial fall in blood pressure is known to usually occur between 30–60 min (14) and then for the remaining 60–180 min. Area under the curve (AUC) analysis for the blood glucose concentrations was calculated using the trapezoidal rule. Because of their diagnostic significance, baseline and 120-min blood glucose concentrations were compared (36). To determine potential relationships between postprandial blood pressure and heart rate with intragastric drink volume, data from the two studies (200 vs. 600 ml) using the same concentration of glucose (12.5%) were analyzed for the first 60 min using linear regression analysis. A  $P$  value of  $<0.05$  was considered significant in all analyses.

## RESULTS

All subjects tolerated the study well and there were no untoward events. None had definite evidence of autonomic neuropathy (mean score  $0.1 \pm 0.1$ ). Four of the 10 subjects had postprandial hypotension (fall in systolic blood pressure  $> 20$  mmHg sustained for at least 30 min); one subject after the drink containing 25 g glucose in 200 ml (12.5% glucose) and three other subjects after the drink containing 75 g glucose in 600 ml (12.5% glucose). In these four subjects, the fall in systolic blood pressure was not  $\geq 20$  mmHg on the three other study days.

### Gastric Emptying

There was no effect of glucose concentration on gastric emptying of the drinks containing 25 g glucose ( $P =$  not significant; Fig. 1A). In contrast, gastric emptying of the drink containing 75 g glucose in 200 ml was slightly faster ( $P = 0.01$ ) overall compared with the 600 ml drink, although this difference was not significant in the first 60 min ( $P = 0.12$ ). In the first postcibal 60 min, duodenal loads of glucose were essentially identical for three of the drinks (Fig. 2). After 60 min, loads of glucose entering the duodenum declined asymptotically after the 200-ml drink, as the stomach became increas-

ingly empty of the drink, whereas the larger, 600-ml drinks continued to empty at a nearly constant rate for the 3-h durations of the tests (Figs. 1A and 2). Thus loads of glucose entering the duodenum for the first 60 min were similar, allowing a comparison (below) of the effects of glucose concentrations in the small intestine, independent of load.

*Intragastric distributions.* For the drinks that contained 25 g glucose there was a trend ( $P = 0.06$ ) for more of the 600-ml drink, when expressed as a percentage of the total volume, to be retained in the proximal stomach compared with 200 ml (Fig. 1B). For the drinks that contained 75 g glucose, this

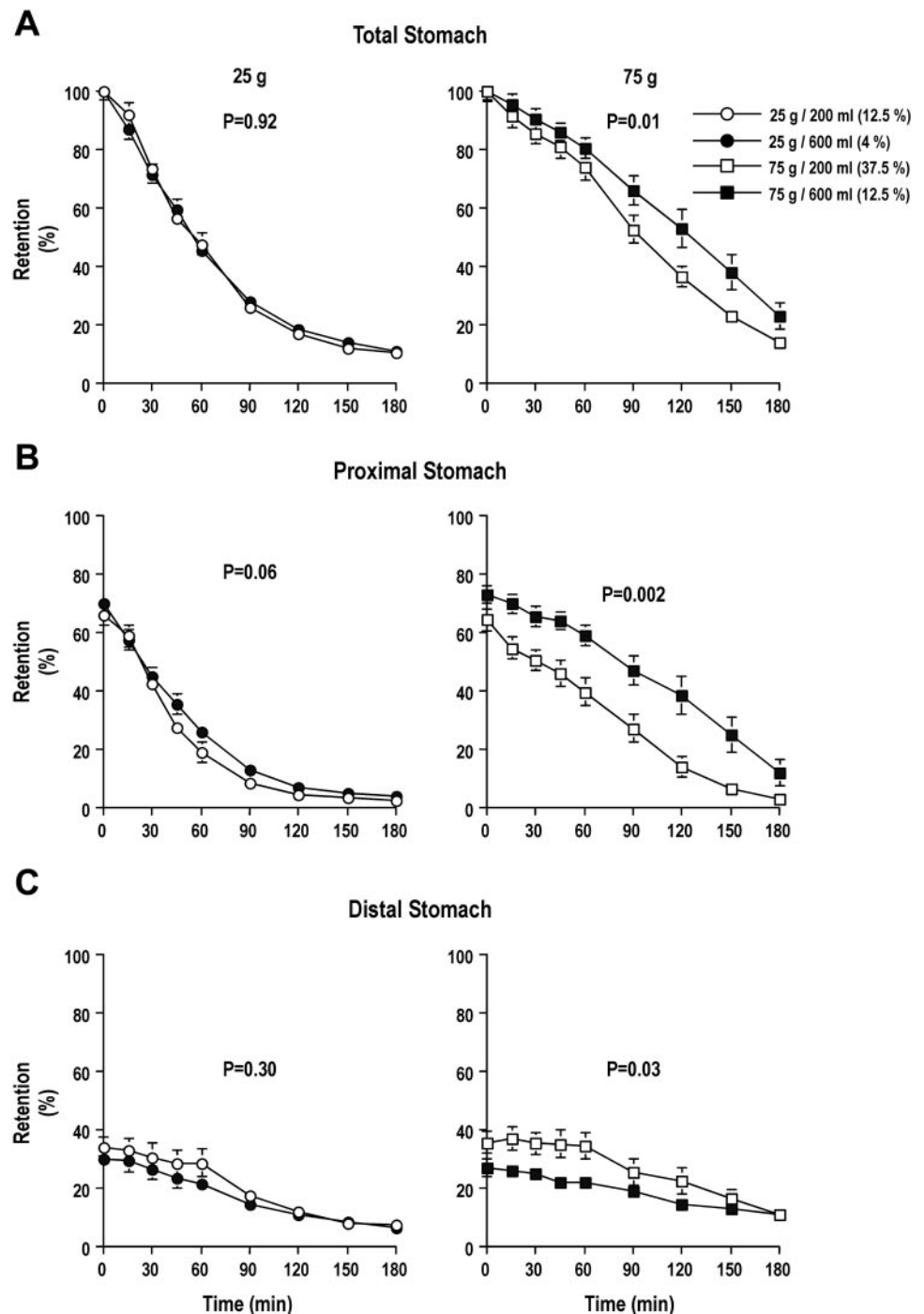


Fig. 1. Gastric emptying of four glucose drinks (25 g/200 ml, 25 g/600 ml, 75 g/200 ml, 75 g/600 ml) from the total (A), proximal (B) and distal (C) stomach. Data are presented as means  $\pm$  SE.  $P$  values indicate "treatment" effect.

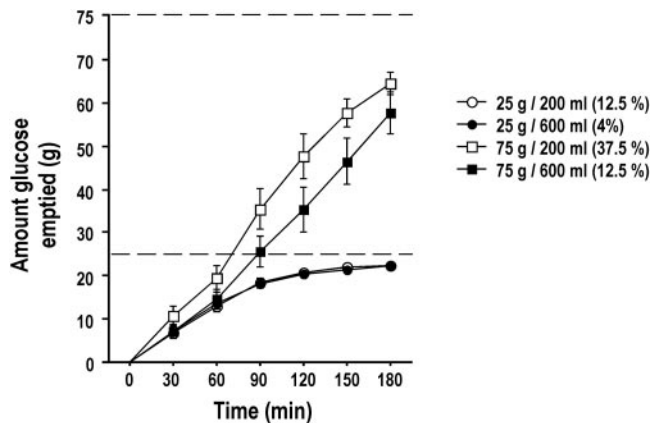


Fig. 2. Duodenal entry of glucose (amount emptied from the stomach) after ingestion of four glucose drinks (25 g/200 ml, 25 g/600 ml, 75 g/200 ml, 75 g/600 ml). Data are presented as means  $\pm$  SE.

difference was significant, i.e., the retention of the 600-ml drinks was greater ( $P = 0.002$ ; Fig. 1B). There was no effect ( $P = 0.3$ ) of concentration on distal stomach retention between the two drinks containing 25 g glucose (Fig. 1C). In contrast, for the 75-g glucose drinks, there was less ( $P = 0.03$ ) retention in the distal stomach for the 600-ml compared with 200-ml drink (Fig. 1C).

#### Glycemic Responses

There was no significant difference in fasting blood glucose concentrations between any of the four study days. The glycemic response to drinks of identical glucose content was not significantly different (no effect of concentration) either in the first 0–60 min or for the duration of the study (0–180 min; Fig. 3). There was no significant effect of concentration on the AUC for blood glucose between 0 and 60 min, after either the 25-g drinks or 75-g drinks or 0–180 min. Because rates of gastric emptying of glucose were sustained much longer after the 75 g of glucose, there were corresponding prolongations of the glycemic responses, so the AUCs were greater ( $P < 0.0001$ ) for the two drinks containing 75 g glucose compared with 25 g glucose from 0 to 180 min (Fig. 3). There was no difference in blood glucose concentrations at 120 min between the two drinks containing 25 g glucose and the two drinks containing 75 g glucose.

#### Blood Pressure and Heart Rate

**Baseline blood pressure and heart rate.** Baseline systolic blood pressure was slightly, but significantly, greater ( $P < 0.05$ ) before ingestion of the drink containing 75 g glucose in 600 ml ( $128.7 \pm 16.8$  mmHg) when compared with the drink containing 75 g glucose in 200 ml ( $123.4 \pm 12.8$  mmHg) but not significantly different from either of the drinks containing 25 g glucose. Otherwise, there were no other significant differences in baseline blood pressure (systolic or diastolic) between any of the four study days (Fig. 4). There were no significant differences in baseline heart rate between the four study days (Fig. 5).

**Postprandial systolic blood pressure.** There was a transient increase in systolic blood pressure immediately ( $t = 0$ –3 min) following ingestion of the 600-ml (25 g:  $P = 0.03$  and 75 g:

$P = 0.004$ ; Fig. 4) but not after the 200-ml drinks. There was a fall in systolic blood pressure after ingestion of the drink containing 25 g glucose in 200 ml ( $P = 0.004$ ) from  $t = 0$ –60 min; there was no significant difference to baseline by  $t = 90$  min (Fig. 4). Similarly, at the same concentration of glucose (12.5%), there was a significant fall in systolic blood pressure after the drink containing 75 g glucose in 600 ml ( $P = 0.04$ ) between  $t = 0$ –60 min, which was sustained ( $P = 0.03$ ) for the duration of the study (Fig. 4).

Systolic blood pressure was higher for the 25 g and the 75 g glucose drink in 600 ml (compared, respectively, to the 200-ml drinks). Conversely, systolic blood pressure was lower during the first 60 min when either the 25 or 75 g glucose drink was ingested at a greater concentration [25 g glucose ( $P = 0.05$ ) and 75 g glucose ( $P = 0.01$ )] (Fig. 4). The fall in systolic blood pressure from baseline was greater ( $P = 0.0006$ ) following ingestion of the drink containing 25 g in 200 ml vs. 600 ml; however, this was not significant ( $P = 0.15$ ) for the drinks containing 75 g glucose.

When comparing systolic blood pressure at the same volume, there was no significant difference in systolic blood pressure in the first 60 min ( $t = 0$ –60 min) for either the 200-ml (12.5 vs. 37.5% glucose; Fig. 6A) or 600-ml (4 vs. 12.5%; Fig. 6B) drinks. In contrast, systolic blood pressure was lower from  $t = 105$  min for the 75-g glucose loads, i.e., 75 g in 200 ml ( $P < 0.05$ ; Fig. 5A) and from  $t = 90$  min for 75 g in 600 ml ( $P < 0.05$ ; Fig. 6B) compared with the 25-g glucose loads at the same volume. However, for both the 25-g glucose drinks, the rates of glucose entry into the duodenum (Fig. 2) had diminished to almost nothing, whereas the 75-g glucose drinks continued to empty steadily.

At the same concentration (12.5%: 25 g glucose in 200 ml and 75 g glucose in 600 ml), systolic blood pressure was less ( $P = 0.02$ ) during the first 60 min at the smaller volume (Fig. 7A); however, the change in systolic blood pressure from baseline was not significant ( $P = 0.14$ ). In contrast, blood pressure was greater ( $P < 0.05$ ) at the smaller volume from 120–180 min (Fig. 7A).

**Postprandial diastolic blood pressure.** There was a significant fall (from  $t = 0$ –60 min) in diastolic blood pressure after

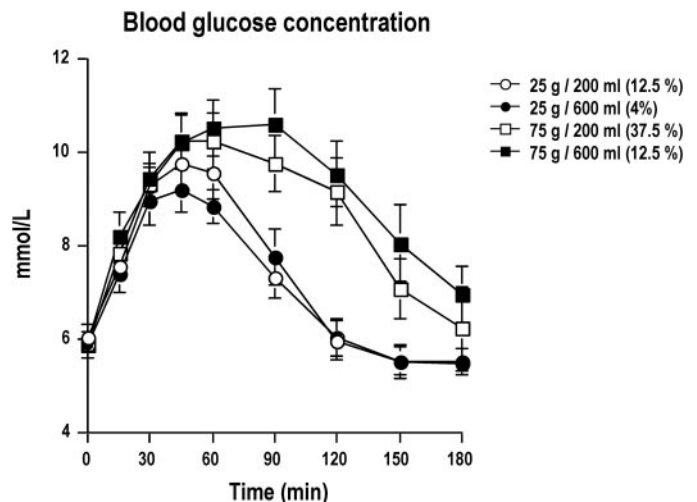
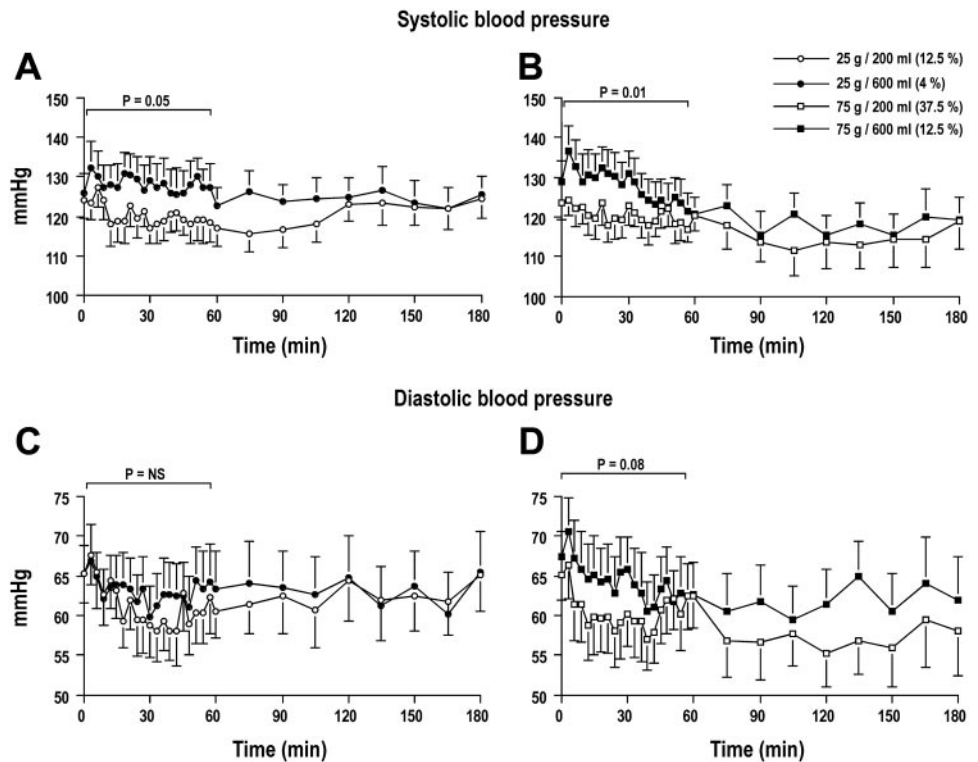


Fig. 3. Blood glucose concentrations following ingestion of four glucose drinks (25 g/200 ml, 25 g/600 ml, 75 g/200 ml, 75 g/600 ml). Data are presented as means  $\pm$  SE.

Fig. 4. Effects of glucose concentration on systolic (A and B) and diastolic (C and D) blood pressure following ingestion of four glucose drinks (25 g/200 ml, 25 g/600 ml, 75 g/200 ml, 75 g/600 ml). Data are presented as means  $\pm$  SE. *P* values indicate "treatment" effect during the first 60 min.



ingestion of all four drinks ( $P < 0.05$ ; Fig. 4); in all cases, diastolic blood pressure had returned to baseline by  $t = 180$  min. Diastolic blood pressure was not different during the first 60 min between the two 25-g glucose loads ( $P = 0.30$ ), and tended to be less after the drink containing 75 g glucose in 200 ml compared with 600 ml ( $P = 0.08$ ; Fig. 4B).

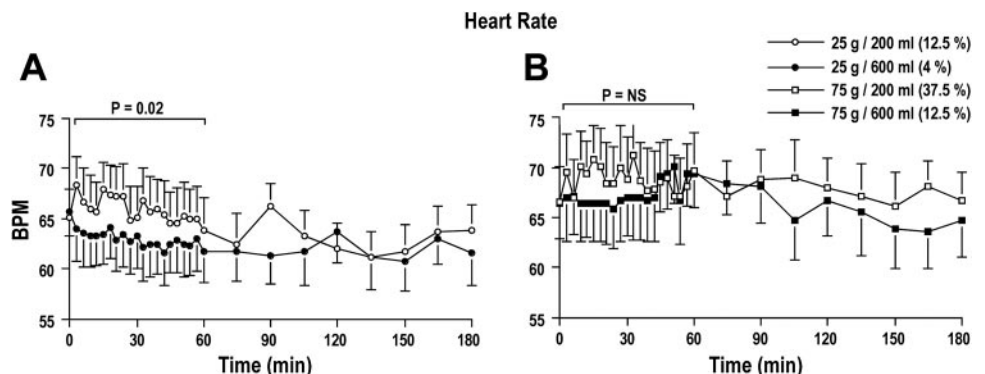
At the same volume, there was no significant difference in diastolic blood pressure in the first 60 min ( $t = 0-60$  min) for the 200-ml (12.5 vs. 37.5% glucose; Fig. 6C) drinks. Diastolic blood pressure was lower, however, from  $t = 90$  min for the 75-g glucose load i.e., 75 g in 200 ml ( $P < 0.05$ ; Fig. 6C). There was no significant difference in diastolic blood pressure for the entire study ( $t = 0-180$  min) for the 600-ml (4 vs. 12.5%; Fig. 6D) drinks.

At the same concentration (12.5%: 25 g glucose in 200 ml and 75 g glucose in 600 ml), there was a nonsignificant trend ( $P = 0.11$ ) for diastolic blood pressure to be less at the smaller volume (Fig. 7B) during  $t = 0-60$  min, but there was no difference after this time.

*Postprandial heart rate.* Between  $t = 0$  and 60 min, heart rate was higher ( $P = 0.02$ ) for the drink that contained 25 g glucose in 200 ml compared with 600 ml (Fig. 5A); there was no significant difference in heart rate between the drinks that contained 75 g glucose (Fig. 5B). At the same concentration (12.5%: 25 g glucose in 200 ml and 75 g glucose in 600 ml), there was no difference in heart rate between the two volumes.

*Relationship between blood pressure and heart rate with gastric drink volume.* There was a significant relationship between both the absolute ( $r = 0.32$ ,  $P < 0.001$ ) and change in systolic ( $r = 0.35$ ,  $P < 0.0005$ ) blood pressure and total intragastric drink volume during the first 60 min (Fig. 8A). There was a trend for a relationship ( $r = 0.17$ ,  $P = 0.09$ ) between the change in diastolic blood pressure and intragastric drink volume during the first 60 min. Both the absolute systolic ( $r = 0.33$ ,  $P < 0.001$ ) and change in systolic ( $r = 0.38$ ,  $P < 0.0001$ ) blood pressure were related to proximal stomach drink volume during the first 60 min (Fig. 8B). Similarly, both the absolute diastolic ( $r = 0.20$ ,  $P < 0.05$ ) and change in diastolic

Fig. 5. Effects of glucose concentration on heart rate following ingestion of four glucose drinks containing 25 g glucose [25 g/200 ml vs. 25 g/600 ml (A)] and 75 g glucose [75 g/200 ml vs. 75 g/600 ml (B)]. Data are presented as means  $\pm$  SE. *P* values indicate significant "treatment" effect during  $t = 0-60$  min.



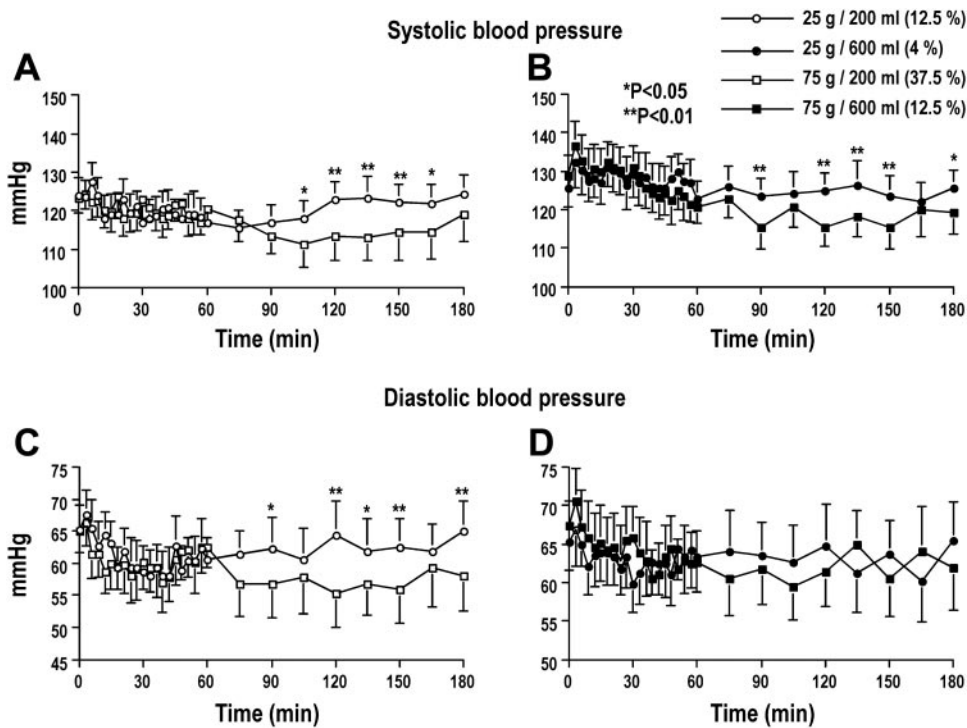


Fig. 6. Effects of glucose concentration load on systolic (A and B) and diastolic (C and D) blood pressure concentrations following ingestion of four glucose drinks in a volume of 200 ml (25 g/200 ml vs. 75 g/200 ml) and 600 ml (25 g/600 ml vs. 75 g/600 ml). Data are presented as means  $\pm$  SE. Significant "treatment by time" interactions were present in A, B, and C; *P* values indicate significant point-by-point comparisons using mean contrasts.

( $r = 0.22$ ,  $P < 0.05$ ) blood pressure were related to proximal stomach drink volume. In contrast, there was no significant relationship between either systolic or diastolic blood pressure with the volume of the drink in the distal stomach. Nor were there any significant relationships between intragastric volume and either heart rate or the change in heart rate from baseline.

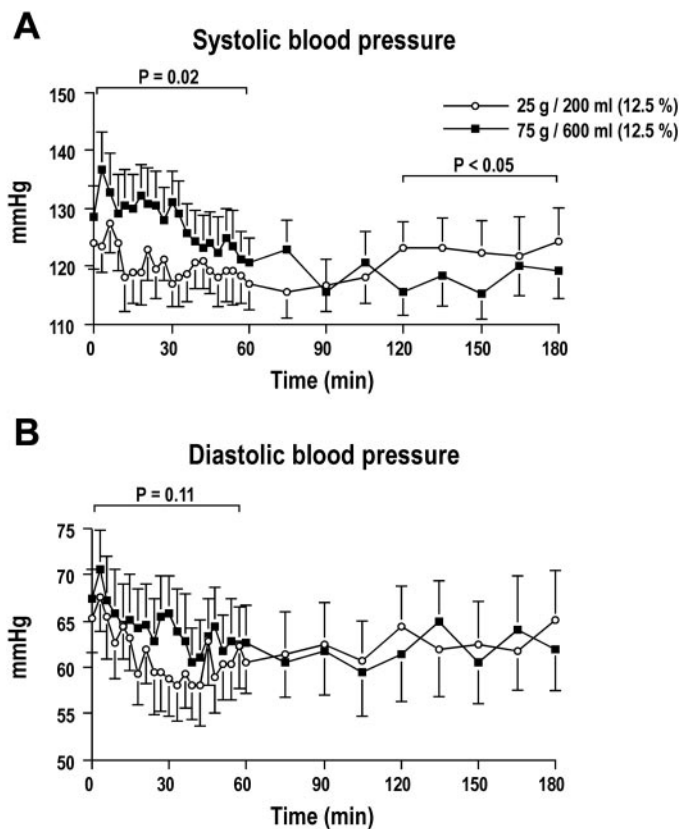


Fig. 7. Effects of drink volume on systolic (A) and diastolic (B) blood pressure after ingestion of 4 glucose drinks (12.5% glucose; 25 g/200 ml vs. 75 g/600 ml). Data are presented as means  $\pm$  SE.

#### DISCUSSION

Observations in monkeys (20), dogs (18), and humans (9) have established that gastric emptying of glucose is highly regulated in a given individual animal or human so that glucose loads to the duodenum remain relatively constant over a wide range of concentrations. We were accordingly able to determine the effects of intragastric glucose concentration on the blood pressure and heart rate response to oral glucose in healthy older subjects when the glucose loads entering the duodenum were constant. Our experimental design also allowed the effects of aqueous drink volume and total glucose content on postprandial hypotension to be evaluated.

Our observations indicate that the hypotensive effect of glucose is modulated by intragastric drink volume (gastric distension). First, immediately after ( $\sim 0$ –3 min) consumption of the 600-ml drinks (whether the drink contained either 25 or 75 g of glucose) there was a significant increase in systolic blood pressure that was not observed with either of the 200-ml drinks. Second, regardless of glucose content, increases in systolic blood pressures correlated with drink volumes in the whole stomach and proximal stomach, but not distal stomach (when sufficient volumes remained for the two 12.5% glucose drinks to make these comparisons). Third, when the concentrations of glucose in the drinks were the same (12.5%), both the amounts of glucose emptied from the stomach and the blood glucose concentrations were similar in the first hour. Despite this, blood pressure was greater for the 600-ml drink

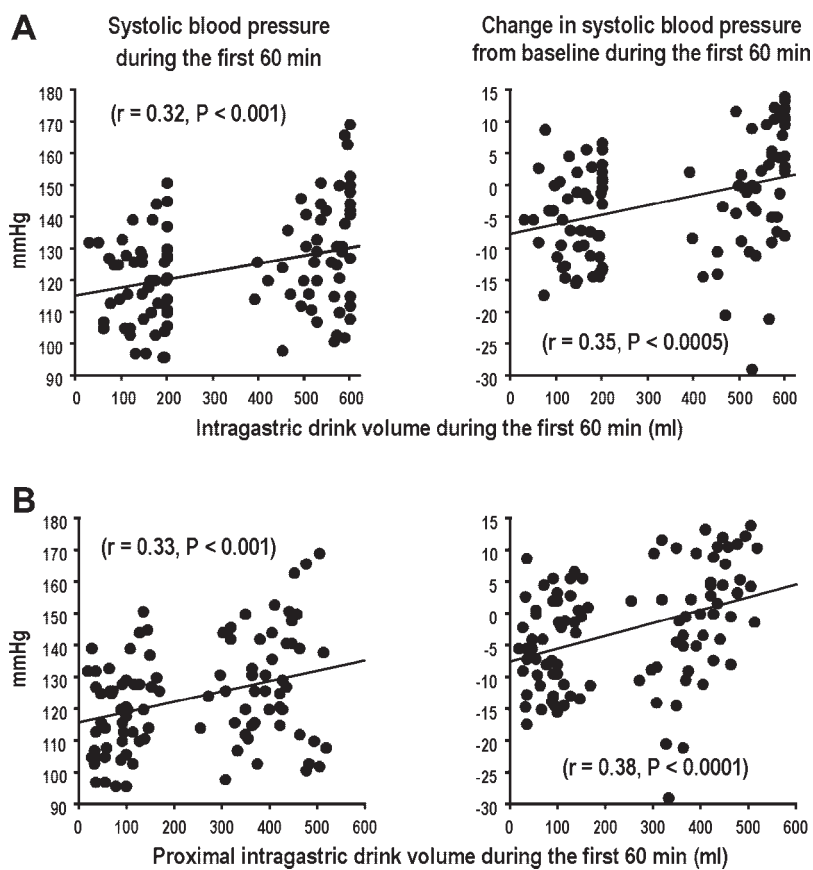


Fig. 8. Relationships between systolic blood pressure and change in systolic blood pressure from baseline with total intragastric drink volume during the first 60 min (A) and systolic blood pressure and change in systolic blood pressure from baseline with proximal drink intragastric volume during the first 60 min (B), following ingestion of two drinks containing 12.5% glucose, i.e., 25 g/200 ml and 75 g/600 ml.

containing 75 g glucose compared with the 200-ml drink containing 25 g glucose. These observations are consistent with the prior findings of Shannon et al. (31) and Rossi et al. (29). Shannon et al. (31) observed in patients with autonomic neuropathy and orthostatic hypotension that postprandial hypotension after a high-carbohydrate meal was attenuated by a 480-ml drink of water taken just before the meal, while Rossi et al. (29) showed that graded balloon distensions of the proximal stomach (reported in pressures, not volumes) in normal volunteers progressively elevated systolic blood pressures and heart rates and increased sympathetic neural tone.

With drinks containing 25 g of glucose, the magnitude of the fall in blood pressure was greater when the glucose concentration of the gastric effluent was greater. Thus in the first hour, systolic blood pressures were lower and the heart rates were higher when the 25-g glucose loads were ingested at the 12.5% than when taken at the 4% concentration. Diastolic blood pressures followed similar patterns, although the mean differences did not reach statistical significance. Nevertheless, because of the probable counterbalancing effects of drink volume (as discussed above), it is impossible to conclude whether the higher concentration of glucose, lower drink volume, or both, accounted for the more marked hypotensive effect of the 25 g glucose in 200 ml (12.5%) compared with 25 g of glucose in 600 ml (4%). A better test for an effect of concentration is to compare different concentrations at the same volumes, i.e., to examine 25 g of glucose (12.5%) vs. 75 g of glucose (37.5%), both in 200 ml, or 25 g of glucose (4%) vs. 75 g of glucose (12.5%), both in 600 ml. In the first comparison (12.5 vs. 37.5% glucose) of the 200-ml drinks, there were no significant

differences in the blood pressure responses; however, it may be suggested that both of these higher concentrations of glucose were supramaximal, i.e., each may be more provocative of hypotension than even lower concentrations, such as 4%. However, this argument is untenable because in the second comparison (4 vs. 12.5%) of the 600-ml drinks, there were no significant differences in blood pressure responses. These observations do not support the concept that postprandial hypotension depends on glucose concentration at similar duodenal loads. Furthermore, the comparable effects of 25 vs. 75 g glucose at constant drink volumes (200 or 600 ml, respectively) indicate that the meal content of glucose per se does not determine the magnitude of the hypotensive response.

The present and previous findings indicate that postprandial hypotension is dependent on duodenal loads (g/min or kcal/min) of glucose, but not the concentration of glucose in the gastric effluent. This is not entirely unexpected, because other "nutrient-driven" feedbacks from small intestinal sensors are known to be load dependent and concentration independent under various conditions; these include stimulation of pancreatic exocrine secretion (23), inhibition of gastric emptying (20), and suppression of food intake (22). Because of its immediate relevance, we will discuss herein only inhibition of gastric emptying by glucose.

McHugh and Moran (20) first observed in monkeys that doubling the volume of 12.5% glucose (0.5 kcal/ml) in gastric instillates did not accelerate gastric emptying of the glucose; that is, the stomach emptied glucose at a mean rate of 0.4 kcal/min whether instillates were 6.25 or 12.5%. In a subsequent study in monkeys, the same investigators (21) demon-

strated that this tight regulation of gastric emptying was accounted for entirely by glucose-triggered feedback from the small intestine. The mechanisms underlying this phenomenon were defined by Lin (18) who demonstrated, in a canine model, that relevant glucose sensors were distributed uniformly throughout the small intestinal length. Over the range of glucose concentrations studied (4.5–18%), the intensity of inhibition of gastric emptying was dependent only on the length of small intestine (that is, number of glucose sensors) contacted by glucose (18). While glucose is rapidly absorbed in the small intestine by active transport mechanisms, each centimeter of small intestine has a maximum absorptive rate ( $\text{g} \cdot \text{min}^{-1} \cdot \text{cm}^{-1}$ ). Therefore, at all concentrations above some value  $< 4.5\%$ , the higher the load ( $\text{g}/\text{min}$ ) of glucose entry into the duodenum the longer the length of small intestine exposed to glucose. Until now, there have been only few corroborating observations in humans. McHugh and coworkers (1) confirmed their above observations in monkeys, observing that humans 1) emptied glucose drinks at the same mean rate (2.11 kcal/min) whether drinks were 5, 12.5, or 25% glucose; and 2) the inhibitory effects of duodenal instillations of 12.5% glucose in 60 ml on gastric emptying was the same as duodenal instillation of 50% glucose in 15 ml. Observations by Hunt et al. (9) were more or less consistent with load-dependent, concentration-independent regulation of gastric emptying by glucose in that gastric emptying of drinks containing Polycose (a glucose polymer that is converted to glucose on entry into the duodenum) at 0.5–2.0 kcal/ml (equivalent to 12.5–50% glucose) emptied at fairly uniform rates (2.1–3.0 kcal/min) despite the variations in concentrations and additional variations in meal volumes (300–600 ml); that is, control of gastric emptying appeared to be governed by the load of glucose entering the duodenum over a range of concentrations and volumes. Our data in the present study (using gamma scintigraphy rather than a gastric aspiration technique) demonstrate an even tighter precision and further corroborate the concept that gastric emptying of glucose and presumably other nutrients is regulated in humans in a load-dependent, concentration-independent fashion.

Whereas the glycemic response to the 75 g of glucose in our study was predictably greater over 180 min, we were unable to demonstrate any effect of either volume or glucose concentration on glycemia in the first hour. This is not entirely surprising because we found that the amount of glucose emptied during the first 60 min was similar, and it was only after the majority of the drinks containing 25 g glucose were emptied that blood glucose concentrations were higher for the drinks containing 75 g glucose. Current and previous studies of gastric emptying suggest that the initial rate of gastric emptying of glucose is the major determinant of the glycemic response (8, 25, 26); in healthy subjects, the blood glucose concentrations at 120 min are inversely, rather than directly, related to gastric emptying (8), reflecting the greater initial rise in plasma insulin. The current observations conflict with two studies reporting dilution of oral glucose increases postprandial glycemia in healthy subjects (33, 34). It should be recognized, however, that in these studies gastric emptying of the drinks was not measured (33, 34) and the cause of the different glycemic responses remains uncertain.

In conclusion, this study has shown in healthy older subjects that ingestion of glucose at a higher volume attenuates the fall

in blood pressure, a phenomenon that is likely to relate to increased gastric distension. Loads of glucose that emptied into the duodenum were similar in the first postprandial hour whether drinks were 200 or 600 ml, whether concentrations varied from 4 to 37%, and whether the glucose content of the drinks was 25 or 75 g. Under these conditions of constant duodenal load, glucose concentration did not affect the postprandial hypotensive responses to glucose. The observations in this study suggest that carbohydrate-containing liquids should be consumed in a larger volume to minimize the risk of postprandial hypotension.

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