Comparative effects of oral and intraduodenal glucose on blood pressure, heart rate and splanchnic blood flow in healthy older subjects

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ABSTRACT

Postprandial hypotension occurs frequently, particularly in the elderly. The magnitude of the fall in blood pressure (BP) and rise in heart rate (HR) in response to enteral glucose are greater when gastric emptying (GE) or small intestinal infusion are more rapid. Meal ingestion is associated with an increase in splanchnic blood flow. In contrast, gastric distension may attenuate the postprandial fall in BP. The aims of this study were to evaluate, in older subjects, the comparative effects of intraduodenal glucose infusion, at a rate similar to GE of oral glucose on BP, HR, superior mesenteric artery (SMA) flow and blood glucose. Eight healthy subjects (5M, 3F, age 66-75yrs) were studied on two occasions. On day 1, each subject ingested 300ml water containing 75g glucose; GE was quantified by three-dimensional ultrasonography between t=0-120 minutes and the rate of emptying (kcal min⁻¹) calculated. On day 2, glucose was infused intraduodenally at the same rate as that on day 1. On both days BP, HR, SMA flow and blood glucose were measured. The mean GE of oral glucose was 1.3±0.1 kcal/min. Systolic BP (P<0.01), SMA flow (P<0.05) and blood glucose (P<0.01) were greater and HR less (P<0.01) after oral, when compared with intraduodenal, glucose. There were comparable falls in diastolic BP during the study days (P<0.01 for both). We conclude that the magnitude of the fall in systolic BP and rise in HR are less after oral, when compared to intraduodenal, glucose presumably reflecting the ‘protective’ effect of gastric distension.

Keywords: postprandial hypotension, gastric emptying, 3D and Doppler ultrasound.
**INTRODUCTION**

Postprandial hypotension, defined as a decrease in systolic blood pressure $\geq 20\text{mmHg}$, occurring within two hours of the end of a meal (23, 25, 38, 39), is an important clinical problem, most commonly affecting the elderly and patients with autonomic dysfunction, the latter often secondary to diabetes (23, 25, 38, 39). Postprandial hypotension is associated with significant complications, including syncope and falls (25) and in some cases, stroke and angina (1, 25, 51).

The stomach is likely to modulate the hypotensive response to a high carbohydrate meal in two ways. Firstly, by controlling the rate at which glucose enters the small intestine; our studies in healthy older subjects (26, 42) and patients with type 2 diabetes (28, 46) have established that there is a direct relationship between the magnitude of the fall in systolic blood pressure with the rate of small intestinal delivery of glucose (26, 28, 41, 42), a response that depends on the total load of glucose entering the duodenum independent of glucose concentration (11, 27). When glucose enters the small intestine, it inhibits gastric emptying in a load-dependent fashion, so that glucose entry is sustained at $\sim 3\text{kcal/min}$ (21, 22). Secondly, the stomach may reduce the hypotensive response induced by the ingestion of carbohydrate via a ‘gastrovascular reflex’ triggered by gastric distension. For example, in healthy older subjects, following ingestion of glucose drinks of varying volumes and concentrations, the rate of duodenal entries of glucose were similar but the meals of larger volume were associated with decreased falls in blood pressure (27). The minimum gastric volume needed to produce this mitigation is poorly established, however, using two-dimensional (2D) ultrasonography to monitor gastric volumes, we have recently estimated that 300ml or less of a meal in the stomach may suffice (14).
Since gastric distension appears to attenuate the effects of duodenal glucose on blood pressure (14, 27), it may also modulate the splanchnic blood flow response to enteral glucose. The role of gastric distension in the regulation of splanchnic blood flow has not yet been evaluated. The aims of this present study were twofold. Firstly, in order to extend our previous observation of intragastric meal volume modulating the hypotensive response to duodenal glucose, we compared the hypotensive response to glucose as it spontaneously emptied from the stomach on ‘day 1’ to the hypotensive response of glucose infused directly into the duodenum at the rate that mimicked spontaneous gastric emptying on ‘day 2’. On the first day, intragastric volumes were monitored continuously using three dimensional (3D) ultrasonography, a new method that has been recently validated as an accurate measure of gastric volume/gastric emptying in both healthy young subjects (12) and patients with diabetic gastroparesis (48). Secondly, on both days, superior mesenteric artery flow was measured to determine whether gastric distension, induced by the oral glucose load, on ‘day 1’ resulted in a reduced flow when compared with ‘day 2’. We postulated that the hypotensive effect after oral glucose would be less than after duodenal glucose because of the ‘gastrovascular reflex’ and that this difference may be reflected in reduced superior mesenteric artery flow.
MATERIALS AND METHODS

SUBJECTS

Eight healthy older subjects, (five male and three female) with a median age of 71 years (range: 66 - 75 years) and body mass index (BMI) of 23.3 kg/m² (range: 20.3 - 27.0 kg/m²), recruited by advertisement, were studied. We calculated that a minimum of five subjects would be required to detect a mean difference in systolic blood pressure of ~13mmHg with power of 0.80, assuming a significance value < 0.05 (56). All subjects were non-smokers. None had a history of gastrointestinal disease or surgery, diabetes, significant respiratory, renal, hepatic or cardiac disease, chronic alcohol abuse or epilepsy, or were taking medication known to influence blood pressure or gastrointestinal function. All of the eight subjects had participated previously in research studies involving intubation.

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.

PROTOCOL

Each subject was studied on two occasions, separated by 3 - 29 days. On each day, subjects attended the University of Adelaide, Discipline of Medicine at the Royal Adelaide Hospital at 0830h following an overnight fast (10.5h for solids; 8.5h for liquids) (11, 13, 14). On the first day (‘day 1’), upon arrival an intravenous cannula was placed in a left antecubital vein for blood sampling and an automated blood pressure cuff positioned around the right arm for measurement of blood pressure and heart rate
Each subject was then allowed to rest comfortably in the recumbent position for about 30 minutes. At $t = -2$ minutes, the subject was seated in a chair and consumed a drink comprising 75g glucose monohydrate dissolved in water with a total volume of 300ml (255kcal). The rate of gastric emptying, blood pressure (systolic and diastolic), heart rate and superior mesenteric artery flow were then measured for 120 minutes. On the second day (‘day 2’), following placement of the intravenous cannula, a silicone-rubber catheter (external diameter ~ 4mm) (Dentsleeve International Ltd, Mui Scientific, Mississauga, Canada), was introduced into the stomach via an anaesthetised nostril (11, 13, 14). The assembly included an infusion channel (internal diameter ~ 1mm) and was positioned so that the infusion port was located ~ 10cm distal to the pylorus (ie in the duodenum), as well as two other channels that were positioned in the antrum (2.5cm proximal to the pylorus) and duodenum (2.5cm 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 (TMPD) between the antral (-40 mV) and the duodenal (0 mV), channel (11, 13, 14). For this purpose, an intravenous cannula filled with sterile saline was placed subcutaneously in the left forearm and used as a reference electrode (11, 13, 14). The tip of the catheter passed into the duodenum by peristalsis, which took between 20 and 120 minutes. An automated blood pressure cuff was placed around the right arm (11, 13, 14). Once intubated, the subject rested in the recumbent position. Approximately 30 minutes after the tube was positioned correctly (at $t = 0$ minutes) the subject received an intraduodenal infusion of glucose for 120 minutes. The energy delivery (kcal/min) of the intraduodenal infusion was determined by visually drawing lines of best fit for each of the individual gastric emptying curves generated on ‘day 1’ ie the rate of nutrient delivery during the intraduodenal infusion mimicked that observed after the oral
glucose load (Figure 1). In some cases the rate of energy delivery varied over time and was not linear for the total 120 minutes eg gastric emptying was clearly initially more rapid in some subjects then slowed. Intraduodenal infusions were performed using a volumetric infusion pump (Gemini PC-1; IMED Corp, San Diego, USA) and the energy delivery of the infusion was regulated as per the pre-determined infusion rates. Blood pressure (systolic and diastolic), heart rate and superior mesenteric artery flow were measured for 120 minutes. At t = 120 minutes the catheter was removed. On one day cardiovascular autonomic nerve function was evaluated immediately after the completion of the study (9, 44). On both study days subjects were given a light meal prior to leaving the laboratory.

MEASUREMENTS

Gastric emptying

Ultrasonography measurements were performed using a Logiq™ 9 ultrasonography system (GE Healthcare Technologies, Sydney, Australia) with TruScan Architecture (ie built-in magnetically sensed 3D) as described previously (12). For 3D positioning and orientation measurement (POM), a transmitter was placed close to the subject and a snap-on sensor attached to a 3.5C broad spectrum 2.5-4 MHz convex transducer (12, 49). As the transmitter produces a spatially varying magnetic field, and ferrous and conductive metals distort the magnetic field, all metal objects were removed from the subject and from the area directly between the POM transmitter and sensor (32). The POM transmitter was placed behind (~ 10 cm) the subject (16), at the level of the stomach, so that the subject was positioned between the ultrasonography scanner and the transmitter. For 3D data acquisition, the subject was scanned at t = -2 minutes, t = 0 minutes (ie immediately following ingestion of the drink) and then at 15 minute
intervals between t = 0 and 120 minutes. Regions-of-interest were drawn around the
total stomach and the volume of the drink in the total stomach was derived and
expressed as a percentage of the original volume at t = 0 minutes in the total stomach (ie
100%) (12). Gastric emptying curves (expressed as % retention over time) were derived
for the total stomach at 0, 15, 30, 45, 60, 75, 90, 105 and 120 minutes.

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, USA) at t = -9, -6 and -3 minutes prior to both ingestion of the drink and
commencement of the intraduodenal infusion, and then every three minutes between t =
0 and 120 minutes (11). ‘Baseline’ blood pressure and heart rate, ie t = 0 minutes, were
calculated as the mean of measurements taken at t = -9, -6 and -3 minutes prior to
ingestion of the drink and commencement of the intraduodenal infusion. Postprandial
hypotension was defined as a fall in systolic blood pressure of ≥ 20 mmHg that was
sustained for at least 30 minutes (25).

Superior mesenteric artery flow

Superior mesenteric artery flow was measured by Duplex ultrasonography (ie B-mode
and Doppler imaging) using a Logiq™ 9 ultrasonography system (GE Healthcare
Technologies, Sydney, Australia), as described previously (43). Each subject was
scanned using a 3.5C broad spectrum 2.5 - 4 MHz convex transducer (13, 43) at t = -2,
5 and 10 minutes and then at 15 minute intervals between t = 0 and 120 minutes. Blood
flow (ml min⁻¹) was calculated immediately using the formula: \( \pi \times r^2 \times TAMV \times 60 \),
where \( r \) = the radius of the superior mesenteric artery and TAMV is the time-averaged mean velocity (43).

**Blood glucose concentrations**

Venous blood samples (~ 2ml) were obtained prior to both ingestion of the drink and the commencement of the intraduodenal infusion (ie \( t = -2 \) minutes) and at 15 minute intervals between \( t = 0 \) and 120 minutes (11). Blood glucose concentrations were determined immediately using a portable blood glucose meter (Medisense Precision Q·I·D™ System, Abbott Laboratories, Medisense Products Inc, Bedford, USA) (11).

**Autonomic function**

Autonomic nerve function was assessed using standardized cardiovascular reflex tests (9, 44). Parasympathetic function was evaluated by the variation (R-R interval) of the heart rate during deep breathing and the heart rate 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 \( \geq 3 \) was considered to indicate autonomic dysfunction (9, 44).

**Statistical analysis**

Data were evaluated using repeated measures two-way Analysis of Variance (ANOVA), with ‘treatment’ and ‘time’ as within subject factors. Systolic and diastolic blood pressure and heart rate were analyzed as changes from baseline. Superior mesenteric artery flow, blood glucose concentrations and duodenal entry of glucose were analyzed as absolute values. Data were analyzed from \( t = -2 \) to 120 minutes to
determine the effects (‘treatment’ and ‘time’) of oral and intraduodenal, glucose. One-
way ANOVA was used to analyze the effects of ‘time’ on systolic and diastolic blood
pressure, heart rate, superior mesenteric artery flow and blood glucose. In all analyses,
post-hoc comparisons of adjusted means were performed using Student’s t-tests. The
maximum fall in systolic blood pressure and rise in heart rate were defined as the
greatest mean changes from baseline in each subject at any given time point for each
treatment. All analyses were performed using Statview (version 5.0; Abacus Concepts,
Berkeley, CA, USA) and SuperANOVA (version 1.11, Abacus Concepts, Berkeley,
CA, USA). Data are presented as mean values ± standard error of the mean (SEM). A P
value < 0.05 was considered significant in all analyses.
RESULTS

The studies were well tolerated. One subject reported diarrhea after completion of the intraduodenal glucose infusion. In this subject the magnitude of the fall in systolic blood pressure was comparable to the remainder of the group. Data for this subject were, accordingly, included in the analysis. No subject had definite autonomic neuropathy; median score 0.6 (range: 0 - 2). While no subject experienced postprandial hypotension (ie a fall in systolic blood pressure > 20 mmHg sustained for at least 30 minutes), in two the magnitude of the fall in systolic blood pressure was > 20 mmHg; one after oral glucose and one during intraduodenal glucose infusion. The number of infusion rates on ‘day 2’, calculated by drawing lines of best fit on the gastric emptying curves, per individual, varied between 1 - 4. The total amount of glucose infused on ‘day 2’ ranged from 99 - 258ml ie 84 - 219 kcal (Figure 1).

Gastric emptying (Figure 1)

The average gastric emptying rate on ‘day 1’ for the total 120 minutes was 1.3 ± 0.1 kcal/min (range: 0.7 - 1.8 kcal/min). The amount of glucose remaining in the stomach at 120 minutes varied from 42 to 201ml (mean 115.9 ± 19.0ml) ie 36 - 171 kcal (mean ~ 98.6 kcal).

Baseline blood pressure and heart rate

There was no significant difference in baseline (ie t = 0 minutes) blood pressure or heart rate between the two days (oral glucose vs intraduodenal glucose infusion): systolic blood pressure (124.0 ± 5.8 mmHg vs 127.6 ± 7.2 mmHg; P = 0.16); diastolic blood pressure (74.0 ± 2.9 mmHg vs 74.5 ± 3.5 mmHg; P = 0.71) and heart rate (63.8 ± 0.9 bpm vs 62.6 ± 1.6 bpm; P = 0.40).
Systolic blood pressure (Figure 2a)
There was a significant ‘treatment x time’ effect for systolic blood pressure (P = 0.01) between the study days. Between t = 0 and 120 minutes there was no significant fall in systolic blood pressure after oral glucose (P = 0.22), however, between t = 60 and 90 minutes systolic blood pressure was less than baseline during intraduodenal glucose infusion (P < 0.05). Systolic blood pressure was greater (P < 0.01) between t = 60 and 120 minutes after oral, when compared with intraduodenal, glucose. At t = 120 minutes, there was no significant difference in systolic blood pressure from baseline after oral (P = 0.19), or intraduodenal (P = 0.20), glucose.

Diastolic blood pressure (Figure 2b)
There was no significant difference in diastolic blood pressure between the two days (P = 0.15). Between t = 0 and 120 minutes there was a fall in diastolic blood pressure after both oral (P < 0.01) and intraduodenal (P < 0.001), glucose. At t = 120 minutes, diastolic blood pressure was significantly lower than baseline after both oral (P = 0.01), and intraduodenal (P = 0.04), glucose.

Heart rate (Figure 2c)
There was a trend for a ‘treatment x time’ effect for heart rate (P = 0.06). Between t = 0 and 120 minutes there was no significant change in heart rate after oral glucose (P = 0.77), however, there was an overall rise during intraduodenal glucose infusion between t = 45 and 75 minutes (P < 0.05). The maximum increases in heart rate after oral (9.6 ± 1.8 bpm), and intraduodenal (10.9 ± 2.2 bpm), glucose were not significantly different (P = 0.73). At t = 120 minutes, heart rate was not significantly different from
baseline after oral (P = 0.89), but was greater than baseline after intraduodenal (P = 0.05), glucose.

**Superior mesenteric artery flow** (Figure 3)
There was no difference in baseline (ie t = -2 minutes) superior mesenteric artery flow between the two days (oral glucose vs intraduodenal glucose: 826.3 ± 77.7 ml/min vs 728.5 ± 52.5 ml/min; P = 0.18). There was a significant ‘treatment x time’ effect (P = 0.0001) for superior mesenteric artery flow. Between t = -2 and 120 minutes there was a rapid rise (P < 0.0001) in superior mesenteric artery flow following oral glucose which was evident from t = 5 minutes (P = 0.002), and then a fall from ~ t = 30 minutes (P = 0.0001). Superior mesenteric artery flow also rose, albeit less, during intraduodenal glucose infusion (P < 0.001) and this was significant from t = 45 minutes (P = 0.001). Between t = 5 and 60 minutes, superior mesenteric artery flow was greater after oral (P < 0.05), when compared with intraduodenal, glucose. At t = 120 minutes, superior mesenteric artery flow was greater than baseline after both oral (P = 0.02) and intraduodenal (P = 0.04), glucose.

**Blood glucose concentrations** (Figure 4)
There was a significant difference in baseline (ie t = -2 minutes) blood glucose concentrations between the two days (oral glucose vs intraduodenal glucose): 5.8 ± 0.21 mmol/L vs 6.2 ± 0.19 mmol/L; P = 0.03). There was a significant ‘treatment x time’ effect (P = 0.0001) for blood glucose concentrations. Between t = -2 and 120 minutes there was a rise in blood glucose concentrations from baseline on both days (P < 0.0001 for both), which was significant from t = 15 minutes following oral (P = 0.0003), and from t = 45 minutes during intraduodenal (P = 0.0002), glucose. Between t
= 15 and 45 minutes, blood glucose concentrations were greater (P < 0.01) after oral, when compared with intraduodenal, glucose. At t = 120 minutes, blood glucose concentrations were greater than at baseline after both oral, and intraduodenal (P = 0.01 for both), glucose.
DISCUSSION

This study establishes that in healthy older subjects the magnitude of the systolic blood pressure response to an oral glucose load is substantially less, and superior mesenteric artery flow greater, when compared with intraduodenal glucose infusion at a comparable rate.

Our previous studies (26, 28, 41, 46) have established that the rate of gastric emptying is an important determinant of the postprandial fall in blood pressure. 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 when compared to infusion at a rate of 1 kcal/min (mean ~ 9 mmHg) (41). While we have shown that both oral (10, 15, 26-28, 46, 56) and enteral glucose (11, 13, 14, 41, 42) decrease blood pressure, the magnitude of the fall in blood pressure is less after oral when compared with intraduodenal glucose. In this current study, there was little change from baseline in systolic blood pressure or heart rate after oral glucose whereas systolic blood pressure fell and heart rate rose in response to intraduodenal glucose infusion. The observed cardiovascular response to oral glucose is likely to be due to activation of the ‘gastrovascular reflex’ as a result of distension of the stomach. In contrast, diastolic blood pressure fell on both study days and to the same extent; the mechanism responsible for this remains unclear. We found in this study that the magnitude of the observed fall in systolic blood pressure, and increase in heart rate, in response to intraduodenal glucose at ~ 1.3 kcal/min was predictably less than that observed previously in response to infusion of glucose at a rate of 3 kcal/min (11, 13, 14, 41, 42). By infusing glucose directly into the small intestine at a rate which
approximated gastric emptying of the oral glucose load (ie mean 1.3 ± 0.2 kcal/min), the potential ‘protective’ effects of gastric distension were eliminated.

Previous studies have shown that gastric distension influences blood pressure (5, 14, 27, 29, 30, 45, 47, 52). However, a limitation of most of these (8, 27, 45, 47, 52) was that changes in intragastric volumes were not quantified. In our recent study, we demonstrated that as little as ~ 300ml of intragastric water markedly attenuates the hypotensive response to intraduodenal glucose at 3 kcal/min while ~ 100ml of intragastric water raises systolic blood pressure 6 - 8 mmHg above baseline during intraduodenal saline infusion, presumably as a result of gastric distension (14). Our findings from the current study are consistent with our previous observations that gastric distension resulting from a relatively low volume of intragastric fluid (~ 300ml) attenuates the hypotensive response to glucose. Moreover, we found that 120 minutes after ingestion of glucose, as little as ~ 100ml was effective at maintaining systolic blood pressure at or above baseline levels. We have also evaluated, in healthy older subjects, the effects of water when compared to glucose and sucrose drinks (54) and the effects of intragastric water during intraduodenal saline infusion (14) and in both cases demonstrated a significant increase in blood pressure which was evident soon after administration of water. In healthy young adults, in whom ingestion of water does not affect blood pressure, there is evidence of an increase in sympathetic vasoconstrictor activity and cardiac vagal tone, which may relate to its hypo-osmotic properties (3). In this group, ingestion of 10% glucose in water has been shown to impair head-up-tilt tolerance relative to water ingestion, associated with increased heart rate and attenuation of the increase in peripheral vascular resistance (35). The current study and these previous observations (14) dictate that studies to characterise the effects of non-
nutrient gastric distension using a barostat device on the responses to enteral glucose in healthy older subjects should be performed and we have now initiated these (53). It will be important to determine whether the effects of gastric distension are mediated by intragastric volume and/or pressure, the region of the stomach that is distended is important, and the relationship between blood pressure with distension, including the minimum volume/pressure that is effective. Further studies are also indicated to evaluate the effects of ‘chronic’ gastric distension, prolonged distension (ie 15 minutes) using a barostat device with volumes in the range of 300 - 600ml, elevates and then stabilizes blood pressure when compared to resting values in healthy young subjects (4).

While there is evidence that gastric distension affects the regulation of splanchnic blood flow, current information is inconsistent and limited to animal studies (33, 40, 50). For example, in the pig, superior mesenteric artery flow has been reported to be decreased (40, 50), increased (50) and unchanged (50) in response to gastric distension while in the cat, superior mesenteric artery flow is increased, albeit insignificantly (33). In this current study, a rise in superior mesenteric artery flow was evident from 5 minutes after oral glucose, however, during intraduodenal glucose, the rise in superior mesenteric artery flow was not statistically significant until 45 minutes (and much less). Furthermore, we observed that while systolic blood pressure and heart rate were essentially unchanged after oral glucose, probably as a result of intragastric volume, superior mesenteric artery flow increased substantially and remained elevated above baseline values for the entirety of the study. van Orshoven et al (52) reported that proximal gastric balloon stepwise distension using a ‘barostat’ device increased blood pressure and total peripheral arterial resistance in healthy older subjects. Hence, our observations and those of van Orshoven et al (52) suggest that the sustained increase in
superior mesenteric artery flow may be a result of vasoconstriction of the peripheral vasculature by the ‘gastrovascular reflex’ that is triggered by gastric distension.

Our current study was associated with some limitations. We evaluated only healthy older subjects, none of which were observed to have postprandial hypotension, hence, the present observations may differ in patients with postprandial hypotension. Our experiment was limited, albeit unavoidably, by its design such that in order to test our hypothesis, subjects ingested an oral glucose load on ‘day 1’ and then swallowed a silicone-rubber catheter to receive an intraduodenal glucose infusion on ‘day 2’, hence, we were unable to exclude an order effect; this is also despite all of the subjects having previously participated in studies involving intubation. It is surprising that after the glucose drink the mean maximum increase in systolic blood pressure, albeit modest, was evident at only ~ 100 minutes, suggesting that it was unrelated to either gastric distension or the delivery of glucose into the small intestine and, possibly, reflected non-specific factors such as the induction of ‘stress’. While we have previously demonstrated that 3D ultrasonography provides a valid measure of gastric emptying of liquid meals (12), it should be noted that some intraindividual variation in gastric emptying of liquids exists. Hence, the technique is associated with some limitations including those of a more technical nature (2, 7, 16, 19, 20) and represents an estimation of gastric emptying. Furthermore, 3D ultrasonography measures total volume of fluid in the stomach (ie drink volume and salivary and gastric secretions (19)). It is, therefore, possible that progressive dilution of glucose on ‘day 1’ resulted in an overestimation of the amount of glucose (kcal) in the stomach over time. It is likely that all of these factors may have contributed to an underestimation of the initial rate of gastric emptying of oral glucose and the subsequent infusion rate of the intraduodenal glucose
and hence a potentially reduced blood pressure response to intraduodenal, when compared with oral, glucose. Moreover, the discrepancies in blood glucose concentration between study days support this concept since variable rates of duodenal glucose delivery have been shown to influence the glycemic response to carbohydrates due to the enhanced stimulation of insulin (6). We also cannot exclude the possibility that differences in glycemia influenced our observations, but this appears unlikely. – In particular, intravenous glucose has little, if any, affect on blood pressure (23, 24) and we have reported that there is no relationship between the effects of different carbohydrate drinks on blood pressure and glycemia (55). Animal studies suggest that oral, pharyngeal and esophageal stimulation have the capacity to modulate blood pressure (17, 34) and may, accordingly, play a role in the postprandial blood pressure response. Nevertheless the pressor effects of water in older subjects are evident after direct intragastric instillation (14). Finally, it should be recognised that gastric emptying is, predominantly a pulsatile, rather than a continuous, process; most liquefied chyme enters the small intestine as a succession of small gushes (31, 36, 37) that may vary considerably as forward, interrupted, and reverse flow may all occur (18, 36). Therefore, this may have influenced how accurately individual intraduodenal infusion rates were determined.

**PERSPECTIVES AND SIGNIFICANCE**

Our observations establish that, in healthy older subjects, the fall in systolic blood pressure and rise in heart rate induced by an oral glucose load are less when compared with glucose infused intraduodenally at a comparable rate, presumably reflecting the loss of ‘protective’ factors related to gastric distension, a hypothesis which should now be addressed by studies evaluating the effects of non-nutrient gastric distension on the
responses to small intestinal glucose. Our observations have clear implications for the management of patients with postprandial hypotension and may also be of relevance in patients who have undergone gastric surgery with a drainage procedure (such as after gastric bypass for morbid obesity) in which the rate of entry of nutrients into the small intestine is accelerated, and the use of enteral nutrition (intragastric vs small intestinal) in the elderly and patients with autonomic dysfunction.
**GRANTS**

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FIGURES AND LEGENDS

Figure 1: Duodenal entry of glucose (kcal) and estimated volume emptied/infused (ml) after oral (○) and during intraduodenal (●), glucose. Data are mean values ± SEM.

Figure 2: Changes in (A) systolic blood pressure, (B) diastolic blood pressure and (C) heart rate from baseline in eight healthy older subjects in response to oral (○) and intraduodenal (●), glucose. Data are mean values ± SEM. *P < 0.01; **P < 0.001.

Figure 3: Superior mesenteric artery flow in eight healthy older subjects in response to oral (○) and intraduodenal (●), glucose. Data are mean values ± SEM. *P < 0.05; **P < 0.001; ***P < 0.0001.

Figure 4: Blood glucose concentrations in eight healthy older subjects in response to oral (○) and intraduodenal (●), glucose. Data are mean values ± SEM. *P < 0.01; **P < 0.001; ***P < 0.0001.