Effects of gastric distension on blood pressure and superior mesenteric artery blood flow responses to intraduodenal glucose in healthy older subjects

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ABSTRACT
Postprandial hypotension occurs frequently and is associated with increased morbidity. Gastric distension may attenuate the postprandial fall in blood pressure (BP). The study aim was to determine the effects of gastric distension, using a barostat, on BP, heart rate (HR) and superior mesenteric artery (SMA) flow responses to intraduodenal glucose in healthy older subjects. 8 subjects (6M,2F; age 65-75yr) had measurements of BP and HR (automated device) and SMA flow (Doppler ultrasound), on 4 days in random order. SMA blood flow was calculated using the radius of the SMA and time-averaged mean velocity. Subjects were intubated with a nasoduodenal catheter incorporating a duodenal infusion port. On 2 of the 4 days they were intubated orally with a second catheter, incorporating a barostat bag, positioned in the fundus; and set at 8mmHg above minimal distending pressure. Each subject received a 60min (t=0–60min) intraduodenal infusion of either glucose (3kcal/min) or saline (0.9%), therefore, the 4 study conditions were intraduodenal glucose+barostat (‘glucose+distension’), intraduodenal saline+barostat (‘saline+distension’), intraduodenal glucose (‘glucose’) and intraduodenal saline (‘saline’). Systolic and diastolic BP fell during ‘glucose’ when compared with ‘saline’ (P=0.05 and P=0.003, respectively) and ‘glucose+distension’ (P=0.01 and P=0.05, respectively), and increased during ‘saline+distension’ when compared with ‘saline’ (P=0.04 and P=0.006, respectively). The maximum changes in systolic BP were -14±5mmHg, +11±2mmHg, -3±4mmHg and +15±3mmHg, for ‘glucose’, ‘saline’, ‘glucose+distension’ and ‘saline+distension’, respectively. There was an increase in HR during ‘glucose’ and ‘glucose+distension’ (maximum rise 14±2bmp and 14±3bmp, respectively), but not ‘saline’ or ‘saline+distension’. SMA flow increased during ‘glucose’ and ‘glucose+distension’ (2388±365ml/min and
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1673±187ml/min, respectively) but not during ‘saline’ and tended to decrease during ‘saline+distension’ (821±115ml/min and 864±116ml/min, respectively). In conclusion, gastric distension has the capacity to abolish the fall in BP, and attenuate the rise in SMA flow, induced by intraduodenal glucose in healthy older subjects.
INTRODUCTION

Postprandial hypotension, defined as a fall in systolic blood pressure ≥20 mmHg, within 2 hours of a meal (16), is recognised as an important clinical problem, particularly in the elderly and in patients with autonomic dysfunction, the latter often secondary to diabetes mellitus (16, 23). Postprandial hypotension occurs in 30-40% of nursing home residents, and is distinct from, and occurs more frequently than, orthostatic hypotension (16).

While the mechanisms underlying postprandial hypotension are poorly defined, the rate of small intestinal nutrient delivery, splanchnic blood flow and neural and hormonal mechanisms are important (15, 16, 23, 24). A series of studies performed by our group, primarily in healthy older subjects, has established that the postprandial fall in blood pressure is triggered by the interaction of nutrients (fat, carbohydrate or protein) with the small intestine, presumably as a result of both neural and humoral mediators (7, 18, 27). When gastric emptying is relatively more rapid, the magnitude of the fall in blood pressure is greater (18). In contrast, intragastric mechanisms, related to gastric distension, attenuate the postprandial fall in blood pressure (8, 17, 19, 30, 31, 33, 34). For example, consumption of water increases systolic blood pressure in healthy older subjects (19) and patients with autonomic failure (19, 31), and attenuates the hypotensive response to a meal (31). In healthy older subjects, that the magnitude of the fall in systolic blood pressure is greater when glucose is ingested at a smaller volume (200ml when compared with 600ml), but the same glucose concentration (17), intragastric administration of 500ml of water markedly attenuates the fall in systolic blood pressure induced by intraduodenal glucose (8), and when glucose is infused
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directly into the proximal small intestine at a rate comparable to gastric emptying of oral glucose, the magnitude of the fall in blood pressure is greater (9). Inherent limitations in these studies are that distension, with liquid nutrient or non-nutrient, cannot be well quantified, nor sustained, ie with intragastric administration gastric distension decreases as gastric emptying proceeds (8), and if the distension stimulus included nutrients, these may induce a fall in blood pressure (8). Moreover, the pressor effort of water may, in part, be mediated by its hyposmolarity (31).

Longhurst et al demonstrated in anaesthetised cats, that gastric distension induces a sympathoexcitatory reflex leading to an increase in blood pressure (22). Gastric distension at predefined volumes and/or pressures can be achieved using a barostat device (30, 33). In healthy, young adults, proximal gastric distension with a barostat has been shown to increase blood pressure, heart rate and muscle sympathetic nerve activity, the so-called ‘gastrovascular reflex’ (30). In a study comparing healthy young and older subjects, gastric distension at a pressure of 8mmHg above minimal distending pressure (MDP) using a barostat, increased mean arterial pressure, heart rate and total peripheral arterial resistance more in the older subjects, while in both groups there was a slight rise in cardiac output (33). No studies have hitherto evaluated the effects of gastric distension, using a barostat, on the hypotensive response to small intestinal nutrients.

Meal ingestion (9) and small intestinal nutrient infusion (7) increase superior mesenteric artery (SMA) blood flow, which can be measured by Doppler techniques (28). There is little information about the effects of gastric distension on SMA blood flow, with the
The majority of these studies in animals (26, 32), and only one study in humans (9). The outcome of these studies is inconsistent, with no effect (32), increases (9, 21, 32) or decreases (26, 32) in SMA blood flow, being reported.

The aims of this study were to determine the effects of gastric distension with a barostat on the blood pressure, heart rate and SMA blood flow responses to intraduodenal glucose infusion in healthy older subjects. The broad hypothesis was that gastric distension would attenuate the hypotensive, and increase in SMA blood flow, responses induced by intraduodenal glucose.

**MATERIALS AND METHODS**

**Subjects**

Eight healthy older subjects (six male and two female), with a median age of 70.5 years (range: 65-75 years) and body mass index (BMI) of 23.5 kg/m² (range: 20.4-27.1 kg/m²), recruited by advertisement, were enrolled in the study. All subjects were non-smokers. None had a history of gastrointestinal disease or surgery, diabetes, significant respiratory, renal, hepatic or cardiac disease, intake of >20g alcohol/day, epilepsy, nor 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 inclusion. All experiments were carried out in accordance with the Declaration of Helsinki.
Each subject was studied on four occasions in randomised order; each study was separated by a minimum of three days. On each day, the subject attended the University of Adelaide, Discipline of Medicine, at the Royal Adelaide Hospital, at 0800h following an overnight fast (10h for solids; 8h for liquids). A silicone-rubber catheter (external diameter ~4 mm; Dentsleeve International Ltd, Mui Scientific, Mississauga, Canada) was introduced into the stomach via an anaesthetized nostril (27). 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 (ie in the duodenum). Two other channels 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 (TMPD) at the antral (-40mV) and duodenal (0mV), channels (12). For this purpose, an intravenous cannula filled with sterile saline was placed subcutaneously in the left forearm and used as a reference electrode (12).

On two of the four study days, the subject swallowed a single-lumen polyvinyl orogastric catheter (OD 4mm, ID 2mm; Tygon® Tubing, Saint Gobain Performance Plastics, Akron, USA), which had an ultrathin, flaccid polyethylene bag (capacity 1200mL), tightly wrapped around the distal end. The proximal end of the catheter was connected via a three-way tap to a gastric barostat (Distender Series II™, G & J Electronics Inc, Ontario, Canada). The bag was unfolded by inflation with 400ml of air, while ensuring that the pressure did not exceed 20 mmHg, and adjusted to be positioned in the proximal stomach, just below the diaphragm. The bag was then deflated, and the
barostat assembly was fixed in this position by taping it to the skin of the cheek (6, 30, 33).

The bag was then inflated in steps of 1 mmHg at 5-minute intervals in order to determine the MDP, which represents the minimal pressure required to overcome the intra-abdominal pressure, defined as the pressure required to achieve a volume > 30 ml in the bag (6). The stomach was then distended using a single ‘staircase’ protocol, in which intragastric pressure was increased by 2 mmHg every 3 minutes, in four steps, to achieve a distension of 8 mmHg above MDP (36). The intraballoon volume was recorded at 3-minute intervals commencing immediately prior to the intraduodenal infusion. Perceptions of fullness, nausea and bloating were assessed using a 7-point Likert scale (30), commencing immediately prior to the distension and during the last minute of each distension step. The subject was asked to quantify these sensations on a scale from 1 (no sensation) to 7 (unbearable sensation) (30, 33).

After the catheters were positioned correctly, and stepwise distension completed, at t=0 min, the subject received either (i) an intraduodenal infusion of glucose (3 kcal/min) (‘glucose’), (ii) intraduodenal infusion of saline (0.9%) (‘saline’), (iii) intraduodenal infusion of glucose (3 kcal/min) with intraballoon pressure set to 8 mmHg above MDP (‘glucose+distension’), or (iv) ID infusion of saline with intraballoon pressure set to 8 mmHg above MDP (‘saline+distension’), for 60 minutes (ie between t=0-60 minutes). The barostat bag was deflated at t=60 minutes. Between t=60-120 minutes saline (0.9%) was infused intraduodenally at an identical rate (27). Intraduodenal infusions were performed using a volumetric infusion pump (Imed Gemini PC-1: IMED Corp, San
Diego, CA, USA). An intravenous cannula was positioned in a left antecubital vein for blood sampling, and an automated blood pressure cuff around the right arm. Each subject remained in a supine position while blood sampling, and measurements of blood pressure, heart rate and SMA blood flow were performed. At t=120 minutes the catheters were removed, the subject 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 (5, 29).

**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, USA) at t=-9, -6 and -3 minutes prior to commencement of the intraduodenal infusions and then every 3 minutes between t=0-120 min (27). ‘Baseline’ blood pressure and heart rate, ie ‘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 minutes (16).

**Superior mesenteric artery blood flow**

Superior mesenteric artery (SMA) blood flow was measured by Duplex ultrasonography (ie B-mode and Doppler imaging) using a Logiq™ 9 ultrasonography system (GE Healthcare Technologies, Sydney, Australia) (28). The subject was scanned using a 3.5C broad spectrum 2.5-4 MHz convex transducer before (t=-2 min) the
commencement of the intraduodenal infusion, and then at 15 minute intervals between t=0-120 min. Blood flow (ml/min) was calculated instantaneously using the formula: \[ \pi \times r^2 \times \text{TAMV} \times 60 \], where \( r \) = the radius of the superior mesenteric artery and TAMV is the time-averaged mean velocity (7, 28).

**Blood glucose concentrations**

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

**Perceptions of distension**

Perceptions of nausea, bloating and fullness were assessed by a Likert scale between 1 (no sensation) and 7 (unbearable sensation) (30).

**Autonomic function**

Autonomic nerve function was assessed using standardized cardiovascular reflex tests (5, 29). 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 \( \geq 3 \) was considered to indicate autonomic dysfunction (5, 29).
**Statistical analysis**

Systolic and diastolic blood pressure, heart rate and perception scores were analyzed as changes in absolute values from baseline. Intragastric volume, SMA blood flow and blood glucose concentrations were analyzed as absolute values. One-way ANOVA was used to analyze the effects of ‘time’ on intragastric volume, systolic and diastolic blood pressure, heart rate, SMA blood flow, blood glucose concentrations and perception scores. The maximum change in systolic and diastolic blood pressure, heart rate, SMA blood flow and blood glucose concentrations were defined as the greatest change from baseline in each subject at any given time point for each treatment. Areas under the curve (AUC), were calculated using the trapezoidal rule, and analyzed by one-way ANOVA, to evaluate a ‘treatment’ effect between t=0–60 min for systolic and diastolic blood pressure and heart rate, between t =-2–60 min for SMA blood flow and blood glucose concentrations. All analyses were performed using SPSS version 16.0.2 (SPSS Inc, Chicago, USA). Data are shown as change from baseline and mean values ± standard error of the mean (SEM), unless stated otherwise. The number of subjects studied was based on power calculations derived from our previous work (8), with systolic blood pressure as the primary endpoint. A P value < 0.05 was considered significant in all analyses.
RESULTS
The studies were well tolerated and there were no adverse events. No subject had definite autonomic neuropathy (mean score 0.9, range: 0-2). One subject had postprandial hypotension (i.e., a fall in systolic blood pressure >20 mmHg that was sustained for at least 30 minutes) following ‘glucose’. In one of the remaining eight subjects, SMA blood flow measurements could not be obtained adequately during the ‘glucose+distension’ visit because the vessel was obscured by abdominal gas; these data were, accordingly, not included.

Intraballoon volume and pressure during gastric distension (Figure 1)
There was no significant difference in baseline (t=-2 min) intraballoon volume between the two days: ‘glucose+distension’ 443±60 ml vs. ‘saline+distension’ 410±80 ml (P=0.59). Between t=0-60 min, there was a prompt rise in intraballoon volume during both ‘glucose+distension’ (P<0.001) and ‘saline+distension’ (P=0.002), with a plateau from ~15 min. There was a trend (P=0.07) for the AUC for intraballoon volume to be greater during ‘glucose+distension’ than ‘saline+distension’. At t=60 min, intragastric volume was greater than baseline after ‘glucose+distension’ (790±71 ml; P=0.001) and tended to be greater after ‘saline+distension’ (637±80 ml; P=0.07) without any difference between them.

During distension, MDP ranged between 3-6 mmHg, so that pressures within the barostat bag ranged from 11-14 mmHg (MDP + 8mmHg). During the intraduodenal infusions, barostat bag volumes ranged from 300-950ml.
Systolic and diastolic blood pressure and heart rate (Figure 2a, b & c and Figure 3)

There was no significant difference in baseline (t=0 min) blood pressure or heart rate between the four days: systolic blood pressure (‘glucose’ 119±7 mmHg vs. ‘saline’ 117±5 mmHg vs. ‘glucose+distension’ 121±5 mmHg vs. ‘saline+distension’ 122±5 mmHg; P=0.52); diastolic blood pressure (‘glucose’ 69±3 mmHg vs. ‘saline’ 68±2 mmHg vs. ‘glucose+distension’ 71±2 mmHg vs. ‘saline+distension’ 69±2 mmHg; P=0.43), and heart rate (‘glucose’ 58±3 bpm vs. ‘saline’ 59±3 bpm vs. ‘glucose+distension’ 59±3 bpm vs. ‘saline+distension’ 60±2 bpm; P=0.45).

Between t=0–60 min, there was a substantial fall in systolic blood pressure during ‘glucose’ (P<0.05), no overall change during ‘saline’ (P=0.19) or ‘glucose+distension’ (P=0.20), and a rise during ‘saline+distension’ (P=0.008). The maximum fall in systolic blood pressure from baseline during ‘glucose’ was -14±5 mmHg, while there was minimal change following ‘glucose+distension’ (-3±4 mmHg) and a maximum increase of +11±2 mmHg and +15±3 mmHg during ‘saline’ and ‘saline+distension’, respectively. There was a significant treatment effect (P=0.01) for the AUC for the change in systolic blood pressure between t=0–60 min. Systolic blood pressure was less during ‘glucose’ when compared with ‘saline’ (P=0.05), ‘glucose+distension’ (P=0.01) and ‘saline+distension’ (P=0.03). Systolic blood pressure was greater during ‘saline+distension’ when compared with ‘saline’ (P=0.04), with no significant difference between ‘glucose+distension’ and ‘saline+distension’ (P=0.56). At t= 120 min, systolic blood pressure was not different from baseline after ‘glucose’ (116±5 mmHg; P=0.40), ‘saline’ (123±6 mmHg; P=0.26), and ‘glucose+distension’ (125±5 mmHg; P=0.15) but was greater after ‘saline+distension’ (132±7 mmHg; P=0.01).
Between t=0–60 min, there was a substantial fall in diastolic blood pressure during ‘glucose’ (P=0.001), a slight fall during ‘glucose+distension’ (P=0.02), a rise during ‘saline+distension’ (P=0.02), and no overall change during ‘saline’ (P=0.48). The maximum fall in diastolic blood pressure from baseline during ‘glucose’ was 12±2 mmHg (at t=43±5 min) and during ‘glucose+distension’ was 9±1 mmHg (at t=45±5 min). There was a significant treatment effect (P<0.001) for the AUC for the change in diastolic blood pressure between t=0–60 min. The magnitude of the fall in diastolic blood pressure was greater during ‘glucose’ compared with ‘saline’ (P=0.003), ‘glucose+distension’ (P=0.05) and ‘saline+distension’ (P=0.002). Diastolic blood pressure during ‘saline+distension’ was greater compared with ‘saline’ (P=0.006) and ‘glucose+distension’ (P=0.01). At t=120 min, diastolic blood pressure was not significantly different from baseline after ‘glucose’ (68±3 mmHg; P=0.26), ‘glucose+distension’ (73±3 mmHg; P=0.17) and ‘saline+distension’ (71±2 mmHg; P=0.28), but was slightly greater than baseline after ‘saline’ (71±2 mmHg; P=0.03).

Between t=0–60, there was a progressive rise in heart rate during ‘glucose’ (P<0.001) and ‘glucose+distension’ (P<0.001), but no overall change during ‘saline’ (P=0.42) or ‘saline+distension’ (P=0.41). The maximum rises in heart rate from baseline during ‘glucose’ (14±2 bpm at t=45±4 min), and ‘glucose+distension’ (14±3 bpm at 44±5 min), were similar with no significant difference between them (P=0.99). There was a significant treatment effect (P=0.002) for the AUC for the change in heart rate between t=0–60 min. The magnitude of the rise in heart rate was greater during ‘glucose’ compared with ‘saline’ (P=0.005), but not ‘glucose+distension’ (P=0.94). Similarly, the
magnitude of the increase in heart rate during ‘glucose+distension’ was greater compared with ‘saline+distension’ (P=0.02). There was no difference in heart rate following ‘saline’ compared with ‘saline+distension’ (P=0.43). At t=120 min, heart rate was not significantly different from baseline after ‘saline’ (60±3 bpm; P=0.56) and ‘saline+distension’ (61±3 bpm; P=0.13), but higher than baseline following ‘glucose’ (56±3 bpm; P=0.007) and ‘glucose+distension’ (64±2 bpm; P=0.02).

Superior mesenteric artery (SMA) blood flow (Figure 2d)

There was no significant difference in baseline (t=-2 min) SMA blood flow between the four days (‘glucose’ vs. ‘saline’ vs. ‘glucose+distension’ vs. ‘saline+distension’): 798±132 ml/min vs. 844±91 ml/min vs. 770±121 ml/min vs. 829±120 ml/min; P=0.81.

Between t=-2-60 min, there was a rise in SMA blood flow during ‘glucose’ (P=0.004), and ‘glucose+distension’ (P=0.001), but no overall change during ‘saline’ (P=0.13), and a trend for a decrease during ‘saline+distension’ (P=0.07). The maximum rise in SMA blood flow from baseline during ‘glucose’ (2388±365 ml/min at 43±6 min) was greater (P=0.05) than the maximum rise during ‘glucose+distension’ (1673±187 ml/min at 41±9 min). There was a significant treatment effect (P<0.001) for the AUC for the change in SMA blood flow between t=-2-60 min, so that the magnitude of the rise in SMA blood flow was greater during ‘glucose’ compared with ‘saline’ (P=0.001), ‘glucose+distension’ (P=0.03), and ‘saline+distension’ (P=0.001). There was a trend for a rise in SMA flow during ‘glucose+distension’ to be greater compared with ‘saline+distension’ (P=0.09) and no significant difference during ‘saline’ compared with ‘saline+distension’ (P=0.14). At t=120 min, SMA blood flow had returned to
baseline after ‘glucose’ (848±134 ml/min; P=0.73), ‘saline’ (747±116 ml/min; P=0.19), ‘glucose+distension’ (894±120 ml/min; P=0.16), and ‘saline+distension’ (839±142 ml/min; P=0.92).

**Blood glucose concentrations (Figure 4)**

There was no significant difference in baseline (t=-2 min) blood glucose concentration between the four days (‘glucose’ vs. ‘saline’ vs. ‘glucose+distension’ vs. ‘saline+distension’): 6.0±0.2 mmol/L vs. 6.1±0.1 mmol/L vs. 6.1±0.1 mmol/L vs. 6.2±0.1 mmol/L; P=0.78.

Between t=-2-60 min, there was a progressive rise in blood glucose concentrations during ‘glucose’ (P<0.001), and ‘glucose+distension’ (P<0.001), but no overall change during ‘saline’ (P=0.55) or ‘saline+distension’ (P=0.48). The maximum rises in blood glucose during ‘glucose’ (11.3±0.7 mmol/L at 56±3 min) and ‘glucose+distension’ (11.5±0.8 mmol/L at 60±0 min), were not different (P=0.69). There was a significant treatment effect (P<0.001) for the AUC for the blood glucose concentration between t=-2-60 min. The magnitude of the rise in blood glucose concentration was greater during ‘glucose’ compared with ‘saline’ (P<0.001), but not different when compared with ‘glucose+distension’ (P=0.94). At t=120 min, blood glucose concentrations were not different from baseline after ‘glucose’ (5.8±0.8 mmol/L; P=0.74), ‘saline’ (6.0±0.2 mmol/L; P=0.28), ‘glucose+distension’ (6.9±0.8 mmol/L; P=0.31), or ‘saline+distension’ (6.1±0.1 mmol/L; P=0.43).
Perceptions of distension

Baseline (at MDP) perceptions on the two days (‘glucose+distension’ vs ‘saline+distension’) were: nausea (1.3±0.2 vs 1.1±0.1; P=0.35), bloating (1.6±0.4 vs 1.1±0.1; P=0.35) and fullness (1.6±0.5 vs 1.5±0.4; P=0.23). Prior to the glucose infusion, the stepwise distension (‘glucose+distension’), there was no change in nausea (P=0.21), or fullness (P=0.12), and a trend for an increase in bloating (P=0.08). On the day that subjects received saline (‘saline+distension’), there were no changes in sensations of nausea (P=0.42), bloating (P=0.52) or fullness (P=0.25). There were no differences in perceptions between the two days ie ‘glucose+distension’ and ‘saline+distension’.

DISCUSSION

This study establishes that gastric distension, induced by a barostat, has the capacity to abolish the fall in systolic blood pressure and attenuate the rise in SMA blood flow, but has no effect on the rise in heart rate, induced by intraduodenal glucose infusion at a rate of 3 kcal/min in healthy older subjects. These observations have implications for the non-pharmacological management of postprandial hypotension.

There is increasing evidence that gastric distension plays a protective role in the regulation of postprandial blood pressure (3, 8, 17, 19, 20, 30, 31, 33). In a recent study in healthy older subjects, we demonstrated that the hypotensive response to intraduodenal infusion of glucose at 3kcal/min was markedly attenuated by the presence of as little as ~300ml of intragastric water, while during intraduodenal saline infusion,
the presence of ~100ml increased systolic blood pressure by 6-8 mmHg above baseline (8). In that study, gastric distension could not be sustained and it was possible that distension of the small intestine due to gastric emptying of the intragastric water could have influenced the response. In the current study we were able to address these limitations by the use of a gastric barostat (30, 33). We distended the stomach to a fixed pressure of 8 mmHg above MDP, as this has been shown to be well tolerated (as proved to be the case) and to increase blood pressure in both healthy young (30, 33) and older subjects (33), in the absence of intraduodenal nutrients. In the current study, there was a trend for a rise in blood pressure (~12-18 mmHg above baseline) during intraduodenal saline when 300-950ml of air was present within the barostat bag, consistent with previous observations (8). It should also be noted that during intraduodenal glucose there was a trend for intraballoon volume to be greater. This is not surprising as intraduodenal carbohydrate is known to be associated with greater gastric relaxation than intraduodenal saline as a result of feedback from small intestinal chemoreceptors (1) and acute hyperglycaemia is known to induce proximal stomach relaxation (10, 11, 35). Hence, while the intragastric pressures were matched in both distension experiments, the distending volume should be considered as comparable, rather than identical. It has been reported that consumption of 480ml of water increases systolic blood pressure in healthy older subjects, and patients with multiple system atrophy and autonomic failure (19), as well as attenuate the fall in blood pressure following a high carbohydrate meal in patients with autonomic failure (31). Furthermore, in healthy older subjects, the magnitude of the fall in systolic blood pressure is greater when glucose was ingested at a smaller volume (200ml compared with 600ml), at the same glucose concentration (17). The latter study also provided evidence that proximal, rather than
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distal, gastric distension, may be primarily responsible for this effect (17). If this proves to be the case, it would be possible to modify the intragastric meal distribution and hence, the regional gastric distension by changes in meal composition and/or ‘posture’ for therapeutic purposes (4, 13).

The normal overall rate of gastric emptying of glucose in healthy young and older subjects is in the range of 1 – 4 kcal/min (2, 14), and we have shown that in healthy older subjects, administration of intraduodenal glucose at a rate of 3 kcal/min induces a substantially greater fall in blood pressure than 1 kcal/min (27, 34). In contrast, infusion of glucose intraduodenally at 3 kcal/min has minimal effect on blood pressure in young adults (34), whereas preliminary data indicate that in patients with postprandial hypotension the response is exaggerated (34). The differential response to intraduodenal glucose in healthy young and older subjects, has been attributed to alterations in baroreceptor function (34). As in previous studies (8), the magnitude of the fall in systolic blood pressure during intraduodenal glucose without gastric distension was substantial (14±5 mmHg) and it is, accordingly, remarkable that gastric distension completely abolished the fall. Interestingly, heart rate increased progressively in response to intraduodenal glucose and this was not influenced by gastric distension. The latter observation was surprising and, while it could reflect the greater variability of heart rate, it suggests that this response may not represent an effect of splanchnic vasodilation and a fall in blood pressure, but some form of ‘entero-cardiac’ reflex.

The mechanism(s) mediating the effects of gastric distension on the hypotensive response to intraduodenal glucose remain uncertain and there are a number of
possibilities which warrant further exploration. The glycemic responses to intraduodenal glucose was comparable in studies with and without gastric distension (8). Furthermore, insulin is unlikely to play a major role in postprandial hypotension, since intravenous glucose has little, if any, effect on blood pressure and postprandial hypotension occurs in type 1 diabetics (23, 25), who are, by definition, insulin deficient. The observed effects of gastric distension in the stimulation of SMA blood flow are of considerable interest, particularly given the paucity of previous information. The current study establishes that gastric distension markedly attenuates the increase in SMA blood flow induced by intraduodenal glucose. In both cases, the pattern of SMA blood flow response differed from that of heart rate – while the increase in heart rate was progressive, whereas SMA blood flow plateaued. – During gastric distension, the plateau occurred substantially earlier, a response which may contribute to the maintenance of blood pressure. While this may suggest the existence of a ‘gastrovascular’ reflex in the peripheral, somatic circulation, gastric distension had no effect on SMA blood flow during intraduodenal saline. Further studies are indicated to explore this issue. In the pig, fasting SMA flow has been reported to be decreased (26, 32), increased (32) or unchanged (32) by gastric distension, whereas, in the cat, a modest increase has been reported (21). A recent study by our group reported that the rise in SMA blood flow was greater following oral, compared to, intraduodenal glucose (9), which may reflect differences in the method of gastric distension - The barostat distends primarily the proximal stomach, while an intragastric load distends the whole stomach. There is hitherto no information relating to the potential regional effects of gastric distension on SMA flow, which would be of interest. It should be recognised that measurement of SMA blood flow using Doppler ultrasound is affected by the presence
of abdominal gas, which may compromise locating and imaging the vessel, thereby degrading image quality, and that this may represent an issue with the barostat bag. For logistical reasons we did not perform studies with the barostat bag deflated. The minimal intragastric pressure required to attenuate the fall in blood pressure induced by intraduodenal glucose, and whether the effect is volume and/or pressure dependent, remain to be determined. We elected to study healthy older subjects, not those with known postprandial hypotension given that the latter occurs frequently in this group (16), which also exhibit a fall in blood pressure in response to intraduodenal glucose; a response that is substantial, but not dramatic (7, 27). Preliminary data also indicate that the magnitude of the fall may be precipitous in patients with known postprandial hypotension (34). Studies in this latter group are now indicated given that they represent the target population.

In summary, in healthy older subjects, the fall in systolic blood pressure and rise in SMA blood flow induced by intraduodenal glucose, are markedly attenuated by modest gastric distension, supporting the concept that maximising non-nutrient gastric distension may represent a simple approach to the management of postprandial hypotension (for example, consumption of water prior to a meal).
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REFERENCES


9. **Gentilcore D, Nair NS, Vanis L, Rayner CK, Meyer JH, Hausken T, Horowitz M, and Jones KL.** Comparative effects of oral and intraduodenal glucose on


26. **Molinari C, Battaglia A, Grossini E, Florio S, Mary DA, Vassanelli C, and Vacca G.** Activation of the renin-angiotensin system contributes to the peripheral
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Gastric distension, duodenal glucose and blood pressure


Figure legends

Figure 1. Intrabag (barostat) volumes during ‘glucose+distension’ (○), and ‘saline+distension’ (□). Data are mean values ± SE (n = 8).

Figure 2. Changes in a) systolic blood pressure, b) diastolic blood pressure, c) heart rate, from baseline and d) superior mesenteric artery (SMA) blood flow, in response to ‘glucose’ (●), ‘saline’ (■), ‘glucose+distension’ (○), and ‘saline+distension’ (□). Data are mean values ± SE (n = 8). Systolic blood pressure treatment effect: * P < 0.05 ‘saline’ compared with ‘glucose’ and ‘saline’ compared with ‘saline+distension’; # P = 0.01 ‘glucose’ compared with ‘glucose+distension’. Diastolic blood pressure treatment effect: * P < 0.01 ‘saline’ compared with ‘glucose’ and ‘saline’ compared with ‘saline+distension’; # P < 0.05 ‘glucose+distension’ compared with ‘glucose’ and ‘glucose+distension’ compared with ‘saline+distension’. Heart rate treatment effect: P = 0.005 ‘saline’ compared with ‘glucose’; P = 0.02 ‘saline+distension’ compared with ‘glucose+distension’. SMA blood flow effect: * P = 0.001 ‘saline’ compared with ‘glucose’; # P = 0.03 ‘glucose+distension’ compared with ‘glucose’.

Figure 3. Individual data in all eight subjects showing the changes in systolic blood pressure from baseline, in response to ‘glucose’ (●) and ‘glucose+distension’ (○).

Figure 4. Blood glucose concentrations during ‘glucose’ (●), ‘saline’ (■), ‘glucose+distension’ (○), and ‘saline+distension’ (□). Data are mean values ± SE (n = 8). Treatment effect: P < 0.001 ‘saline’ compared with ‘glucose’.
Intragastric volume

- glucose+distension
- saline+distension

Intragastric volume vs. Time (min)
(a) Systolic BP

(b) Diastolic BP

(c) Heart Rate

(d) SMA Blood Flow

- **SMA Blood Flow**
  - **P = 0.001 vs S**
  - **# P = 0.03 vs GB**
- **Diastolic BP**
  - **P < 0.01 vs S**
  - **# P < 0.05 vs GB**
- **Heart Rate**
  - **P = 0.05 G vs S**
  - **P = 0.02 GB vs SB**
- **Systolic BP**
  - **P < 0.05 vs S**
  - **# P = 0.01 vs GB**
Blood glucose

- glucose
- saline
- glucose+distension
- saline+distension

P < 0.001 G vs S

mmol/L

Time (min)