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## The hypotensive response to oral fat is comparable but slower compared with carbohydrate in healthy elderly subjects

Renuka Visvanathan<sup>1,2\*</sup>, Michael Horowitz<sup>1</sup> and Ian Chapman<sup>1</sup>

<sup>1</sup>Department of Medicine, University of Adelaide, Adelaide, South Australia

<sup>2</sup>Aged and Extended Care Service, The Queen Elizabeth Hospital, Woodville South, Adelaide, South Australia

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The objective of the present study was to determine the comparative hypotensive responses to drinks containing predominantly fat and carbohydrate (CHO) in healthy elderly subjects. Using a randomised, cross-over study, the participants, twelve elderly subjects, six of them female (72.2 (SD 5.7) years), were investigated. On three separate days, blood pressure (BP) and heart rate were measured following ingestion of 300 ml drinks containing: (1) CHO (75 g glucose and 93 g Polyjoule (CHO polymer) providing 2732 kJ (653 kcal)); (2) 88 % fat (cream blended with milk providing 2732 kJ (653 kcal)); (3) water. Systolic BP decreased following the CHO drink ( $P < 0.001$ ) and the high-fat drink ( $P < 0.001$ ) but not water; there was no difference in the magnitude of the decrease between the CHO drink and the drink containing fat (13.4 v. 15.6 mmHg). However, the onset of the fall was slower after the fat-containing drink (13.0 v. 26.5 min ( $P = 0.01$ ); area under the curve for 0–30 min for CHO drink – 6.5 v. fat-containing drink 125.4 mmHg × min ( $P = 0.043$ )). We conclude that ingestion of a high-fat drink results in a comparable fall in BP to a CHO drink although the onset is relatively slower. These observations may have implications for the management of postprandial hypotension.

### Postprandial hypotension: Blood pressure: Elderly

Postprandial hypotension (PPH), defined as a decrease in systolic blood pressure (SBP) of 20 mmHg or more within 2 h of the start of a meal, occurs frequently (prevalence 20–45 %) and represents a major cause of morbidity in older individuals (Jansen & Lipsitz, 1995; Smith *et al.* 2003). Although it has been established that older individuals and patients with autonomic neuropathy (most frequently due to diabetes) who have PPH are at increased risk for falls, syncope, angina and transient ischaemic attacks, patients presenting with these symptoms are rarely assessed for PPH. Current approaches to the management of PPH are also suboptimal (Jansen & Lipsitz, 1995).

Macronutrient composition is known to be an important determinant of the hypotensive response to a meal (Jansen & Lipsitz, 1995). It is frequently stated that ingestion of carbohydrate (CHO), particularly glucose, sucrose and to a lesser degree starch, but not fructose or xylose, lowers blood pressure (BP) more than ingestion of fat, protein or water (Mathias *et al.* 1989; Jansen *et al.* 1990; Heseltine *et al.* 1991; Visvanathan *et al.* 2005). However, it should be recognised that only a limited number of studies have been performed and some of the reported observations are inconsistent, particularly in relation to the effects of fat on BP (Hoeldtke *et al.* 1985; Potter *et al.* 1989; Jansen *et al.* 1990; Sidery *et al.* 1993; Jansen & Lipsitz, 1995). Two studies involving older individuals (>60 years)

performed more than a decade ago found that ingestion of high-fat meals or drinks were not associated with significant falls in BP in contrast to CHO-containing meals (Potter *et al.* 1989; Jansen *et al.* 1990). In contrast to this, several other studies have shown a fall in BP following a high-fat meal (Hoeldtke *et al.* 1985; Bannister *et al.* 1987; Sidery *et al.* 1993).

Therefore, the effect of a high-fat meal on BP in older individuals is currently not clearly defined and this has both therapeutic and research implications. The aim of the present study was to evaluate the effects of high-fat and -CHO drinks on post-ingestion BP in healthy old individuals (water being the control drink).

### Methods

#### Subjects

Twelve healthy, elderly subjects (six female) were recruited by advertisement. The mean age was 72.2 (SD 5.7) years and the BMI was 24.6 (SD 1.8) kg/m<sup>2</sup>. All subjects were non-smokers and had no history of gastrointestinal disease or surgery, diabetes mellitus, significant respiratory disease or CVD, autonomic dysfunction, chronic alcohol abuse or epilepsy. No subject was taking medication known to influence BP and all medications remained unchanged during the study.

**Abbreviations:** AUC, area under the curve; BP, blood pressure; CHO, carbohydrate; DBP, diastolic blood pressure; HR, heart rate; PPH, postprandial hypotension; SBP, systolic blood pressure.

\*Corresponding author: Dr Renuka Visvanathan, fax 08 82228593, email [renuka.visvanathan@adelaide.edu.au](mailto:renuka.visvanathan@adelaide.edu.au)

### Protocol

Each subject had BP, heart rate (HR) and blood glucose measurements on 3 d separated by at least 72 h, before and after ingestion of the following drinks (all 300 ml):

- (1) a CHO drink made from 75 g glucose and 93 g CHO polymer (Polyjoule; Nutricia Pty Ltd, Castle Hill, NSW, Australia) (100% CHO content; total energy 2732 kJ (653 kcal)) plus lemon flavouring;
- (2) a high-fat drink made from 110 ml rich cream blended with 190 ml full-cream milk (88% fat, 7% CHO (mostly lactose), 5% protein; total energy 2732 kJ (653 kcal)) with low-energy flavouring;
- (3) tap water (control).

The studies were randomised but not blinded and separated by at least 72 h. All drinks were served at a temperature of 22°C to avoid the potential effect of temperature on BP (Kuipers *et al.* 1991).

On the study days, subjects attended the Department of Medicine following an overnight fast (10 h for solids with small sips of water permitted until 06.00 hours). In individual subjects, all three studies were performed at the same time. Subjects were seated comfortably in a chair. An intravenous cannula was inserted (left cubital fossa) and a BP cuff was attached to the right upper arm. Cardiovascular autonomic function was evaluated first thing in the morning on one of the study days. Each subject provided written, informed consent and the study was approved by the research ethics committee of the Royal Adelaide Hospital.

### Measurements

**Blood pressure and heart rate.** SBP, diastolic BP (DBP) and HR were measured using an automated oscillometric BP monitor (DINAMAP ProCare; GE Medical Systems, Sydney, NSW, Australia). Following a 20 min 'rest' post-cannula insertion, three measurements were obtained at 9, 6 and 3 min before drinks ingestion ( $t = 0$ ). The mean of these three readings formed the 'baseline' value ( $t = 0$ ). The study drink was consumed within 3 min and so the first measurement post-drink ingestion was at  $t = 3$  min. BP and HR measurements were then measured every 3 min for 90 min (to  $t = 90$  min) post-drink ingestion.

**Blood glucose.** Venous blood was obtained from the intravenous cannula for glucose estimation at baseline and  $t = 5, 10, 15, 30, 45, 60, 75$  and 90 min. Blood glucose was determined using a glucometer (True Sense; Abbott Diagnostic Division, Botany, NSW, Australia).

**Total triacylglycerols.** Plasma total triacylglycerol concentrations were measured in stored ( $-70^{\circ}\text{C}$ ) plasma samples. Only samples from eleven subjects and limited time-points ( $t = 0, 15, 30, 60$  and 90 min) were available for analysis. Plasma was processed on an Olympus 5400 analyser using triacylglycerols-liquid reagent (Integrated Sciences Pty. Ltd, Willoughby, NSW, Australia) at the Institute of Medical and Veterinary Science Laboratories in Adelaide, South Australia.

**Autonomic function.** Autonomic nerve function was evaluated using standardised cardiovascular reflex tests (Ewing & Clarke, 1982; Piha, 1991). Parasympathetic function was evaluated by the variation (R-R interval) of the HR during deep

breathing and upon standing (R-R interval at beat 30/R-R interval at beat 15). Sympathetic function was assessed by the fall in SBP in response to standing. Each of the test results was scored according to age-adjusted predefined criteria as 0 = normal, 1 = borderline, and 2 = abnormal for a total maximum score of 6. A score  $>3$  was considered to indicate autonomic dysfunction (Ewing & Clarke, 1982; Piha, 1991; Jones *et al.* 2001).

### Statistical analysis

All values are expressed as means and standard deviations. Two-way repeated measures ANOVA was used to examine the overall effects of time and types of drink (treatment) and the treatment  $\times$  time interaction on changing BP and HR from baseline. One-way repeated measures ANOVA were conducted to evaluate the effects of each drink on BP, HR, blood glucose and total triacylglycerols over the first 90 min. One-way repeated measures ANOVA were also conducted to compare the differences between the baseline BP, HR, blood glucose and total triacylglycerols values between the study days. The time to BP decrease was defined as the first time-point after drink ingestion when the SBP was less than baseline; the maximum fall in BP was the lowest value. The BP and HR areas under the curve (AUC) following the CHO and high-fat drink ingestion at  $t = 0-30$ ,  $t = 33-60$  and  $t = 63-90$  min were also determined using the trapezoidal method. These values derived for CHO and fat were then compared using paired Student's *t* tests. All analyses were performed using Statview version 5.0 (SAS Institute Inc., Cary, NC, USA) and SuperANOVA (Abacus Concepts Inc., Berkeley, CA, USA). *P* values  $<0.05$  were considered statistically significant.

### Results

The study drinks were all well tolerated. No subject had autonomic dysfunction (mean score  $0.9 \pm 0.8$ ).

#### Blood pressure

There were no significant differences in the baseline BP (SBP (CHO drink 120.6 (SD 13.5) v. high-fat drink 121.5 (SD 15.44) v. water 120.7 (SD 14.6) mmHg;  $P=0.93$ ) and DBP (CHO drink 66.2 (SD 7.11) v. high-fat drink 67.0 (SD 7.9) v. water 64.9 (SD 7.8) mmHg;  $P=0.84$ ) between the study days. Three subjects had PPH (one following both the CHO and high-fat drinks, one following the CHO drink and another after the fat-containing drink); in all cases the PPH was asymptomatic.

For SBP (change from baseline), there were significant treatment ( $P=0.04$ ) and time ( $P<0.001$ ) effects and treatment  $\times$  time interaction ( $P<0.001$ ) over the first 90 min. SBP decreased from baseline following CHO drink ( $P<0.001$ ; maximum fall 13.4 (SD 7.4) mmHg) and high-fat drink ( $P<0.001$ ; maximum fall 15.6 (SD 10.5) mmHg) ingestion to a similar extent but not after water ( $P=0.11$ ). While there was no difference ( $P=0.47$ ) in the maximum fall between the CHO and high-fat drinks, the decrease in SBP was evident earlier after CHO than high-fat drink ingestion (13.0 (SD 11.7) v. 26.5 (SD 17.1) min;  $P=0.01$ ). Consistent

with this, the AUC for SBP following CHO and high-fat drink ingestion between 0 and 30 min were  $-6.5$  (SD 137.6) and  $125.4$  (SD 258.3) mmHg  $\times$  min respectively ( $P=0.043$ ). There was no significant difference in the SBP AUC between 33 and 60 min following CHO and high-fat drink ingestion ( $-116.4$  (SD 178.7) *v.*  $-138.8$  (SD 255.4) mmHg  $\times$  min;  $P=0.749$ ). SBP had not returned to baseline at 90 min (Fig. 1 (a)).

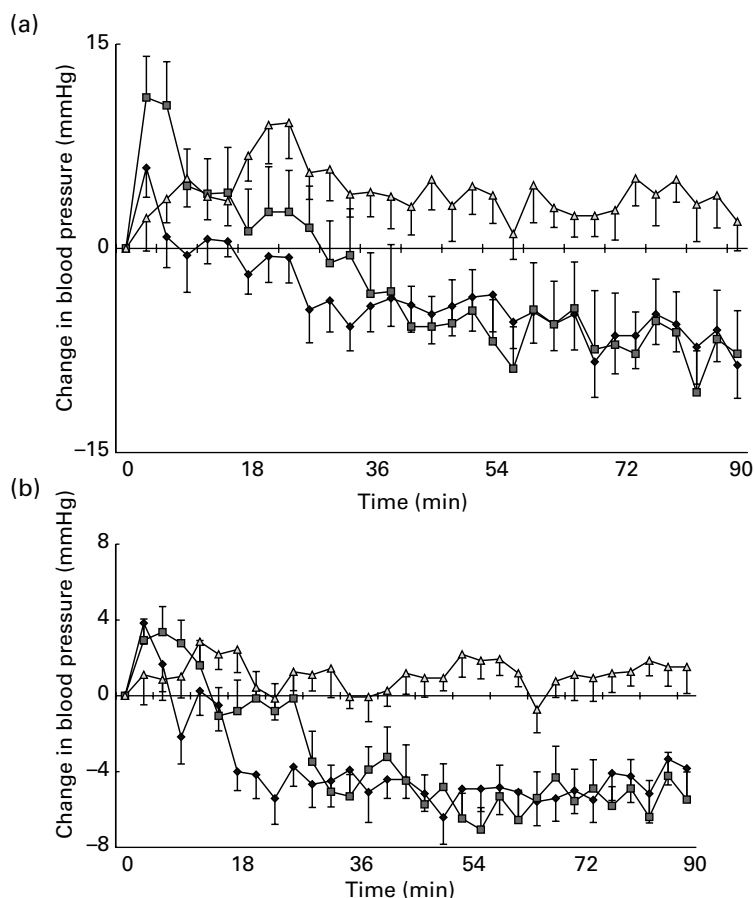
For DBP (change from baseline) there were also significant treatment and time effects and treatment  $\times$  time (all  $P<0.001$ ) interaction. In the first 90 min, DBP (Fig. 1 (b)) decreased from baseline to a similar extent following the CHO drink ( $P<0.001$ ; maximum fall  $10.2$  (SD 3.5) mmHg) and the high-fat drink ( $P<0.001$ ; maximum fall  $10.9$  (SD 3.6) mmHg) but not after water ( $P=0.85$ ). While there was no difference ( $P=0.68$ ) in the magnitude of the fall, the decrease in DBP occurred earlier following CHO than high-fat drink ingestion ( $10$  (SD 5.3) *v.*  $15$  (SD 9.7) min;  $P=0.01$ ). Consistent with this, the AUC for DBP following CHO and high-fat drink ingestion between 0 and 30 min were  $-49.8$  (SD 79.0) and  $17.8$  (SD 100.4) mmHg  $\times$  min respectively ( $P=0.08$ ). There was no significant difference in the DBP AUC between 33 and 60 min following CHO and fat-containing drink ingestion ( $-131.7$  (SD 87.2) *v.*  $-138.6$  (SD 112.2) mmHg  $\times$  min;  $P=0.87$ ). DBP following CHO and high-fat drink ingestion had not returned to baseline at 90 min (Fig. 1 (b)).

### Heart rate

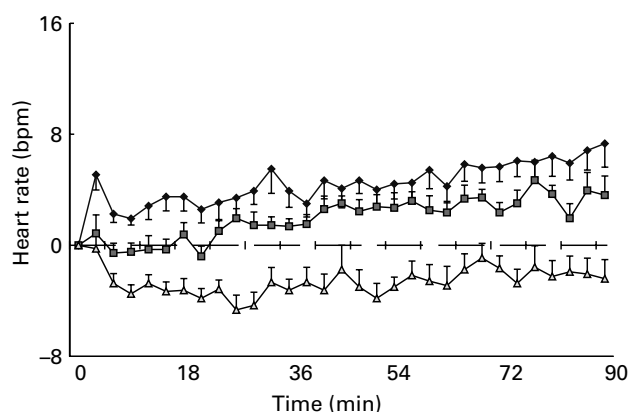
There was no significant difference in baseline HR (CHO drink  $61.3$  (SD 8.3) *v.* high-fat drink  $64.1$  (SD 8.3) *v.* water  $63.8$  (SD 9.3) beats per min;  $P=0.84$ ). There were significant treatment and time effects and treatment  $\times$  time interaction (all  $P<0.001$ ). HR increased following the CHO and fat-containing drinks ( $P<0.001$ ) and decreased following water ingestion ( $P<0.001$ ) (Fig. 2). The rise in HR occurred sooner following the CHO drink than the high-fat drink (CHO drink  $3.8$  (SD 2.6) *v.* high-fat drink  $21.3$  (SD 13.1) min;  $P=0.001$ ) and the magnitude of the rise was greater (AUC 0–30 min CHO drink  $90.4$  (SD 74.0) *v.* high-fat drink  $8.6$  (SD 43.1);  $P=0.010$ ; AUC 33–60 min CHO drink  $116.1$  (SD 98.9) *v.* high-fat drink  $64.8$  (SD 51.5) beats;  $P=0.062$ ). Following CHO and high-fat drink ingestion HR was still elevated at 90 min (Fig. 2).

### Blood glucose

There were no significant differences in baseline blood glucose (CHO drink  $5.7$  *v.* fat-containing drink  $5.8$  *v.* water  $5.8$  mmol/l;  $P=0.94$ ). Blood glucose increased following the CHO drink ( $P<0.001$ ) but not after the high-fat drink ( $P=0.55$ ) or water ( $P=0.83$ ) (Fig. 3).



**Fig. 1.** Systolic (a) and diastolic (b) blood pressure expressed as changes from baseline following ingestion of 300 ml drinks containing carbohydrate ( $\blacklozenge$ ), 88% fat ( $\blacksquare$ ) and water ( $\triangle$ ). Values are means for twelve subjects, with standard errors represented by vertical bars.



**Fig. 2.** Heart rate (beats per min; bpm) expressed as changes from baseline following ingestion of 300 ml drinks containing carbohydrate ( $\blacklozenge$ ), 88% fat ( $\blacksquare$ ) and water ( $\triangle$ ). Values are means for twelve subjects, with standard errors represented by vertical bars.

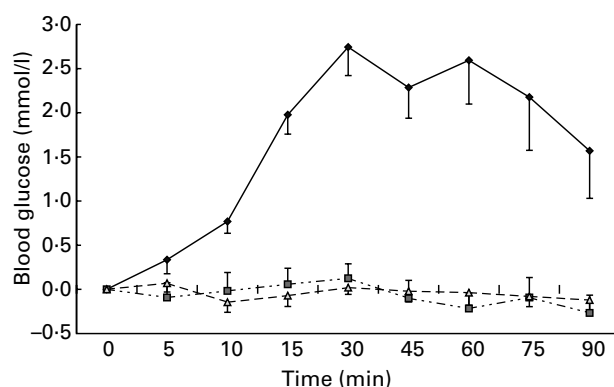
#### Total triacylglycerols

There were no significant differences in baseline total triacylglycerol values (CHO drink 1.1 v. fat-containing drink 1.2 v. water 1.2;  $P=0.628$ ). Total triacylglycerols values increased from baseline following the high-fat drink ( $P=0.001$ ) but not after the CHO drink (0.61) or water (0.26). A significant rise in plasma triacylglycerols following fat ingestion occurred somewhere between  $t=30$  and  $t=60$  min (values at  $t=30$  v. baseline  $P=0.067$  and values at  $t=60$  v. baseline  $P=0.005$ ) (Fig. 4).

#### Discussion

The present study has demonstrated that in unselected healthy elderly subjects, ingestion of a high-fat drink decreases SBP substantially (mean maximum fall of 17 mmHg) and as much as an isoenergetic CHO load of the same volume, but the onset of the decrease is slower. Also, the ingestion of nutrient-containing meals (i.e. the CHO and high-fat drinks) results in a HR increase whilst the ingestion of water is associated with a decrease in HR (Joannides *et al.* 1999; Routledge *et al.* 2002; Visvanathan *et al.* 2004; O'Donovan *et al.* 2005). Confirming the results of a previous study by our group, the BP response to a meal is not related to changes in blood glucose measurements (Visvanathan *et al.* 2004).

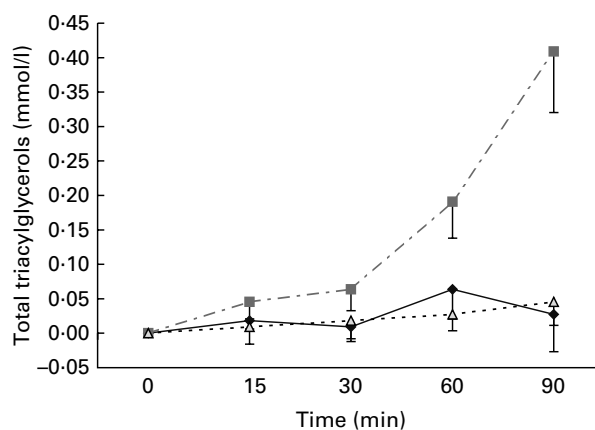
The observed trend for an increase in BP and fall in HR after water is consistent with previous studies and is presumably mediated by gastric distension leading to an increase in sympathetic vasoconstriction and cardiac vagal activity (Joannides *et al.* 1999; Routledge *et al.* 2002; Shannon *et al.* 2002). Where oral glucose ingestion leads to a fall in BP, intravenous infusion of glucose has less, if any, effect, indicating that the response is mediated from the gastrointestinal tract (Jansen & Hoefnagels, 1987). This and the observation that BP falls in response to oral glucose ingestion in patients with type 1 diabetes (insulin-dependent) argue against a significant role for insulin in the pathophysiology of PPH (Jansen & Hoefnagels, 1987; Stevens *et al.* 1991). In older individuals with PPH, the magnitude and duration of hypotension in response to equal-volume CHO drinks are both progressively greater with increasing CHO loads (25 g v. 65 g v. 125 g) (Vloet *et al.*



**Fig. 3.** Blood glucose concentration expressed as changes from baseline following ingestion of 300 ml drinks containing carbohydrate ( $\blacklozenge$ ), 88% fat ( $\blacksquare$ ) and water ( $\triangle$ ). Values are means for twelve subjects, with standard errors represented by vertical bars.

2001). Currently, it is widely believed that the hypotensive effects of nutrient-containing meals are related predominantly to their CHO content and that fat has very little effect (Potter *et al.* 1989; Jansen *et al.* 1990; Jansen & Lipsitz, 1995; Jones *et al.* 2001). The fall of BP following the ingestion of the high-fat meals in the present study contradicts this and this has research and therapeutic implications.

The observation that ingestion of a high-fat drink resulted in a fall in BP of similar magnitude to CHO was unexpected as in a previous study of ten hypertensive older individuals, a similar high-fat drink did not induce a fall in BP (Jansen *et al.* 1990). However, falls in BP following high-fat meals and drinks have been demonstrated in small numbers of young patients (less than six) with autonomic dysfunction (Hoeldtke *et al.* 1985; Bannister *et al.* 1987). In one other study evaluating BP changes following high-fat meals in older individuals, only a fall in DBP was seen (no SBP fall; Sidery *et al.* 1993). The fall in BP observed after the high-fat drink in the present study is unlikely to be due to the small amount (7%; 192 kJ (46 kcal)) of CHO (mainly lactose), particularly as we have previously demonstrated that



**Fig. 4.** Plasma total triacylglycerol concentration expressed as changes from baseline following ingestion of 300 ml drinks containing carbohydrate ( $\blacklozenge$ ), 88% fat ( $\blacksquare$ ) and water ( $\triangle$ ). Values are means for twelve subjects, with standard errors represented by vertical bars.

intra-duodenal infusion of a greater amount of glucose (4.2 (1 kcal)/min for 60 min (251 (60 kcal))) has no effect on BP or HR in healthy elderly individuals, whereas BP falls and HR increases in response to an infusion rate of 12.6 kJ (3 kcal)/min (O'Donovan *et al.* 2002).

The pathophysiology of PPH is currently not clearly defined. The ingestion of nutrient-containing meals such as fatty and CHO meals are associated with increases in splanchnic blood flow, muscle sympathetic nerve activity and cardiac output in most studies (Hawley & Channer, 1992; Waaler & Eriksen, 1992; Fagius & Berne, 1994). Failure in BP homeostasis involving either one or a combination of the cardiac system (i.e. cardiac output), vascular system (i.e. splanchnic blood flow), nervous system (i.e. muscle sympathetic nerve activity), gastric system (i.e. gastric emptying) or hormonal system is very likely (Jansen & Lipsitz, 1995). A limitation of the present study was that none of these systems were evaluated and so the exact cause for the postprandial BP decrease in the study could not be defined.

We speculate that the hypotensive response to fat is mediated by fat digestion products and that the delayed hypotensive response to fat compared with CHO reflects the time taken for the generation of a sufficient quantity of NEFA to trigger this response. In support of this, the fall in SBP following fat ingestion appeared to correspond with the rise in total triacylglycerols (at approximately 30 min). This hypothesis is further supported by the results of recent studies by our group. In one study, the fall in BP following oral sucrose was comparable with glucose but slower, suggesting that digestion of sucrose to glucose may be necessary to produce this effect (Visvanathan *et al.* 2005). In support of this, in another study, co-administration of acarbose, an  $\alpha$ -glucosidase inhibitor, with sucrose attenuated this fall in blood pressure (Gentilcore *et al.* 2005). In a similar manner, inhibition of fat digestion may attenuate the postprandial BP fall. This requires further evaluation.

In the present study fat and CHO ingestion was associated with a rise in HR. As with the BP changes, the rise in HR occurred later following fat ingestion than CHO ingestion. Similar rises in HR have been observed in other studies by our group following CHO ingestion although, to date, its role in the development of PPH is currently not known (Jones *et al.* 2001; O'Donovan *et al.* 2002). It may be that this rise in HR is a reflection of compensatory measures (i.e. increased cardiac output) in response to splanchnic pooling. With nutrient ingestion, there is increased mesenteric blood flow, increased cardiac output and redistribution of blood flow in favour of the gut (Waaler & Eriksen, 1992; Hoost *et al.* 1996). In the present study also, there was a fall in HR following water ingestion. Water (devoid of nutrients) ingestion does not result in increased mesenteric blood flow (Waaler & Eriksen, 1992). Instead, water ingestion is associated with an increase in sympathetic vasoconstrictor activity and increased cardiac vagal activity (Joannides *et al.* 1999; Routledge *et al.* 2002).

The changes in blood glucose measurements following fat, CHO and water ingestion was as expected (Erdmann *et al.* 2004; Visvanathan *et al.* 2004). Fat and CHO ingestion were associated with similar changes in BP but discrepant changes in blood glucose measurement. As in our previous study, there was no association between postprandial BP changes and

postprandial changes in blood glucose measurements (Visvanathan *et al.* 2004).

In conclusion, the ingestion of a high-fat drink resulted in a similar, although delayed, fall in BP and rise in HR to a CHO drink. Hence, the presence of both fat and CHO in the intestine results in a fall in BP and may contribute to the development of PPH in those at risk. The slower onset of the decrease in BP after fat than CHO may indicate that lipolysis of fat is a prerequisite for its blood pressure-lowering effect. If so, inhibition of fat digestion may ameliorate this fall in BP. This may have therapeutic importance and warrants further evaluation. The results of the present study also need to be confirmed in a population with confirmed PPH.

### Acknowledgements

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