Original Article

# Haemodynamic Effects of Fructose and Sucralose in Healthy, White Caucasian Males

Muhammad Qasim Memon, Terence Bennett, Ian A Macdonald


## ABSTRACT

**OBJECTIVE: To determine the acute haemodynamic changes produced by the ingestion of fructose or sucralose solutions in water.**
**SETTING: Medical School, University of Nottingham, Queen's Medical Centre, Nottingham, UK.**
**MATERIAL AND METHODS: Ten, healthy, non-smoking, white Caucasian males, aged between 18-40 years ingested solutions containing fructose (0.75 g/kg body weight) or sucralose dissolved in 500 ml of water, on separate days. Volunteers rested semi-recumbent on a bed in a thermo-regulated environment and a 'Finometer' was used to record beat-to-beat blood pressure (BP), cardiac output (CO), heart rate (HR), total peripheral resistance (TPR) and stroke volume (SV) for 30 min baseline, 5 min during ingestion and for 60 min post ingestion.**
**RESULTS: There was a significant rise in diastolic BP (DBP) and mean arterial pressure (MAP) from the baseline with fructose and sucralose drinks and in systolic BP (SBP) with the fructose drink ($P < 0.05$). Trends for a rise in systolic BP (sucralose), TPR, HR and CO (both fructose and sucralose) were observed. However, there was no statistically significant difference between the drinks containing either fructose or sucralose in the responses of the above variables.**
**CONCLUSION: Ingestion of fructose and sucralose increases BP. Sucralose produce effects that are similar but smaller than fructose.**


**KEY WORDS: Fructose, Sucralose, Blood pressure, Finometer.**

## INTRODUCTION

Consumption of fructose in the human diet has increased many-fold and constitutes around 8% of daily energy intake through items such as bakery products, soft drinks, fruit and fruit products[1,2]. Fructose has been in increasing use especially in soft drinks, which have become almost an integral part of the diet [1,3]. Fructose, as compared to glucose, does not stimulate insulin secretion or raise blood glucose levels [4] but its consumption is linked with detrimental cardiovascular effects and serious metabolic complications, especially in overweight and obese individuals [5]. In studies conducted on rats, it has been found that a high fructose diet resulted in hyperinsulinaemia, insulin resistance and a rise in systolic BP in male rats [6]. Animal studies also suggest that there is an increase in left ventricular weight in rats fed on a fructose-rich diet. Such a diet also increased angiotensin-II (AT-II) levels leading to an increase in TPR and BP with consequent left ventricular hypertrophy [7].

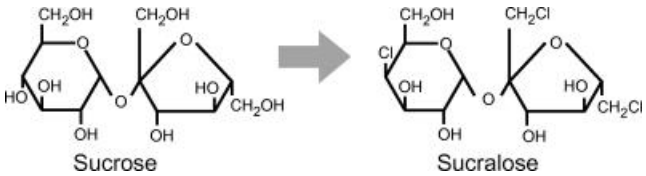
A recent study demonstrated a direct relationship between the acute consumption of fructose and an increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in humans. In addition, ingestion of fructose significantly increased heart rate and cardiac output, together with a rise in respiratory quotient and oxygen consumption [8].

High carbohydrate diets rich in fructose and sucrose (a disaccharide containing 1 molecule of fructose and 1 of glucose) have potential effects on the serum triacylglycerol (TG) level, tending to increase it. Once fructose is ingested and absorbed, it is converted to fructose-1-phosphate in the liver by the enzyme, fructokinase, and subsequently glycerol-3-phosphate is formed which becomes the backbone for the synthesis of the TGs [9]. HDL cholesterol concentrations, on the other hand, are decreased, predisposing an individual to cardiovascular disease (CVD) [10,11]. Hence, diets high in fructose increase serum TG levels especially in men, whereas women show no such change [12,13], presumably because of female sex hormones [14].

Sucralose, a synthetic sweetener, is a non-caloric intense sweetener with 600 times more sweetness than sucrose. It is manufactured by substitution of hydroxyl group by chloride in a sucrose molecule.

**FIGURE I: CONVERSION OF SUCROSE TO SUCRALOSE**

(Taken from British Nutritional foundation Nutrition Bulletin, 2003)




It is reportedly safe to consume, well-tolerated by hu-

mans [15] with no effects on blood glucose and insulin levels or diabetic control, as assessed by HbA1c [16,17]. Sucralose is poorly absorbed and does not accumulate or dissociate in the human body and is excreted mostly unchanged [18]. However, evidence suggests that when rats were fed on sucralose at a concentration of 50,000 ppm, i.e., equivalent to 5% of the diet, a number of effects were evident at 4-8 weeks [19]. These included decrease in food intake by the animal, decrease in body weight gain and in the weight or relative weight of various organs. The organs affected were thymus, brain, spleen, adrenals, pituitary and heart, presumably because of consumption of a non-nutritive substance along with a decrease in food intake. Gavage feeding of larger doses for longer periods resulted in enlargement of the caecum and an increase in kidney weight [19].

In order to control for the sweetness of fructose, its effects were compared to those of sucralose. Thus, this study looked at acute effects of fructose and sucralose on the CV system in healthy, white Caucasian males.

## MATERIALS AND METHODS

Ten healthy, non-smoking white Caucasian males were recruited for this study through recruitment posters in the Medical School, University of Nottingham and the Queen's Medical Centre, Nottingham. Subjects were aged 27 ± 2 years, weighed 77 ± 3 kg, and were 182 ± 2 cm tall; they were not on any regular medication. The study, of six months duration, was organized and funded by the School of Biomedical Sciences, University of Nottingham and approved by the University of Nottingham Medical School Ethics Committee.

Before coming for a medical screening session, volunteers were requested to avoid eating or drinking anything for at least 2h. The screening involved recording resting BP, height and weight, and a 6 lead electrocardiogram, and completing a medical screening questionnaire and consent form.

The study itself involved 2 visits. Subjects were advised to avoid sugar, sugar-containing soft drinks, bakery products, fruit or fruit products and strenuous exercise for 24 hr before each experimental visit and to use the lift to come to the haemodynamics laboratory.

Test-drinks were freshly prepared and volunteers were not told of the order of the drinks, which was randomized. Since the volunteers were of different weights, offering a fixed quantity of fructose to every volunteer could have resulted in GI upsets in some. Therefore, it was prudent to use fructose in quantities which would not cause GI upset but were sufficient enough to have effects, hence the fructose dose was calculated according to the body weight of the volunteer. Evidence suggests that 70g fructose is safe to consume and is fully absorbed [20]. Ten kg weight windows were created i.e., 65-74.9 kg, 75-84.9 kg and so on. A mid- point for each weight window was taken i.e., 70 kg for 65-74.9, 80 kg for 75-84.9; and a dose of 0.75 g/kg body weight fructose was calculated according to the weight window of the volunteer. (Personal experience indicated that a large amount, i.e., 1g/kg body weight may have caused some GI upset).

Taste-matching of the fructose containing drink and sucralose drink was done in preliminary studies by some staff of the School of Biomedical Sciences. The number of sucralose tablets was determined that taste-matched 52.5 g of fructose (i.e., corresponding to the 70 kg weight window). Employing simple calculations, the number of sucralose tablets to taste-match various measured quantities of fructose was then determined.

### *Protocol:*

Upon arrival, volunteers were requested to void their bladder before the experiment began. Subject's age, gender, height and weight were entered in the Finometer (FMS, Finapres Medical Systems BV, The Netherlands), which was switched to Research Mode.

During the experiment, the volunteer lay relaxed on a bed, semi-recumbent, in a thermo- regulated room and had the Finometer attached, with the finger cuff placed around the middle phalanx of the middle finger of the left hand, and the brachial arterial cuff around the ipsilateral upper arm providing continuous measurement of BP, HR and also an estimate of SV, CO, and TPR, beat- by- beat, non-invasively.

Following a baseline recording period of 30 min, volunteers were offered a drink, containing either fructose (Fruisana; Danisco Sweeteners OY. Kotka, Finland) or sucralose (Splenda; McNeil Nutritionals Ltd) dissolved in 500 ml of water and a teaspoonful of cooking lemon juice, to be consumed over 5 min. Post -drink recording then continued for 60 min. The same protocol was followed on a separate day (at least 3 days later but usually within one week) with the exception that the test drink differed from the one consumed on the first experimental visit (i.e., sucralose or fructose).

### *Data analysis:*

Collected data were down-loaded from the Finometer onto a remote PC using the 'Beat scope' software program. Data were averaged at 5 min intervals, resulting in 18 time points (0-17). The mean for time points 2, 3 and 4 was calculated for each variable, for each subject and for both visits and was used as the baseline. Time points 0, 1 and the time period when the sub-

jects consumed the test drink (i.e., time points 5 and 6) were not used. The subsequent time points were used as the post-drink period, i.e., 5 – 55 min post drink. Data were transferred to 'Biomed' (software program) data sheets which allowed statistical analysis to be performed using Quade, Friedman and Wilcoxon tests. CO, TPR and SV were factored by the weight of the subject and statistical significance was set as $P < 0.05$.

**FIGURE II: PROTOCOL FOR DATA ENTRY**

Mean

0-1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17

Baseline Post-drink period (5-55 min)

## RESULTS

Significantly higher baseline HR and CO values were recorded during the fructose experimental visits compared to the sucralose visits. Higher baseline TPR values were observed during the sucralose visits, compared to the fructose visits **(Table I)**. All other baseline variables were similar for the two visits.

*Haemodynamic changes with fructose and sucralose drinks:*

***Fructose:***

With the fructose drink there were significant increases from the baseline ($P < 0.05$) in DBP (by 8% i.e., 5mmHg), in SBP (by 6%, 7 mmHg) and in MAP (by 6%, 5 mmHg), HR and CI (cardiac index) did not change significantly **(Figure III(a); Table II)**. The peak increases in DBP and MAP occurred 5 min post drink, whereas the SBP peak value was observed 20 min after the consumption of the drink.

As can be seen in Fig III (a), SBP remained elevated above baseline for 50 min after the drink (all values statistically significant by Quade test, $P < 0.01$ or $< 0.001$). DBP and MAP were significantly elevated above baseline for 45 min (P value varied between $< 0.05$ and $< 0.001$). No sustained changes in TPR, SV, HR or CI were noted after the fructose drink **(Figure III (b))**.

***Sucralose:***

Similar changes in BP were observed after the sucralose drink, with peak increases from the baseline in DBP (7%) and in MAP (6%) ($P < 0.05$), occurring 5 min after the sucralose drink. The apparent rise in SBP (4%) 5 min post-drink was not significant **(Figure IV(a); Table II)**.

DBP and MAP were significantly increased above baseline (P values ranged from $< 0.05$ to $< 0.001$) for most of the post-sucralose period, the only exception being time points 35 and 40 min in case of DBP and time point 40 in the case of MAP.

The peak rise in HR (8%) was observed 5 min after the drink ($P < 0.05$), which was however not sustained. TPR, SV and CI did not change significantly after the sucralose drink **Figure IV(b)**.

***Comparison of fructose and sucralose effects:***

There were no statistically significant differences between responses to the two drinks **(Figure V(a;b))**. It can be seen in Fig 5 (a) that there was a trend for greater BP responses to fructose compared to sucralose. However, when a Wilcoxon signed rank test was used to compare the AUC responses to the drinks, there were no significant differences, with all P values being substantially greater than 0.1.

**TABLE I: BASELINE HAEMODYNAMIC VALUES FOR THE FRUCTOSE AND SUCRALOSE VISITS**
**Values are mean±SD**

| | Fructose | | Sucralose | |
|---|---|---|---|---|
| | **Baseline mean** | **SD** | **Baseline mean** | **SD** |
| SBP mmHg | 122 | 7 | 117 | 4 |
| DBP mmHg | 70 | 4 | 68 | 5 |
| MAP mmHg | 87 | 5 | 85 | 4 |
| HR beats/min | 56* | 8 | 50 | 6 |
| CO l/min | 6* | 0.78 | 5 | 0.57 |
| TPR r units | 0.9 | 0.09 | 1.0* | 0.09 |
| SV ml | 104 | 8.95 | 100 | 7.34 |

l/min = Litres/min; r units = Resistance units; * = Significant difference in baseline value ($P < 0.05$).

**TABLE II: PEAK % CHANGE AND ABSOLUTE CHANGE FROM BASELINE WITH FRUCTOSE AND SUCRALOSE DRINKS** Peak ΔTP* = time point of peak change post-drink (in min) Data are mean ± SEM

| | Fructose % | Units | Peak Δ TP* | Sucralose% | Units | Peak Δ TP |
|---|---|---|---|---|---|---|
| SBP mmHg | 6 ± 2 | 7 ± 2 | 20 | 4 ±1 | 5 ± 3 | 5 |
| DBP mmHg | 8 ± 2 | 5±2 | 5 | 7 ± 2 | 5 ± 2 | 5 |
| MAP mmHg | 6 ± 2 | 5 ± 2 | 5 | 6 ± 1 | 5 ± 2 | 5 |
| HR beats/min | 6±3 | 3±2 | 5 | 8±3 | 4±2 | 5 |
| TPR r units | 10 ± 5 | 0.07±0.03 | 35 | 4 ± 7 | 0.06±0.06 | 45 |

**FIGURE III (a): CHANGE FROM BASELINE OBSERVED IN SBP, DBP AND MAP WITH FRUCTOSE DRINK. VALUES AT '0' ARE THE MEAN BASELINE, WHILE THE SUBSEQUENT VALUES (5-55 MIN) ARE AFTER COMPLETING THE DRINK. DATA ARE MEAN ± SEM. %Δ = PERCENT CHANGE**

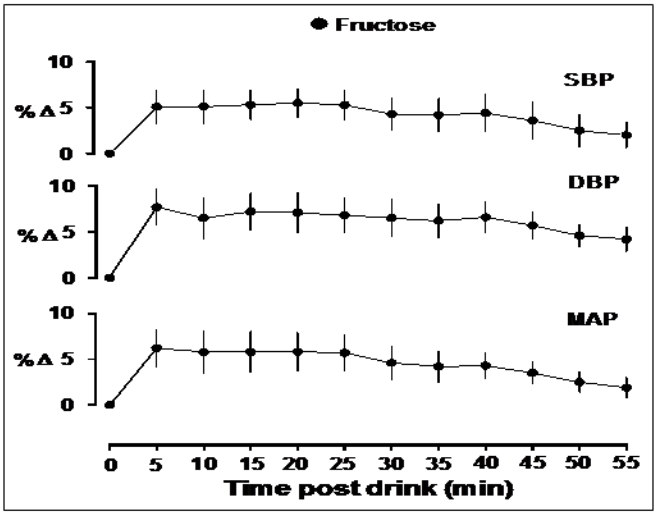



**FIGURE III (b): NO SUSTAINED CHANGES FROM BASELINE WERE OBSERVED IN TPR, SV, HR AND CI WITH FRUCTOSE DRINK. VALUES AT '0' ARE THE MEAN BASELINE, WHILE THE SUBSEQUENT VALUES (5-55 MIN) ARE AFTER COMPLETING THE DRINK. DATA ARE MEAN ± SEM. %ΔF = PERCENT CHANGE FACTORED (BY WEIGHT OF THE VOLUNTEER)**

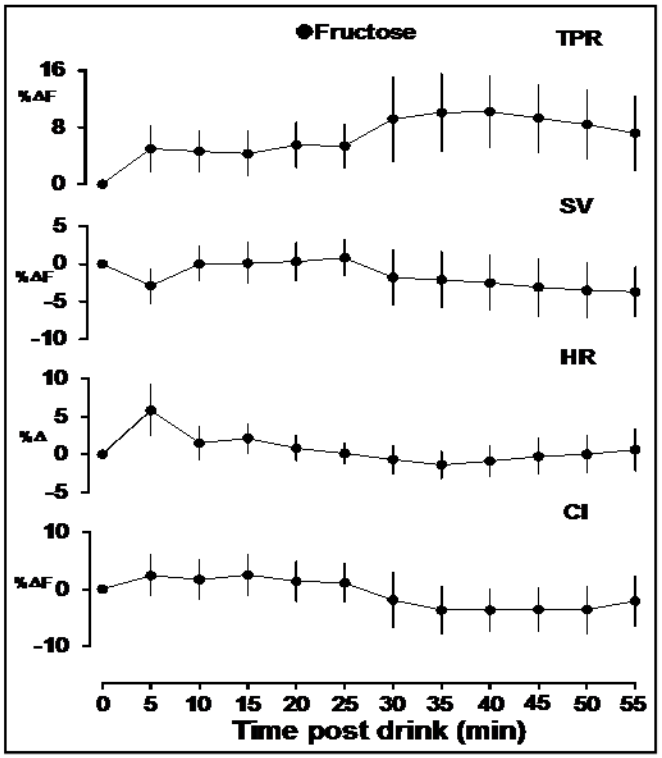



**FIGURE IV(a): CHANGE FROM BASELINE OBSERVED IN SBP, DBP AND MAP WITH SUCRALOSE DRINK. VALUES AT '0' ARE THE MEAN BASELINE, WHILE THE SUBSEQUENT VALUES (5-55 MIN) ARE AFTER COMPLETING THE DRINK. DATA ARE MEAN ± SEM. %Δ = PERCENT CHANGE**

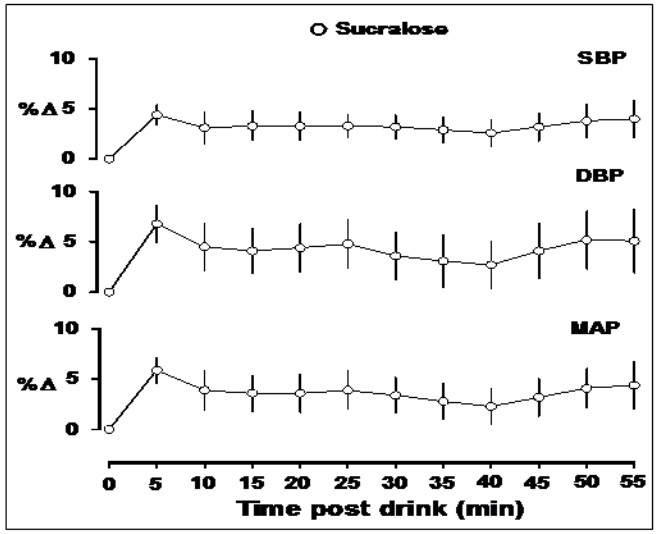



**FIGURE IV(b): SIGNIFICANT CHANGE FROM BASELINE WAS OBSERVED IN HR, WHEREAS TPR, SV AND CI DID NOT CHANGE WITH SUCRALOSE DRINK. VALUES AT '0' ARE THE MEAN BASELINE, WHILE THE SUBSEQUENT VALUES (5 -55 MIN) ARE AFTER COMPLETING THE DRINK. DATA ARE MEAN ± SEM. %ΔF = PERCENT CHANGE FACTORED (BY WEIGHT OF THE VOLUNTEER)**

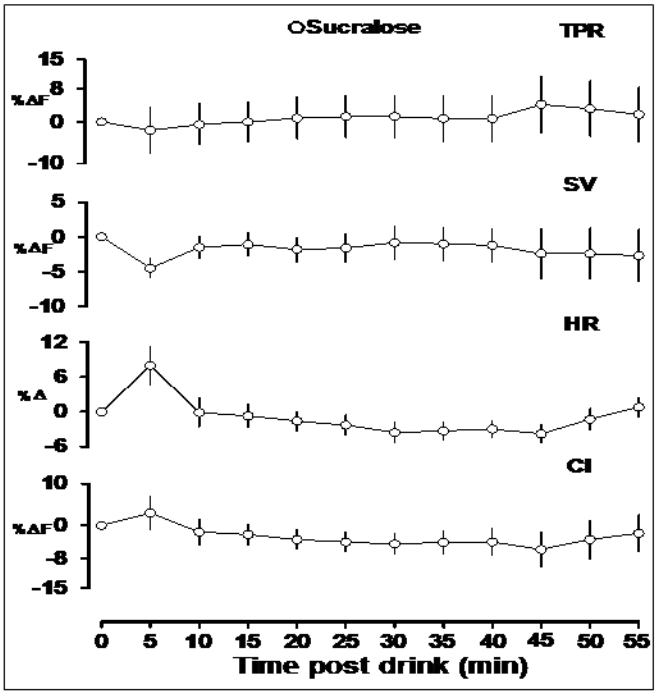


**FIGURE V(a): SHOWING NO SIGNIFICANT DIFFERENCE IN BP RESPONSES WITH FRUCTOSE AND SUCRALOSE DRINKS. VALUES AT '0' ARE THE MEAN BASELINE WHILE 5-55 ARE MINUTES AFTER COMPLETING THE DRINK. DATA ARE MEAN; SEM VALUES ARE OMITTED FOR CLARITY OF THE FIGURE AND BECAUSE THERE ARE NO DIFFERENCES BETWEEN THE RESPONSES. %Δ = PERCENT CHANGE**

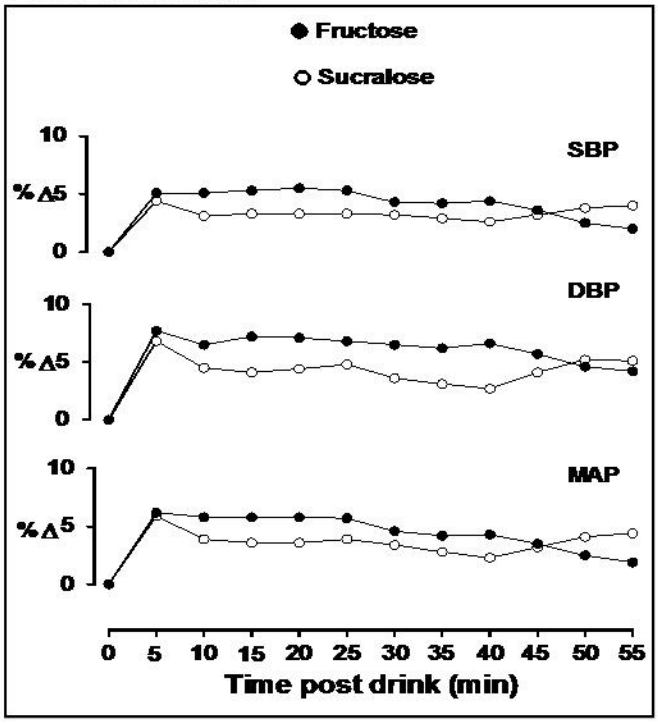
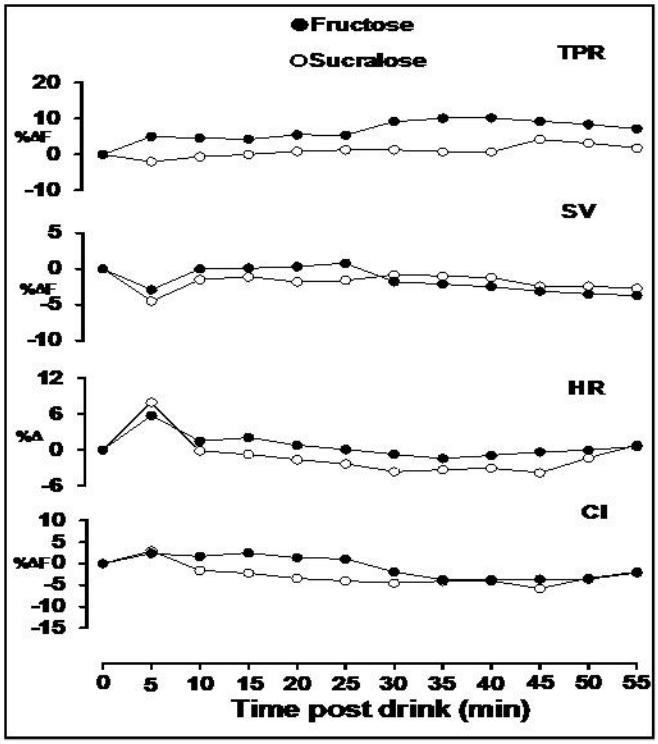



**FIGURE 5 (b): SHOWING NO SIGNIFICANT DIFFERENCE IN RESPONSES WITH FRUCTOSE AND SUCRALOSE DRINKS. VALUES AT '0' ARE THE MEAN BASELINE WHILE 5-55 ARE MINUTES AFTER COMPLETING THE DRINK. DATA ARE MEAN; SEM VALUES ARE OMITTED FOR CLARITY OF THE FIGURE AND BECAUSE THERE ARE NO DIFFERENCES BETWEEN THE RESPONSES. % ΔF = PERCENT CHANGE FACTORED (BY WEIGHT OF THE VOLUNTEER)**




## DISCUSSION

Adverse effects of dietary sugars on CV and metabolic systems have been seen in both human and animal studies [8,11,21,22]. Excessive and long-term use of fructose, especially in food items containing high-fructose corn syrup, may result in insulin resistance, hypertension, and hypertriglyceridaemia [21,23]. The present study employed a randomized, single blind, cross-over design and used a non-invasive method to assess the acute CV effects of fructose ingestion. Using the Finometer, beat-to-beat CV parameters were recorded non-invasively. The effects were compared with the responses to sucralose, which was used as a sweet, non-nutritional control. Subjects rested on a bed, semi-recumbent, so as to minimize any discomfort that could have been caused if they were made to sit in a chair for the study duration [8]. After oral ingestion, fructose reaches a peak serum level in 30-60 min [24]; keeping this in view the post-drink recording time was set as 60 min. The quantity of fructose was carefully determined to avoid any possible GI side effects that may have occurred affecting the volunteer or the experiment.

It was found that there was a rise in DBP and MAP with consumption of both the drinks. SBP rose significantly with fructose, but not with sucralose, although a trend for such a rise was observed. These changes were evident and usually maximal 5 min post drink except for SBP (fructose) when the peak change happened 20 min after the drink was consumed. There was a significant but transient rise in HR observed 5 min after the sucralose drink. TPR, SV and CI did not change from baseline with either drink. The fact that the BP changes occurred fairly quickly and after both fructose and sucralose suggests that they may have been initiated either by the act of drinking or by the sweet taste. Unfortunately, a water control was not included and so we cannot determine which factors may have influenced the responses. There was a trend for the fructose responses to be larger than those to sucralose and the peak SBP response occurred later than that to sucralose, suggesting that the absorption of fructose may have contributed to the response.

There could be a number of possible mechanisms contributing to any possible increase in BP after fructose ingestion. Chronic ingestion of fructose in rats produced an increase in AT-II level but no change in BP [22] whereas fructose feeding in mice increased AT-II and SBP [25]. In the latter study, this rise in BP was associated with increased sympathetic activity, but no change in baroreflex sensitivity (BRS). By contrast Brown *et al.* (2008) showed acute fructose ingestion by human subjects was associated with an increased BP and cardiac sympathetic activity and a reduction in BRS. Research also suggests possible endothelial dysfunction ensuing from production of free radicals [26] and attenuated release of nitric oxide (NO) [27] in rats fed a fructose rich diet. Although fructose was used acutely in this study, this might have played a role in the failure of vasculature to relax, thereby increasing resistance in the system. A trend for a rise in TPR, although non-significant, on ingestion of fructose was observed that may be reflective of absent or defective vasodilatation. Lack of insulin secretion in response to fructose ingestion [28] and its role in producing vasodilatation may also contribute to the rise in BP. It is likely that ingestion of glucose may activate the SNS, which would normally increase BP, but glucose also stimulates insulin release, which could induce vasodilatation and prevent a change in BP. Thus, ingestion of a sweet drink may enhance SNS activity which in the absence of insulin response (e.g., fructose) leads to an increase in BP. Furthermore, sucralose would also not lead to an insulin response, so such a mechanism would explain similarities in effect of fructose and sucralose on TPR if the initial effect is due to the sweet taste. Activation of the SNS in producing a rise in BP has been shown to be of importance, as in fructose fed rats sympathectomy resulted in abrogation of development of hypertension [29]. Evidence suggests that thermogenesis, i.e., the increase in energy expenditure after nutrient ingestion, is greater for fructose than for the equivalent amount of glucose [30] and as the SNS is a regulator of adaptive thermogenesis, i.e., non-shivering thermogenesis and dietary thermogenesis [31,32], it is possible that the SNS is activated by the consumption of fructose.

This study differed from the one conducted by Brown *et al.*(2008) in various ways. Their volunteers, 9 males and 6 females, sat in a chair, with CV and haemodynamic parameters recorded using finger plethysmography for BP, electrocardiography for HR and impedance cardiography for SV. The CV effects of ingestion of water and 60 g fructose and/or glucose (used as a standardized dose) dissolved in water were determined with 10 ml of lemon juice added to the drinks. Data were averaged at 15 min intervals. In contrast, in the present study 10 volunteers, all male, rested in bed and the Finometer recorded beat-to-beat CV parameters. The quantity of fructose was determined according to the body weight of the volunteer to avoid any untoward effects (i.e., GI upset) and that of sucralose to match the sweetness of the fructose used. A teaspoon (5 ml) of lemon juice was used. Data were averaged at 5 min enabling to monitor any changes more closely.

A transient rise in HR was observed 5 min after ingestion of the two drinks with a corresponding, statistically non-significant, fall in SV. This may be reflective of a continuation of the change that took place due to the drinking process and associated movement of the body. A transient statistically non-significant rise in CI was also observed 5-15 min post drink, in the case of fructose, but overall there were no substantial changes in CI after fructose or sucralose which is consistent with the results presented by Brundin and Wahren, who found no change in cardiac output 60 min after fructose ingestion in healthy, male volunteers [33].

There is little or no evidence suggestive of CV effects of sweeteners, such as sucralose, but the present study produced results showing such effects. Sucralose appeared to have CV effects that were similar in direction but smaller in magnitude than the values recorded with fructose. It is concluded that consumption of fructose and sucralose increases BP. Sucralose may produce effects that are smaller in magnitude as compared to fructose. However, further studies with more statistical power and with non-sweetened water as a control are required for this to be said more confidently.

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*AUTHOR AFFILIATION:*

**Dr. Muhammad Qasim Memon** *(Corresponding Author)*
Medical Research Centre
Liaquat University of Medical and Health Sciences,
Jamshoro, Sindh-Pakistan.
E-mail: memon.qasim@lumhs.edu.pk

**Prof. Terence Bennett**
Centre for Integrated Systems Biology and Medicine,
School of Biomedical Sciences,
The University of Nottingham, Nottingham, UK.

**Prof. Ian A Macdonald**
Centre for Integrated Systems Biology and Medicine,
School of Biomedical Sciences,
The University of Nottingham, Nottingham, UK.