FLOW-MEDIATED VASODILATATION;
EFFECT ON CARDIOVASCULAR FUNCTION WITH AND WITHOUT FRUCTOSE AND SUCRALOSE IN HEALTHY, WHITE EUROPEAN MALES

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ABSTRACT: Objective: To assess whether flow-mediated dilatation (FMD) affected cardiovascular (CV) parameters after consuming fructose or sucralose. **Data source:** Finometer. **Design of study:** Randomized, cross-over, single-blind design. **Setting:** School of biomedical sciences, University of Nottingham, UK. **Period:** July, 2009. **Materials and methods:** Ten healthy, white European males were studied twice. A Finometer continuously recorded CV parameters. Following 30 min baseline, a BP cuff, around mid-point of right arm was inflated 50 mmHg above Systolic BP for 5 min. Upon deflation, FMD measurements were made. Volunteers then consumed 500 ml of fructose or sucralose containing drink. Forty min later, 2nd FMD was done. **Results:** Pre-fructose FMD: SBP increased in late-occlusion and post-occlusion period (POP). HR and CO decreased and SV and TPR increased during POP (P < 0.01 & 0.001). Post-fructose: DBP rose (2 mmHg; P = 0.04) during occlusion; HR (P = 0.02) and CO (P < 0.05) increased whereas TPR decreased (0.023; P < 0.04) in recovery period. Pre-sucralose: SBP, DBP and MAP increased in POP and thereafter. Decreased HR and CO and increased TPR and SV were noted (P < 0.01 & 0.001). Post-sucralose: SBP rose in POP and thereafter (5 mmHg; P < 0.01); MAP (3 mmHg; P = 0.04) and SV (P = 0.05) increased in POP. **Conclusions:** Attenuated BP and TPR, after fructose, indicate fructose's possible vascular effects.

Key words: Fructose; Cardiovascular Physiological Phenomena; Endothelium

INTRODUCTION

The capacity of blood vessels to react to physical and chemical stimuli or to increased shear stress, by increasing flow through dilatation, is known as flow-mediated dilatation (FMD). Measuring the FMD response is used to assess endothelial function and involves applying an arterial occlusion cuff (typically for 5 min) on lower arm and then measuring the reactive hyperaemia and change in vessel diameter of the brachial artery using ultrasound[1].

Acute fructose consumption is reported to have potentially detrimental effects on human health[2,3]. Animal studies suggest that chronic fructose ingestion may stimulate release of angiotensin-II in rats and mice[4,5] and results in hyperinsulinaemia leading to oxidative stress, reducing the amount of nitric oxide (NO) in the vasculature and thus impairing FMD[6-8]. Evidence suggests that inflation of the occlusion cuff (as is required for the FMD measurement procedure) results in an increase in BP and total peripheral resistance (TPR) and decrease in SV[9]. The aim of the present study was to assess whether the FMD procedure affected the CV response to acute consumption of fructose and sucralose in healthy, white European males, as this could have an impact in any studies seeking to assess the effects of food components on the FMD response.

MATERIALS AND METHODS
Ethical approval

This study was conducted and funded by the School of Biomedical Sciences, University of Nottingham, UK, approved by the University's Medical School Ethics Committee and conformed to standards set by the Declaration of Helsinki.

Ten healthy, non-smoking, white, European males were medically screened and recruited for this study; their written consent was obtained. Volunteers fasted overnight before experiments and avoided sugar-containing soft drinks, bakery

products, fruit or fruit products and exercise for 24 hr before the experiments. All experiments took place, at the same time, in the morning.

Protocol

Upon arrival, volunteers voided their bladder, were weighed and offered 3 ml / kg body weight water to ensure adequate hydration. They rested on a bed, semi-recumbent, in a thermo-regulated room. By placing pillows in appropriate positions, their arms were positioned at the same height relative to the heart. After 30 min rest, the Finometer (FMS, Finapres Medical Systems, The Netherlands) arm cuff was attached to their left upper arm with the finger cuff wrapped around the middle phalanx of left hand's middle finger. The Finometer then generated CV data throughout the study period, which started with a 30 min baseline period.

A few min before the end of 30 min baseline, a BP cuff was applied on right forearm of the volunteer, over a single layer of 'soffban' padding. At the end of the baseline period, the cuff was inflated to 50 mmHg above the volunteer's systolic BP and remained inflated for 5 min; at deflation, blood velocity and brachial arterial diameter measurements (FMD) were made for the next 90 sec employing an ultrasound machine (Toshiba Diagnostic Ultrasound System – Model SSA-770A; Toshiba Medical Systems Corporation, Japan); the cuff was then released.

After 15 min, volunteers consumed (over 5 min) 500 ml of a lemon flavoured drink which contained either 0.75 g / kg body weight fructose, or sucralose (taste-matched with fructose drink). Post-drink recordings continued for next 40 min followed by 2nd five min occlusion and subsequent FMD measurements. Data collection continued for another 15 min, all equipment was then removed and the experiment ended. Same protocol was followed on a separate day with the exception that the drink was different from the one consumed on the first experimental visit.

Data analysis

Collected data were averaged over 2 min, 1 min and 20 sec intervals at different points within the

protocol. Data averaged at 2 min (3 values each, representing 6 min) were used for the end of the baseline period and post FMD period; 1 min averaging was used for the occlusion time (4 values each representing 4 min) and 20 sec intervals for the FMD i.e., post occlusion period (POP) (5 values each representing 100 sec). Period when the subjects consumed test-drink and data for the last min of occlusion were not included on the data sheets. Statistical analysis was 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 $P < 0.05$.

RESULTS

Comparison of pre and post-drink baseline values of fructose and sucralose

Pre-drink baseline values were similar on two occasions. SBP, DBP and MAP were noted to be higher post-fructose and post-sucralose drinks than the pre-drink baseline values (P ranged between 0.04 and 0.01). A trend for higher HR (post-fructose and-sucralose) was also noted (P = 0.05). Higher CO was recorded after the fructose drink (P < 0.05); CO did not significantly change after sucralose, but the change with fructose was not different from the change with sucralose (Table I).

Effect of FMD on CV variables

Effects of FMD on the CV variables, pre and post fructose and sucralose consumption, are shown in Table II and III respectively.

Comparison of effects of FMD without fructose and sucralose on the CV variables

No significant difference in the effect of the FMD procedure was noted between the two experiments (P > 0.05; Wilcoxon signed rank test) (Figure 1).

Comparison of effects of FMD with fructose and sucralose on the CV variables

No significant difference in the effect of FMD was noted between the two drinks (P > 0.05; Wilcoxon signed rank test) (Figure 2).

	Fructose		Sucralose	
	Pre-drink	**Post drink**	**Pre-drink**	**Post drink**
SBP, mmHg	125 ± 2	134 ± 2**	126 ± 3	131 ± 2**
DBP, mmHg	71 ± 2	75 ± 2**	72 ± 2	75 ± 2**
MAP, mmHg	91 ± 2	96 ± 2**	91 ± 2	95 ± 2**
HR, bpm	63 ± 3	67 ± 3*	62 ± 2	65 ± 3*
CO, L / min	6.6 ± 0.3	7.4 ± 0.3**	6.5 ± 0.27	7.0 ± 0.3
TPR, r units	0.855 ± 0.04	0.802 ± 0.04	0.856 ± 0.03	0.864 ± 0.05
SV, mL	105 ± 5	111 ± 4	106 ± 3	105 ± 4

Table-I. Values for baseline CV variables before and after fructose and sucralose drinks were consumed. Significant difference was noted between pre and post drink values; Data are mean ± SEM.
$*P = 0.05;**P < 0.05.$

Pre-fructose FMD				Post-fructose FMD			
Variable	**Units**	**Δ%**	**Δ Time point**	**Variable**	**Units**	**Δ%**	**Δ Time point**
SBP, mmHg	↑4 ††	3%	Late occl	SBP	NC	NC	NC
	↑5 ††	4%	Early POP				
DBP, mmHg	NC	NC	NC	DBP	↑2***	3%	Occl
HR, bpm	↓4 †††	6%	POP	HR	↑3†	4%	RP
CO, mL	↓285 ††	4%	POP	CO	↑300**	4%	RP
SV, mL	↑4 ††	5%	POP	SV	NC	NC	NC
TPR, units	↑0.042 ††	5%	POP	TPR	↓0.023****	3%	RP

Table-II. Effects of FMD on CV variables, pre and post fructose.
$** = P < 0.05;$ $*** = P = 0.04;$ $**** = P < 0.04;$ $† = P = 0.02;$ $†† = P < 0.01;$ $††† = P < 0.001$
POP = Post occlusion period; NC = No change; RP = Recovery Period; Occl = Occlusion

When Area Under the Curve of pre and post-fructose and pre and post-sucralose experiments were compared, no difference was noted in both cases ($P > 0.05$). However, MAP was noted to be higher after sucralose was consumed ($P = 0.05$).

Pre-sucralose FMD				Post-sucralose FMD			
Variable	**Units**	**Δ%**	**Δ Time point**	**Variable**	**Units**	**Δ%**	**Δ Time point**
SBP, mmHg	↑5††	4%	POP	SBP	↑5††	4%	POP/RP
	↑6††	4%	RP				
DBP, mmHg	↑3†††	3%	POP	DBP	NC	NC	NC
	↑3††	4%	RP				
MAP, mmHg	↑4††	4%	POP/RP	MAP	↑3***	3%	POP
Hrm bpm	↓5†††	8%	POP	HR	NC	NC	NC
CO, mL	↓400††	6%	POP	CO	NC	NC	NC
SV, mL	↑4†††	3%	POP	SV	↑2.5*	3%	Late POP
TPR, units	↑0.056†††	6%	POP	TPR	NC	NC	NC

Table-III. Effects of FMD on CV variables, pre and post sucralose.
$* = P = 0.05;*** = P = 0.04; †† = P < 0.01; ††† = P < 0.001$
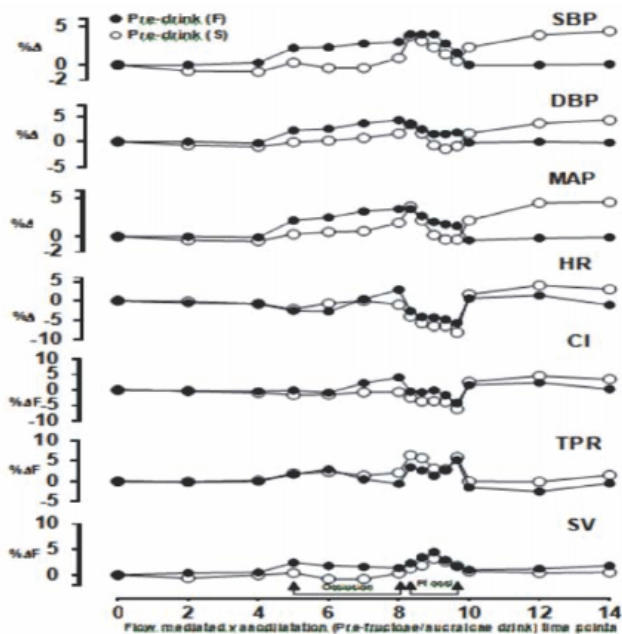*POP = Post occlusion period;   NC = No change;   RP = Recovery Period*

Figure 1: No difference was noted between two experiments (P > 0.05). Data are mean / SEM.
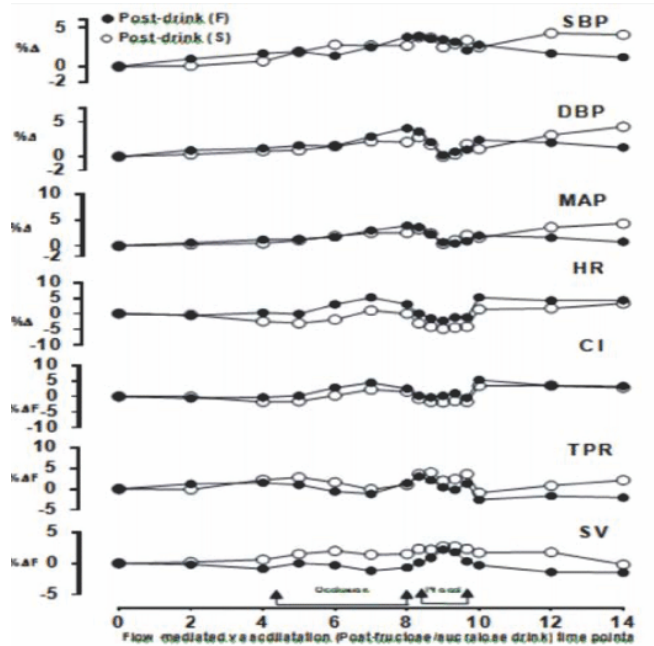*Pt occl = Post occlusion; %Δ = Percent change; %ΔF = Percent change factored.*

Figure 2: No difference was noted for two experiments (P > 0.05). Data are mean / SEM

DISCUSSION

Present study employed a randomized, cross-over, single-blind design and used non-invasive techniques to assess effects on the CV system of forearm occlusion with and without acute consumption of fructose and sucralose. This occlusion protocol is a part of the method used to asses forearm endothelial function by measuring FMD, but it was thought important to assess the potential effects of the occlusion protocol on haemodynamic variables, and whether these were modulated by fructose ingestion, which is the basis of this paper.

It was found that acute consumption of fructose after first FMD procedure resulted in an increase in CO, a trend for an increase in HR and an unchanged TPR. There are two possible explanations for a high CO after the first FMD and fructose ingestion. Firstly, volunteers were offered an extra quantity of water before the experiment, increasing extra-cellular volume. Secondly, a rise in HR and CO, although non-significant, was noted during the pre-drink occlusion, indicating possible SNS stimulation and release, particularly of, noradrenaline, which in small amounts

has been shown to induce vasodilatation and increase blood flow in the thyroid and skeletal muscle[10,11]. Evidence also exist that vasodilatation following FMD may continue for at least 20 min after the occlusion is released[12]. During the 2nd occlusion and in immediate POP after fructose consumption, no significant changes were noted in CV parameters except for DBP rising significantly during occlusion. In the subsequent recovery period, significant increases in HR and CO and a decrease in TPR were noted. It is likely that such decrease in TPR following deflation of the cuff after fructose consumption may have been due to fructose, because such a phenomenon was not evident from a similar study in which no fructose was used and where an increase in TPR was found in POP[9]. In the pre-fructose FMD an increase in TPR, although transient, was noted in POP and values in the recovery period were not different from the baseline values. The decrease in TPR was also not evident after FMD with and without sucralose; hence it is probable that fructose resulted in a decrease in TPR when it was consumed between the baseline and post-fructose FMD. It was further determined that there were greater decrease in

BP after fructose compared to when no fructose was consumed. SBP and TPR increased by 4% and 5%, respectively, in the early POP without fructose but there was no effect on SBP during and after the previously mentioned period when fructose was consumed. It was noted, in the case of sucralose, that SBP, DBP, MAP and TPR, transiently but significantly, increased by 4%, 3%, 4% and 6%, respectively, in POP without sucralose and there were significant elevations in SBP (4%) and MAP (3%) in the same period after sucralose was consumed. The results discussed so far may support the hypothesis that fructose has some vascular effects and these effects become apparent when vasodilatation takes place. This further leads to the hypothesis that there is a fructose interaction with endothelium-derived relaxing factors, or more specifically with NO.

CONCLUSIONS

The present study found that FMD may result in prolonged vasodilatation. The release of occlusion resulted in decreased TPR and attenuated increase in BP, specifically after fructose is indicative of possible vascular effects of fructose.
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