american physiological society

AMERICAN JOURNAL OF PHYSIOLOGY
REGULATORY, INTEGRATIVE AND COMPARATIVE PHYSIOLOGY

Am J Physiol Regul Integr Comp Physiol 320: R641–R652, 2021.
First published February 3, 2021; doi:10.1152/ajpregu.00310.2020

RESEARCH ARTICLE

Cardiovascular and Renal Integration

Sugar-sweetened soft drink consumption acutely decreases spontaneous baroreflex sensitivity and heart rate variability

Christopher L. Chapman,[1,2] Emma L. Reed,[1,2] Morgan L. Worley,[1,3] Leonard D. Pietrafesa,[1] Paul J. Kueck,[1] Adam C. Bloomfield,[1] Zachary J. Schlader,[3] and Blair D. Johnson[1,3]

[1]*Center for Research and Education in Special Environments, Department of Exercise and Nutrition Sciences, University at Buffalo, Buffalo, New York;* [2]*Department of Human Physiology, University of Oregon, Eugene, Oregon; and* [3]*Department of Kinesiology, School of Public Health, Indiana University, Bloomington, Indiana*

Abstract

In healthy humans, fructose-sweetened water consumption increases blood pressure variability (BPV) and decreases spontaneous cardiovagal baroreflex sensitivity (cBRS) and heart rate variability (HRV). However, whether consuming commercially available soft drinks containing high levels of fructose elicits similar responses is unknown. We hypothesized that high-fructose corn syrup (HFCS)-sweetened soft drink consumption increases BPV and decreases cBRS and HRV to a greater extent compared with artificially sweetened (diet) and sucrose-sweetened (sucrose) soft drinks and water. Twelve subjects completed four randomized, double-blinded trials in which they drank 500 mL of water or commercially available soft drinks matched for taste and caffeine content. We continuously measured beat-to-beat blood pressure (photoplethysmography) and R-R interval (ECG) before and 30 min after drink consumption during supine rest for 5 min during spontaneous and paced breathing. BPV was evaluated using standard deviation (SD), average real variability (ARV), and successive variation (SV) methods for systolic and diastolic blood pressure. cBRS was assessed using the sequence method. HRV was evaluated using the root mean square of successive differences (RMSSD) in R-R interval. There were no differences between conditions in the magnitude of change from baseline in SD, ARV, and SV ($P \geq 0.07$). There were greater reductions in cBRS during spontaneous breathing in the HFCS (-3 ± 5 ms/mmHg) and sucrose (-3 ± 5 ms/mmHg) trials compared with the water trial ($+1 \pm 5$ ms/mmHg, $P < 0.03$). During paced breathing, HFCS evoked greater reductions in RMSSD compared with water (-26 ± 34 vs. $+2 \pm 26$ ms, $P < 0.01$). These findings suggest that sugar-sweetened soft drink consumption alters cBRS and HRV but not BPV.

blood pressure; blood pressure variability; fructose; parasympathetic activity; soda

INTRODUCTION

Long-term, daily consumption of sugar-sweetened soft drinks is associated with an increased risk of cardiometabolic diseases, stroke, and chronic kidney disease (1–3). To date, however, few laboratory-controlled studies have examined the acute cardiovascular response to sugar-sweetened soft drink consumption. Thus, it is unclear if the epidemiological data indicating increased health risks are directly caused by sugar-sweetened soft drinks or if their consumption is reflective of a combination of other factors that reduce overall health (e.g., increased caloric intake, environmental/socioeconomic factors).

Cardiovascular risk profile can be assessed using calculations of blood pressure variability, cardiovagal baroreflex sensitivity, and heart rate variability. Blood pressure variability is an index of the fluctuations in successive blood pressure measurements and can be calculated in laboratory-controlled studies using beat-to-beat measures of blood pressure (e.g., finger photoplethysmography) or in the clinic on a within- or between-day basis (4). Elevations in blood pressure variability are associated with cardiovascular and kidney damage (4), hypertension (5), and increased cardiovascular mortality (6, 7). In addition, blood pressure variability can be influenced by changes in cardiovagal baroreflex sensitivity (8). Decreases in cardiovagal baroreflex sensitivity may increase blood pressure variability (9) and are associated with other deleterious health outcomes (10). Some cardiovagal baroreflex sensitivity techniques assess the reflex control of heart rate in response to pharmacologically stimulated changes in blood pressure, or it can be calculated from beat-to-beat measures of systolic blood pressure and R-R interval (i.e., spontaneous cardiovagal baroreflex sensitivity) (11). Autonomic cardiac control can be quantified using heart rate variability techniques (12).

Correspondence: B. D. Johnson (bj33@indiana.edu).
Submitted 3 November 2020 / Revised 15 January 2021 / Accepted 2 February 2021

Reductions in heart rate variability, which are indicative of a lower relative cardiac parasympathetic activity, are associated with increased cardiovascular events and mortality in some populations, including those with cardiovascular disease (13, 14).

The composition of sugar-sweetened soft drinks, which commonly are caffeinated and sweetened with high-fructose corn syrup (HFCS), may present several variable physiological challenges that increase cardiovascular risk due to the high beverage osmolality and the fructose and caffeine content. For instance, the act of drinking a bolus of fluid may modify these processes, as consuming an ∼500-mL bolus of water has been reported to increase spontaneous cardiovagal baroreflex sensitivity and heart rate variability (15). In contrast, there is evidence that consuming a 500-mL bolus of fructose-sweetened water increases blood pressure variability and decreases cardiovagal baroreflex sensitivity and heart rate variability in healthy adults (16). Sugar-sweetened soft drinks are also commonly caffeinated with contents ranging between 0 and 80 mg of caffeine per 500-mL serving (17). Caffeine elicits variable cardiovascular effects that are modified by several factors including dose, an individual's sensitivity to caffeine, habituation of the consumer, and health status (18). Although sugar-sweetened soft drinks have a high beverage osmolality (19), we have previously observed modest increases in plasma osmolality of ∼2 mosmol/kg within 30 min of consuming HFCS-sweetened (beverage osmolality of ∼850 mosmol/kg) and sucrose-sweetened (beverage osmolality of ∼730 mosmol/kg) soft drinks (19). Similar increases in plasma osmolality (∼3 mosmol/kg) induced by hypertonic saline have not demonstrated alterations in spontaneous cardiovagal baroreflex sensitivity or heart rate variability (20). We have found that copeptin, a surrogate marker of vasopressin, increases following acute HFCS-sweetened soft drink consumption (19). However, it also does not appear that vasopressin explains the reduction in spontaneous cardiovagal baroreflex sensitivity following fructose-sweetened drinks because vasopressin sensitizes the arterial baroreceptors (21).

In a recent study (19), we observed that consuming a 500-mL bolus of a HFCS-sweetened soft drink increased both resting and sympathetically mediated increases in vascular resistance in the kidneys, which occurred alongside increases in circulating uric acid and copeptin. These findings were independent of caffeine content because all of the experimental beverages had the same caffeine content and were independent of increases in plasma osmolality, as both the HFCS- and sucrose-sweetened soft drinks elicited an ∼2 mosmol/kg increase in plasma osmolality. These responses to the HFCS-sweetened soft drink (19) and the previously mentioned physiological responses that occur to the various ingredients in sugar-sweetened soft drinks (15, 16, 18, 21, 22) suggest that sugar-sweetened soft drinks may alter cardiovascular control. With this background, the aim of this study was to examine how sugar-sweetened soft drinks, specifically those that are caffeinated and sweetened with HFCS, may impact blood pressure variability, cardiovagal baroreflex sensitivity, and heart rate variability. We collected beat-to-beat cardiovascular measurements during our previous work (19) to address this secondary aim. As such, we tested the hypotheses that HFCS-sweetened soft drink consumption increases blood pressure variability and decreases spontaneous cardiovagal baroreflex sensitivity and heart rate variability compared with artificially and sucrose-sweetened soft drinks and water.

METHODS

The experimental protocol and data presented herein are secondary outcomes of study 2 from our previous publication (19).

Subjects

In this study, 12 healthy, nonobese adults (10 males and 2 females) who reported to be casual consumers of soft drinks (weekly consumed soft drink volume: 346 ± 481 mL) completed the study. Subject characteristics were as follows: age: 24 ± 4 yr, height: 177 ± 8 cm, weight: 76 ± 9 kg, and body mass index: 24.1 ± 3.1 kg/m^2. Subjects were not caffeine naïve and consumed 51 ± 74 mg of caffeine per day based on dietary food logs. After being fully informed of the experimental procedures and possible risks associated with the study, subjects provided written consent. Subjects self-reported to be nonsmokers and physically active. In addition, subjects self-reported to be free from any known cardiovascular, metabolic, kidney, or neurological diseases. Female subjects self-reported to be normally menstruating and not using hormonal contraceptives. A urine pregnancy test was used before every visit to confirm that females were not pregnant. In addition, female subjects were tested in the first 10 days following menstruation. Subjects provided written consent after being fully informed of all procedures and risks associated with the study. This study was approved by the Institutional Review Board at the University at Buffalo and performed in accordance with the standards set by the latest revision of the Declaration of Helsinki, except for registration in a database.

Instrumentation and Measurements

Nude body weight and height were measured using a stadiometer and scale (Sartorius, Bohemia, NY). Duplicate measurements of urine specific gravity were used to confirm hydration status with a refractometer (Atago, Bellevue, WA) at the beginning of each study visit. Twenty-four-hour food and beverage logs were collected and analyzed using online software (myfitnesspal, Under Armour, Baltimore, MD), and we reported no differences in diet and fluid intake across the study (19). Heart rate was continually measured using a 3-lead ECG (DA100C, Biopac Systems, Goleta, CA). Changes in beat-to-beat blood pressure over time were measured via the Penaz method (Finometer Pro, FMS, Amsterdam, The Netherlands). Blood pressure obtained from the Finometer was calibrated to brachial artery blood pressure using the return-to-flow technique with an upper arm cuff (23). Heart rate and blood pressure data were sampled at 1,000 Hz using a data acquisition system (Biopac MP150, Goleta, CA). Plasma osmolality was measured in duplicate via freezing point depression (model 3250, Advanced Instruments, Norwood, MA). Sodium, potassium, chloride, and uric acid in the serum were measured via standard clinical techniques by Kaleida Health, Department of Pathology and Laboratory Medicine (Williamsville, NY). A commercially available fructose ELISA kit (LifeSpan

BioSciences, Seattle, WA) was used to measure serum fructose. Serum copeptin was measured using a human copeptin ELISA kit (LifeSpan Biosciences).

Experimental Protocol

Subjects completed four randomized, double-blinded, crossover experimental trials. Subjects completed a control trial consisting of consuming filtered tap water (water trial) and three soft drink trials that were matched for taste and caffeine content but differed based on the type of sweetener used: an artificial sweetener [Diet Mountain Dew, PepsiCo, Purchase, NY (diet trial)], sucrose [Mountain Dew Throwback, PepsiCo, Purchase, NY (sucrose trial)], or HFCS [Mountain Dew, PepsiCo, Purchase, NY (HFCS trial)]. The soft drinks were decarbonated for 48 h to eliminate the acoustic shadowing of the renal vasculature in our previous study (19), which interfered with our ability to obtain Doppler ultrasound measurements of renal hemodynamics if the drinks were carbonated. This study was designed to provide direct insights into the cardiovascular response to soft drinks by specifically using the same commercially available soft drink sweetened by various ingredients that might impact cardiovascular function. A previous study reported that the HFCS-sweetened soft drink contains ~60% fructose and ~40% glucose (24). The HFCS- and sucrose-sweetened soft drinks were matched for taste, caffeine content, and total calories, and both beverages had high osmolality (19). Thus, the relatively higher fructose content of the HFCS-sweetened soft drink allowed us to isolate the effects of increasing the fructose content of the soft drink versus the sucrose-sweetened soft drink, which was composed of 50% glucose and 50% fructose. Details of the experimental drinks are presented in Table 1.

Subjects arrived at the laboratory at the same time of day for each of their four study visits. They reported to the laboratory with instructions to abstain from exercise, caffeine, and alcohol for 12 h and food for 3 h. Subjects kept a food and beverage log for the 24 h preceding each experimental visit and were instructed to keep dietary practices the same before each visit. Upon arrival to the laboratory, subjects completely voided their bladder into a collection urinal. After confirming a euhydrated status via urine specific gravity of ≤1.020 (25), subjects drank 250 mL of water to maintain urine production over the following 60 min for our previous study (19). Subjects were then instrumented and rested in the supine position for 20 min. Following the supine rest period, beat-to-beat measures of heart rate and blood pressure were obtained for 8 min during spontaneous breathing. Then, 8 min of data were obtained during paced breathing at a breathing frequency of 15 breaths/min in concert with a metronome (26). Paced breathing was used as an additional control due to the modulatory influence of respiratory rate on the high-frequency component of heart rate variability, and therefore, its use allowed for examination of parasympathetic modulation of heart rate independent of respiration (27). After completing the paced breathing segment, subjects voided their bladder in a collection urinal. Then, subjects consumed 500 mL of the experimental beverage within 5 min. After 20 min of quiet rest, subjects repeated the spontaneous and paced breathing protocols. Venous blood samples were obtained before and 30 min after drink consumption and stored at −80°C for analysis that occurred within 2 mo of collection (19).

Table 1. *Properties of soft drinks*

	Diet	Sucrose	HFCS
Osmolality, mosmol/kg			
Fresh	69 (4)	741 (3)	861 (2)
24-h decarbonated	61 (2)	738 (3)	850 (2)
48-h decarbonated	59 (2)	730 (2)	846 (2)
Total energy, kcal	5	240	240
Sugar, g	<1	62	65
Sodium, mg	70	92	85
Caffeine, mg	76	76	77

Data are presented as mean (SD). Soft drinks were matched for caffeine content and taste and were either artificially sweetened (Diet, diet Mountain Dew), sucrose-sweetened (Sucrose, Mountain Dew Throwback), or sweetened with high-fructose corn syrup (HFCS, regular Mountain Dew). Drink values per 500 mL. Data from Chapman et al. (12).

Data Analyses

Data were analyzed from beat-to-beat recordings over the final 5 min of each 8-min period of spontaneous and paced breathing. This approach was specifically utilized to allow subjects 3 min to get accustomed to the breathing protocol in an effort to reduce artifacts during the final 5-min recording period. Five-minute recordings are the recommended duration in which to obtain measures of short-term heart rate variability (12).

Blood pressure variability.

Blood pressure variability was measured using beat-to-beat techniques due to its association with cardiovascular and kidney damage (4), and several parameters were calculated using offline software (AcqKnowledge 4.2, Biopac Systems, Inc., Goleta, CA). Blood pressure variability was assessed using several calculations for systolic and diastolic blood pressure. The standard deviation was calculated to quantify the overall variation of each 5-min period during spontaneous and paced breathing (28). In addition, blood pressure variability was measured using average real variability and successive variation, which account for the variation between each beat-to-beat measure of blood pressure (29). Moreover, it has been suggested that average real variability and successive variation better reflect variability over time compared with standard deviation-based assessments (30). Average real variability encompasses the average absolute difference between consecutive measurements (30), where successive variation is calculated as the average squared difference between consecutive measurements (31). Blood pressure waveforms were visually inspected before analysis and were excluded if any artifact (i.e., noise in the blood pressure waveform) was detected. Acceptable blood pressure waveforms were obtained for data analysis in the water (n = 10), diet (n = 11), sucrose (n = 11), and HFCS (n = 12) trials during spontaneous and paced breathing.

Spontaneous cardiovagal baroreflex sensitivity.

Spontaneous cardiovagal baroreflex sensitivity was calculated with offline software (WinCPRS, Absolute Aliens Oy, Turku, Finland) using the sequence method of the beat-to-beat time series of systolic blood pressure and R-R interval (32). The sequence method was utilized to assess arterial baroreflex sensitivity at resting values of arterial blood pressure and R-R interval (i.e., the gain around the operating point) in response to consuming the experimental beverages (33). This technique does not generate a full stimulus-response curve of the arterial baroreflex, such as with the modified Oxford technique (34), but is reflective of the control of blood pressure at rest (11). Sequences of at least four consecutive cardiac cycles in which directional changes in systolic blood pressure and R-R interval were the same (i.e., consecutive up or down sequences) were identified as baroreflex sequences. Parameters were set to detect sequences when changes in systolic blood pressure were ≥1 mmHg and the variation in R-R interval was ≥5 ms (35). Linear regression analyses were applied to each potential sequence and the R^2 value was calculated. Acceptable baroreflex sequences were determined when $R^2 \geq 0.85$ (26, 33). The number of included sequences was ≥3 for either up or down baroreflex sequences (35). Spontaneous cardiovagal baroreflex sensitivity was determined for up (increases in systolic blood pressure and R-R interval) and down (decreases in systolic blood pressure and R-R interval) sequences. Overall spontaneous cardiovagal baroreflex sensitivity was calculated as the average of spontaneous cardiovagal baroreflex sensitivity for up and down sequences only for those up or down sequences that were ≥3 for a given collection period, as described earlier (36). Sequence method-based calculations of spontaneous cardiovagal baroreflex sensitivity have moderate between-day reliability in healthy adults (37). Based on these defined criteria, 10 of the 12 subjects had adequate baroreflex sequences during all conditions.

Heart rate variability.

R-R intervals from the continuous ECG recordings were visually inspected for ectopic beats and analyzed using offline software (WinCPRS) to provide insight into autonomic cardiac function. Heart rate variability was assessed using time and frequency domain methods as described in detail elsewhere (12). Time domain analyses were performed using the standard deviation of R-R intervals (SDNN) to provide an estimate of overall heart rate variability and the square root of the mean squared differences between consecutive R-R intervals (RMSSD) to provide insight into cardiac parasympathetic activity (12). Power spectral density analysis was achieved by using Fast Fourier transformations to allow analysis of the high-frequency (0.15–0.4 Hz, HF) and low-frequency (0.04–0.15 Hz, LF) power components. Similar to RMSSD, the HF component provides insights into cardiac parasympathetic activity. The physiological interpretation of the LF component is less clear and is controversial (38), as it reflects both cardiac sympathetic and parasympathetic activity (12, 27). Thus, for transparency, we have reported the LF component data without interpretation (12). Acceptable ECG recordings for heart rate variability analyses were obtained in the water (n = 11), diet (n = 12), sucrose (n = 11), and HFCS (n = 12) trials during spontaneous breathing. During paced breathing, acceptable ECG recordings were obtained in the water (n = 12), diet (n = 12), sucrose (n = 10), and HFCS (n = 11) trials.

Statistical Analyses

Statistical analyses were performed using Prism software v. 8.4.3 (GraphPad Software, LLC, La Jolla, CA). Pre-drink consumption values were analyzed using one-way repeated-measures ANOVA for spontaneous breathing and paced breathing controls. Because of the variation in some of the pre-drink consumption parameters at baseline, which was likely reflective of the inherent day-to-day variability of these measures, the effects of the experimental beverages were analyzed as the magnitude of change (Δ) from baseline using a mixed-effects model to account for the variation at baseline and missing values (described in *Data Analyses*). In all instances, when an ANOVA or mixed-effects model revealed a significant F value, post hoc Sidak test pairwise comparisons were made. Pearson correlations were used to assess the relation between overall spontaneous cardiovagal baroreflex sensitivity and indices of heart rate variability reflective of vagal tone (i.e., R-R interval, SDNN, RMSSD, and HF) during paced breathing (i.e., independent of respiratory rate). Statistical significance was set a priori at $P \leq 0.05$, and actual P values are reported where possible. There were no previous studies that had examined the acute effect of soft drink consumption on renal hemodynamics (our primary end point in Ref. 12) or spontaneous indices of cardiovascular control for this study. Thus, we were unable to perform an a priori power analysis. All data except correlations are reported as means ± SD. Correlations are reported as r, 95% confidence interval, and P value.

RESULTS

Blood Pressure Variability

Spontaneous breathing.

There were several modest but statistically significant baseline differences at pre-drink consumption, including a larger standard deviation (systolic and diastolic) in diet compared with water (Table 2). In addition, HFCS had a smaller standard deviation (diastolic only) compared with diet ($P < 0.03$) and smaller average real variability (systolic only) and successive variation (systolic only) compared with sucrose ($P < 0.02$, Table 2). There were no additional differences at pre-drink consumption. Diet induced greater reductions in standard deviation (systolic only) compared with water ($P < 0.05$, Table 3). HFCS elicited greater increases in successive variation (systolic only) compared with diet ($P < 0.02$, Table 3). There were no additional differences in the change in blood pressure variability parameters between conditions during spontaneous breathing (Table 3).

Paced breathing.

There were no differences at pre-drink consumption or in the magnitude of change following at post-drink consumption between conditions for any index of blood pressure variability during paced breathing (Tables 2 and 4).

Spontaneous Cardiovagal Baroreflex Sensitivity

Spontaneous breathing.

There were no baseline differences at pre-drink consumption in spontaneous cardiovagal baroreflex sensitivity (Table 5). HFCS and sucrose consumption elicited greater reductions in spontaneous cardiovagal baroreflex sensitivity during up and overall sequences compared with water ($P < 0.03$, Fig. 1, *A* and *E*). In addition, HFCS elicited greater reductions in spontaneous cardiovagal baroreflex sensitivity during down sequences compared with water (P = 0.02, Fig. 1*B*) and sucrose elicited greater reductions in spontaneous cardiovagal baroreflex sensitivity during overall sequences compared with water and diet

Table 2. *Blood pressure variability pre-drink consumption values*

	Spontaneous Breathing					Paced Breathing				
	Water	Diet	Sucrose	HFCS	*P* Value	Water	Diet	Sucrose	HFCS	*P* Value
Blood pressure, mmHg										
SBP	120 ± 10	123 ± 10	119 ± 12	119 ± 9	0.72	119 ± 11	123 ± 10	117 ± 12	120 ± 8	0.49
DBP	70 ± 7	69 ± 5	67 ± 6	66 ± 5	0.15	68 ± 7	69 ± 5	66 ± 6	66 ± 5	0.38
Blood pressure variability										
Standard deviation, mmHg										
SBP	4 ± 1	6 ± 2[W]	6 ± 2	5 ± 2	0.048	4 ± 1	5 ± 2	5 ± 1	6 ± 2	0.17
DBP	3 ± 1	4 ± 1[W]	3 ± 1	3 ± 1[D]	0.001	3 ± 1	4 ± 1	3 ± 1	3 ± 1	0.25
Average real variability, mmHg										
SBP	1.8 ± 0.4	2.0 ± 0.5	2.0 ± 0.5	1.8 ± 0.4	0.23	2.1 ± 0.6	2.1 ± 0.6	2.1 ± 0.4	2.2 ± 0.5	0.18
DBP	1.4 ± 0.4	1.5 ± 0.5	1.5 ± 0.5	1.4 ± 0.4	0.74	1.5 ± 0.5	1.4 ± 0.5	1.5 ± 0.5	1.4 ± 0.4	0.61
Successive variation, mmHg										
SBP	2.3 ± 0.4	2.4 ± 0.6	2.5 ± 0.6	2.2 ± 0.5[S]	0.08	2.6 ± 0.7	2.5 ± 0.6	2.5 ± 0.4	2.6 ± 0.5	0.25
DBP	1.8 ± 0.6	1.9 ± 0.6	1.9 ± 0.6	1.7 ± 0.5	0.43	1.9 ± 0.6	1.8 ± 0.6	1.8 ± 0.6	1.7 ± 0.5	0.57

Data are presented as absolute values and means ± SD; n = 12 (10 M, 2 F). Comparisons between conditions within Spontaneous Breathing or Paced Breathing were made using separate one-way ANOVA with post hoc Sidak's test pairwise comparisons. *P* value columns are main effect of drink. [W]Different from Water ($P < 0.05$); [D]different from Diet ($P = 0.03$); [S]different from Sucrose ($P < 0.01$). DBP, diastolic blood pressure; HFCS, high-fructose corn syrup; SBP, systolic blood pressure.

($P = 0.01$, Fig. 1*E*). HFCS elicited greater reductions in spontaneous cardiovagal baroreflex sensitivity during down sequences compared with diet ($P = 0.0573$, Fig. 1*E*).

Paced breathing.

There were no baseline differences at pre-drink consumption in spontaneous cardiovagal baroreflex sensitivity (Table 5). HFCS induced greater reductions in spontaneous cardiovagal baroreflex sensitivity during up, down, and overall sequences compared with water ($P < 0.04$, Fig. 1, *B*, *D* and *F*). In addition, sucrose elicited greater reductions in spontaneous cardiovagal baroreflex sensitivity compared with diet and water during down sequences ($P < 0.04$, Fig. 1*D*) and compared with diet during overall sequences ($P = 0.04$, Fig. 1*F*). HFCS elicited greater reductions in spontaneous cardiovagal baroreflex sensitivity during overall sequences compared with diet ($P = 0.0581$, Fig. 1*F*).

Heart Rate Variability

Spontaneous breathing.

There were no baseline differences at pre-drink consumption between conditions for heart rate, R-R interval, and all measures of heart rate variability (Table 5). Heart rate increased and R-R interval decreased in HFCS and sucrose compared with water and diet ($P < 0.02$, Fig. 2, *A* and *C*). In addition, the magnitude of change from pre-drink consumption did not differ between conditions for measures of heart rate variability ($P \geq 0.07$, Fig. 3, *A*, *C*, *E*, and *G*).

Paced breathing.

There were no baseline differences at pre-drink consumption between conditions for heart rate, R-R interval, and all measures of heart rate variability (Table 5). Heart rate increased and R-R interval decreased in HFCS compared with water ($P \leq 0.02$, Fig. 2, *B* and *D*). There were no other differences in the change in heart rate and R-R interval between conditions ($P \geq 0.07$, Fig. 2). HFCS evoked greater reductions in RMSSD compared with water ($P < 0.01$, Fig. 3*D*). There were no differences in the magnitude of change from baseline between conditions in SDNN, HF, and LF ($P \geq 0.09$, Fig. 3, *B*, *F*, and *H*).

Correlations

Statistically significant relations were found between overall cardiovagal baroreflex sensitivity and indices of heart rate variability that are reflective of vagal tone: R-R interval

Table 3. *Change in blood pressure and blood pressure variability following drink consumption during spontaneous breathing*

	Water	Diet	Sucrose	HFCS	Main Effect of Drink
Blood pressure mmHg					
SBP	6 ± 9	5 ± 9	4 ± 13	6 ± 5	0.87
DBP	2 ± 7	7 ± 5	4 ± 6	5 ± 5	0.27
Blood pressure variability					
Standard deviation, mmHg					
SBP	−1 ± 1	−2 ± 2[W]	−1 ± 2	0 ± 2	0.030
DBP	0 ± 1	−1 ± 1	0 ± 1	0 ± 1	0.021
Average real variability, mmHg					
SBP	−0.1 ± 0.1	−0.2 ± 0.3	−0.1 ± 0.3	0.1 ± 0.3	0.037
DBP	−0.1 ± 0.3	−0.1 ± 0.4	0.1 ± 0.4	−0.1 ± 0.3	0.45
Successive variation, mmHg					
SBP	−0.2 ± 0.2	−0.2 ± 0.3	−0.2 ± 0.4	0.1 ± 0.3[D]	0.030
DBP	−0.1 ± 0.3	−0.2 ± 0.4	0.9 ± 0.5	0.0 ± 0.3	0.38

Data are presented as the change (Δ) from pre-drink consumption as means ± SD; n = 10 (8 M, 2 F). Comparisons between conditions were made using mixed-effects model with post hoc Sidak's test pairwise comparisons. [W]Different from Water ($P < 0.05$); [D]different from Diet ($P < 0.02$). DBP, diastolic blood pressure; HFCS, high-fructose corn syrup; SBP, systolic blood pressure.

Table 4. *Change in blood pressure and blood pressure variability following drink consumption during paced breathing*

	Water	Diet	Sucrose	HFCS	Main Effect of Drink
Blood pressure, mmHg					
SBP	4 ± 9	1 ± 8	5 ± 11	4 ± 4	0.57
DBP	1 ± 7	3 ± 6	3 ± 7	4 ± 5	0.64
Blood pressure variability					
Standard deviation, mmHg					
SBP	0 ± 1	−1 ± 2	0 ± 1	0 ± 1	0.33
DBP	0 ± 1	0 ± 1	0 ± 1	0 ± 1	0.35
Average real variability, mmHg					
SBP	0.0 ± 0.3	0.0 ± 0.5	0.2 ± 0.5	0.1 ± 0.5	0.47
DBP	−0.5 ± 0.3	0.0 ± 0.6	0.1 ± 0.6	0.0 ± 0.3	0.69
Successive variation, mmHg					
SBP	0.0 ± 0.3	0.0 ± 0.6	0.2 ± 0.5	0.1 ± 0.5	0.39
DBP	−0.1 ± 0.3	−0.1 ± 0.7	0.2 ± 0.6	0.1 ± 0.3	0.46

Data are presented as the change (Δ) from pre-drink consumption as means ± SD; n = 10 (8 M, 2 F). Comparisons between conditions were made using mixed-effects model. DBP, diastolic blood pressure; HFCS, high-fructose corn syrup; SBP, systolic blood pressure.

(r = 0.38 [0.05, 0.63], P = 0.03), SDNN (r = 0.67 [0.44–0.81], P < 0.01), RMSSD (r = 0.76 [0.59–0.87], P < 0.01), and HF (r = 0.61 [0.36–0.78], P < 0.01).

Blood Parameters

At pre-drink consumption, serum copeptin was elevated in HFCS compared with diet (P = 0.02) and lower in diet compared with water (P < 0.01, Table 6). There were no other differences in pre-drink consumption blood parameters revealed by post hoc tests (Table 6). There were no differences in the magnitude of change between drinks at post-drink consumption in sodium, potassium, chloride, and copeptin (Table 6). At post-drink consumption, there were greater increases in blood glucose and fructose in HFCS and sucrose compared with diet and water (P < 0.05, Table 6). There were no differences between HFCS and sucrose in blood glucose (P = 0.97), but there were larger increases in blood fructose in the HFCS trial compared with the sucrose trial (P = 0.04, Table 6). In addition, plasma osmolality was elevated in HFCS compared with diet (P = 0.03) and in sucrose compared with water and diet ($P \leq$ 0.04, Table 6). There were no differences in plasma osmolality between HFCS and sucrose (P = 0.99, Table 6). Serum uric acid was elevated at post-drink consumption in HFCS compared with water and diet ($P \leq$ 0.04), but there were no differences between HFCS and sucrose (P = 0.26, Table 6)

DISCUSSION

In support of our hypothesis, HFCS-sweetened soft drink consumption decreased spontaneous cardiovagal baroreflex sensitivity within 30 min in healthy, young adults. Reductions in spontaneous cardiovagal baroreflex sensitivity also occurred in the sucrose trial and were not different from HFCS. In addition, we observed greater reductions in the parasympathetic modulation of heart rate with HFCS-sweetened soft drink consumption. Contrary to our hypothesis, we did not find that HFCS-sweetened soft drink consumption increased blood pressure variability.

We hypothesized that spontaneous cardiovagal baroreflex sensitivity would be decreased to a greater extent with HFCS-soft drink consumption compared with water based on the work of Brown et al. (16), who observed reductions in spontaneous cardiovagal baroreflex sensitivity following fructose-sweetened water consumption. In this study, we found that consuming both the HFCS- and sucrose-sweetened soft drinks reduced spontaneous cardiovagal baroreflex sensitivity during up and overall sequences compared with water. These findings suggest that the presence of sugar in soft drinks decreases spontaneous cardiovagal baroreflex sensitivity. Our observations of greater reductions in spontaneous cardiovagal baroreflex sensitivity in the HFCS and

Table 5. *Spontaneous cardiovagal baroreflex sensitivity and heart rate variability pre-drink consumption values*

	Spontaneous Breathing					Paced Breathing				
	Water	Diet	Sucrose	HFCS	*P* Value	Water	Diet	Sucrose	HFCS	*P* Value
Heart rate, beats/min	56 ± 7	58 ± 8	58 ± 7	59 ± 9	0.26	59 ± 9	60 ± 8	58 ± 8	62 ± 11	0.22
R-R interval ms	1,092 ± 153	1,059 ± 147	1,063 ± 143	1,047 ± 155	0.34	1,043 ± 160	1,026 ± 142	1,055 ± 162	1,001 ± 170	0.26
Spontaneous baroreflex sensitivity										
Up, ms/mmHg	27 ± 10	28 ± 13	27 ± 10	26 ± 10	0.60	25 ± 12	23 ± 9	20 ± 7	22 ± 11	0.04
Down, ms/mmHg	24 ± 8	22 ± 7	24 ± 8	24 ± 11	0.54	23 ± 10	21 ± 9	22 ± 9	20 ± 9	0.32
Overall, ms/mmHg	25 ± 9	25 ± 10	25 ± 9	25 ± 10	0.96	24 ± 10	22 ± 9	21 ± 8	21 ± 10	0.17
Heart rate variability										
SDNN, ms	82 ± 31	82 ± 31	81 ± 30	79 ± 35	0.90	80 ± 34	80 ± 30	77 ± 28	79 ± 35	0.95
RMSSD, ms	83 ± 43	79 ± 41	76 ± 40	79 ± 44	0.42	82 ± 49	81 ± 47	73 ± 33	75 ± 50	0.12
HF, ms^2	1,803 ± 1,375	1,468 ± 1,408	1,579 ± 1,399	1,488 ± 1,275	0.49	2,202 ± 2,394	2,030 ± 2,005	1,181 ± 866	1,846 ± 2,024	0.14
LF, ms^2	2,170 ± 2,010	2,044 ± 1,525	1,984 ± 1,682	2,297 ± 1,697	0.68	1,476 ± 1,145	1,369 ± 989	1,421 ± 1,364	1,657 ± 1,974	0.67

Data are presented as absolute values and means ± SD; n = 12 (10 M, 2 F). Comparisons between conditions within Spontaneous Breathing or Paced Breathing were made using separate one-way ANOVA. P value columns are main effect of drink. HF, high frequency; HFCS, high-fructose corn syrup; LF, low frequency; RMSSD, square root of the mean squared differences between consecutive R-R intervals; SDNN, standard deviation of R-R intervals.

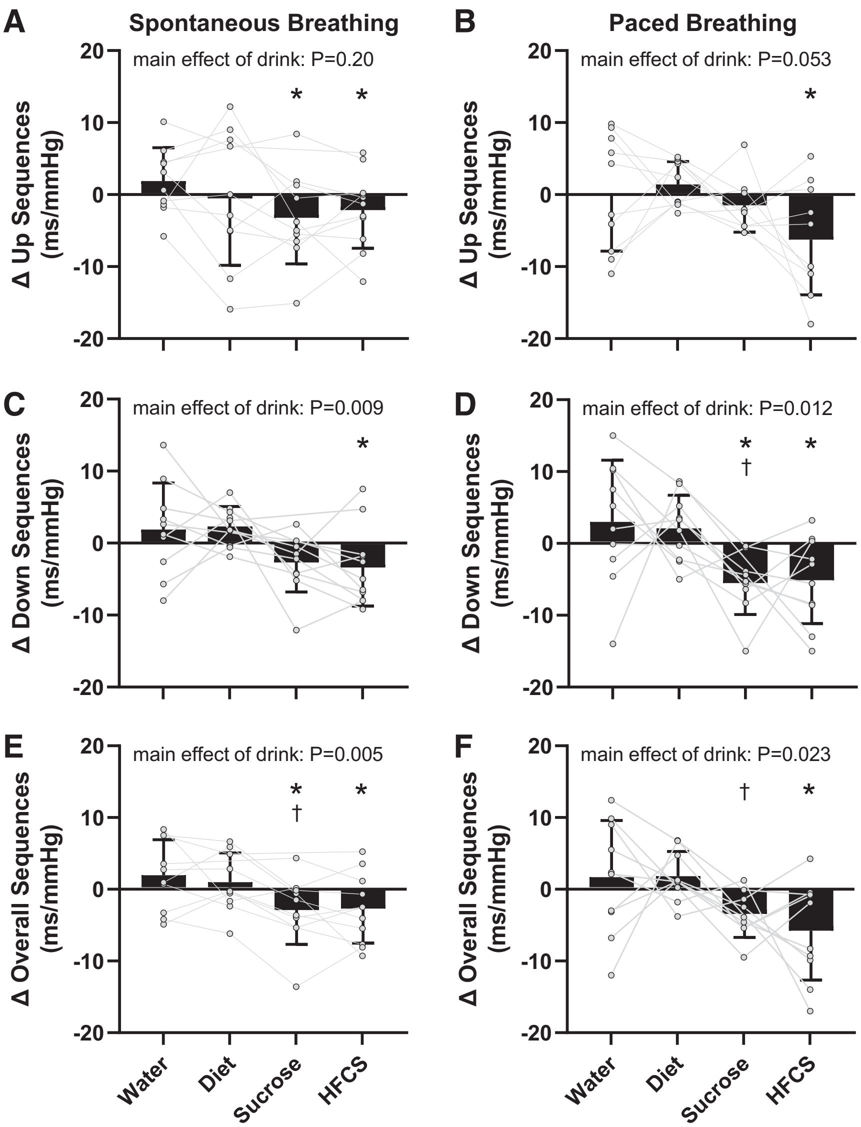

Figure 1. Comparisons between the magnitude of change (Δ) in spontaneous cardiovagal baroreflex sensitivity (cBRS) during up (increased systolic blood pressure and R-R interval, *A* and *B*), down (decreased systolic blood pressure and R-R interval, *C* and *D*), and overall (combined average of up and down sequences, *E* and *F*) sequences at 30 min following soft drink consumption during spontaneous breathing (*left panels*) and paced breathing (*right panels*). Statistical analysis performed using mixed-effects model with post hoc Sidak's test pairwise comparisons. *Different from water ($P \leq 0.04$); †different from diet ($P \leq 0.02$); $n = 10$ (8 M, 2 F). HFCS, high-fructose corn syrup

sucrose trials compared with the diet trial further support the interpretation that a caloric sweetener mediates these changes in cardiovascular control independent of caffeine content. Therefore, our findings of a reduced spontaneous cardiovagal baroreflex sensitivity with HFCS- and sucrose-sweetened soft drinks may provide a mechanism by which the cardiovascular risk profile is increased with chronic excessive consumption of sugar-sweetened soft drinks.

Because of experimental design, we were able to compare drinks containing sugar (sucrose and HFCS) versus those that do not (water and diet). Our findings indicate that the soft drinks containing sugar stimulate acute reductions in spontaneous cardiovagal baroreflex sensitivity, but the physiological mechanism underlying this response is unclear. Previously, we observed similar increases in plasma osmolality between HFCS- and sucrose-sweetened soft drinks (19), and other investigators found that modest increases in plasma osmolality do not alter spontaneous cardiovagal baroreflex sensitivity (20, 28). Therefore, increases in plasma osmolality do not appear to be driving our findings. Large increases in circulating insulin occur following the consumption of caffeinated soft drinks that are sweetened with HFCS or sucrose (22). Hyperinsulinemia increases sympathetic activity (39–41) to limit insulin-mediated nitric oxide vasodilation (42–44). Therefore, hyperinsulinemia following the consumption of HFCS and sucrose beverages may have influenced baroreflex sensitivity. Previous evidence by Young et al. (45) indicates that insulin increases sympathetic baroreflex sensitivity (i.e., baroreflex control of muscle sympathetic nerve activity). However, the investigators also found that spontaneous cardiovagal baroreflex sensitivity was not altered during a hypersinsulinemic-euglycemic clamp (45). The findings of this study suggest that increases in blood glucose, such as in a hyperinsulinemic-hyperglycemic state, elicited by sugar-sweetened soft drink consumption (22), may be needed to cause the modifying effects of insulin on the cardiovagal baroreflex. Collectively, these results indicate that hyperinsulinemia alone does not alter

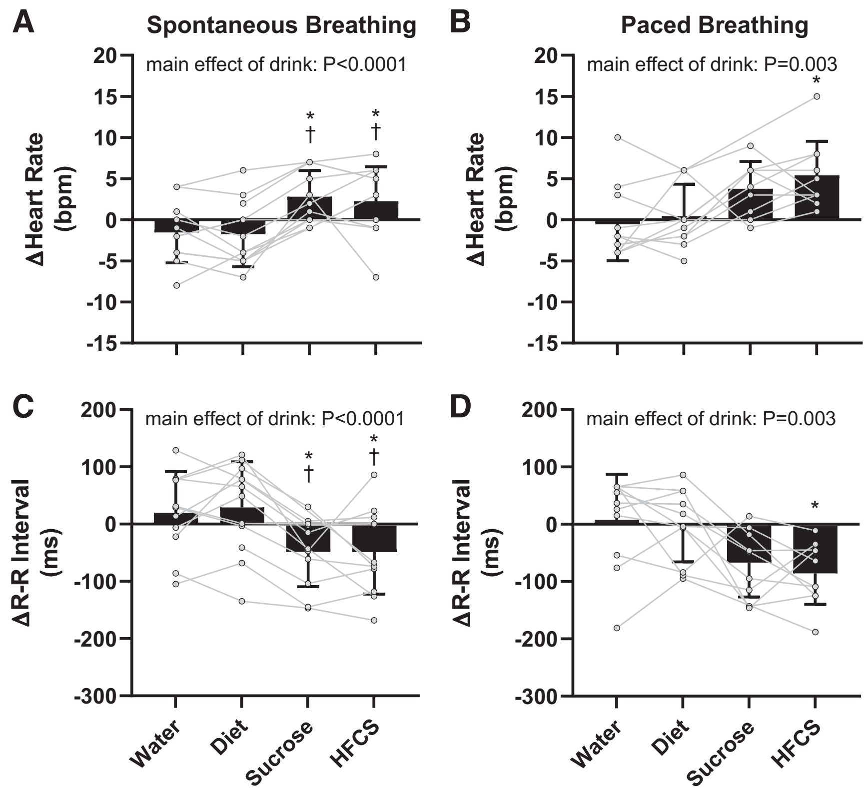

Figure 2. Comparisons between the magnitude of change (Δ) in heart rate (*A* and *B*) and R-R interval (*C* and *D*) at 30 min following soft drink consumption during spontaneous breathing (*left panels*) and paced breathing (*right panels*). Statistical analysis performed using mixed-effects model with post hoc Sidak's test pairwise comparisons. *Different from water ($P \leq 0.02$); †different from diet ($P < 0.01$). Sample size: spontaneous breathing—water ($n = 11$; 9 M, 2 F), diet ($n = 12$; 10 M, 2 F), sucrose ($n = 11$; 9 M, 2 F), and HFCS ($n = 12$; 10 M, 2 F); paced breathing—water ($n = 12$; 10 M, 2 F), diet ($n = 12$; 10 M, 2 F), sucrose ($n = 10$; 8 M, 2 F), and HFCS ($n = 11$; 9 M, 2 F). HFCS, high-fructose corn syrup.

cardiovagal baroreflex, whereas it has a greater influence on sympathetic baroreflex sensitivity. In our previous study (19), we observed increases from baseline in serum uric acid following HFCS-sweetened (~0.3 mg/dL) and sucrose-sweetened (~0.2 mg/dL) soft drink consumption. Although chronic exposure to high levels of uric acid (i.e., hyperuricemia) may increase cardiovascular risk (46–48), acute hyperuricemia induced by uric acid infusion does not appear to reduce spontaneous cardiovagal baroreflex sensitivity (49). Given this discussion, further investigations into the mechanisms underlying acute decreases in spontaneous cardiovagal baroreflex sensitivity following sugar-sweetened soft drink consumption are warranted.

Our findings of a greater reduction in RMSSD during paced breathing after HFCS-sweetened soft drink consumption are suggestive of a lower heart rate variability mediated by a relative reduction in cardiac parasympathetic activity compared with following water consumption. We were able to examine the parasympathetic modulation of heart rate independent of respiratory rate by using paced breathing. We found statistically significant correlations between overall cardiovagal baroreflex sensitivity and indices of heart rate variability that are reflective of vagal tone during paced breathing. The findings in this study are in line with previous studies investigating relation of cardiac baroreflex responses and vagal tone (50), although it is acknowledged that vagal tone may be mediated by mechanisms independent of the baroreflex (51). Our findings indicate that the fructose content of the soft drink may modulate heart rate variability because RMSSD decreased in the HFCS trial, but not the sucrose-sweetened soft drink trial, compared with the water trial. Brown et al. (16) found that HF power exhibited a biphasic response to the consumption of fructose-sweetened water such that HF power increased within the first 15 min, which was then followed by a decrease at 75 min postconsumption during spontaneous breathing in healthy subjects. The investigators also found that LF increased within 15 min following the consumption of fructose-sweetened water. It is currently unclear why we observed differing heart rate variability responses following HFCS consumption. We speculate that another ingredient in the soft drinks used in this study, such as caffeine, has co-modulatory interactions with fructose that contributed to the divergent responses. However, by itself, caffeine does not appear to affect parameters of heart rate variability in people who frequently consume caffeinated products (52). Our findings of a reduced RMSSD with HFCS-sweetened soft drink consumption differ from studies that have investigated the postprandial effects on indices of heart rate variability following eating a meal. There is some evidence suggesting that the LF/HF ratio is increased following a meal (53) or is associated with elevations in blood glucose (54), but this is not a consistent finding in healthy participants (55). Overall, the mechanisms underlying the acute reductions in heart rate variability with HFCS-soft drink consumption are currently not known.

We did not find greater increases in systolic or diastolic blood pressure following HFCS-sweetened soft drink consumption compared with the water, diet, and sucrose trials. Furthermore, we did not find blood pressure variability to be influenced by any of the experimental beverages. In our previous study (19), although we did not observe changes in Modelflow-derived cardiac output or total peripheral resistance, we did find that renal vascular resistance increases following consumption of HFCS-sweetened soft drinks compared with drinking water. Previous reports have

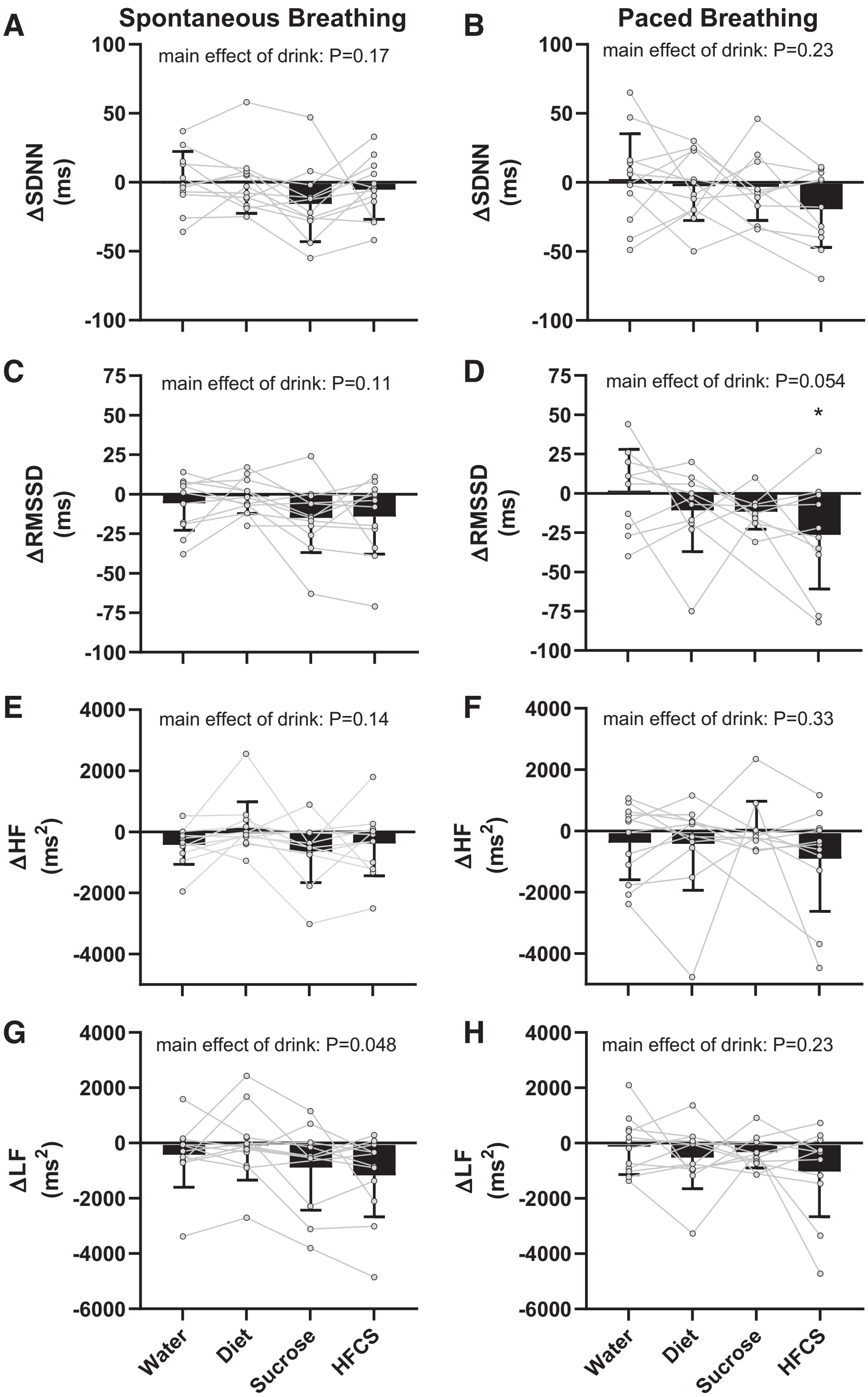

Figure 3. Comparisons between the magnitude of change (Δ) in the indices of heart rate variability at 30 min following soft drink consumption during spontaneous breathing *(left panels*) and paced breathing (*right panels*). Statistical analysis performed using mixed-effects model with post hoc Sidak's test pairwise comparisons. *Different from water ($P < 0.01$). Sample size: spontaneous breathing—water (*n* = 11; 9 M, 2 F), diet (*n* = 12; 10 M, 2 F), sucrose (*n* = 11; 9 M, 2 F), and high-fructose corn syrup (HFCS) (*n* = 12; 10 M, 2 F); paced breathing—water (*n* = 12; 10 M, 2 F), diet (*n* = 12; 10 M, 2 F), sucrose (*n* = 10; 8 M, 2 F), and HFCS (*n* = 11; 9 M, 2 F). *A* and *B*: standard deviation of R-R intervals (SDNN); *C* and *D*: square root of the mean squared difference (RMSSD); *E* and *F*: high-frequency power component (HF); *G* and *H*: low-frequency power component (LF).

observed that elevations in blood pressure occur within 20–30 min (16, 56) and are sustained for at least 120 min following fructose-sweetened water consumption (16). The postprandial elevation in blood pressure is attenuated when the proportion of glucose to fructose is increased, which lowers total peripheral resistance and thus mitigates the impact of increases in cardiac output on blood pressure (56). The HFCS and sucrose soft drinks we used contained a substantial proportion of glucose (40% and 50%, respectively). Thus, it is reasonable to speculate that the glucose content may have mitigated the blood pressure-elevating effects of fructose. Finally, it does not appear that reductions in cardiovagal baroreflex sensitivity that we found following sucrose and HFCS consumption influenced our resting measures of blood pressure. Although the sympathetic component of the baroreflex was not assessed in this study, we previously discussed that sympathetic baroreflex sensitivity is increased during hyperinsulinemia (45). Thus, we speculate that an increased

Table 6. *Blood parameters*

	Pre-Drink Consumption					Post-Drink Consumption (Δ from Pre)				
	Water	Diet	Sucrose	HFCS	*P* Value	Water	Diet	Sucrose	HFCS	*P* Value
Sodium, mmol/L	139 ± 1	139 ± 1	138 ± 1	139 ± 2	0.21	0 ± 1	0 ± 1	0 ± 1	0 ± 2	0.94
Potassium, mmol/L	4.2 ± 0.3	4.4 ± 0.4	4.3 ± 0.3	4.2 ± 0.2	0.17	0.0 ± 0.2	0.0 ± 0.3	−0.2 ± 0.2	−0.1 ± 0.2	0.12
Chloride, mmol/L	105 ± 1	104 ± 2	103 ± 2	105 ± 2	0.017	0 ± 1	−1 ± 1	0 ± 2	−1 ± 2	0.16
Glucose, mg/dL	88 ± 6	88 ± 5	85 ± 7	88 ± 6	0.35	−4 ± 9	1 ± 5	42 ± 21^{W,D}	36 ± 28^{W,D}	<0.001
Fructose, µmol/L	127 ± 37	133 ± 40	128 ± 37	127 ± 43	0.057	2 ± 12	8 ± 12	189 ± 81^{W,D}	286 ± 99^{W,D,S}	<0.001
Osmolality, mosmol/kg	284 ± 2	285 ± 2	284 ± 2	285 ± 3	0.67	−1 ± 2	0 ± 1	2 ± 2^{W,D}	2 ± 2^{D}	0.005
Copeptin, pmol/L	9.5 ± 2.8	7.6 ± 1.9^{W}	8.5 ± 2.3	9.6 ± 2.7^{D}	0.016	0.3 ± 0.9	0.1 ± 1.2	0.1 ± 1.2	0.8 ± 1.0	0.36
Uric acid, mg/dL	6.0 ± 1.0	6.0 ± 1.1	5.9 ± 1.2	6.3 ± 1.2	0.29	−0.1 ± 0.1	−0.1 ± 0.8	0.2 ± 0.2	0.3 ± 0.4^{W,D}	0.006

Data are presented as absolute values for pre-drink consumption and change values from pre-to-post drink consumption as means ± SD; n = 12 (10 M, 2 F). Comparisons at pre-drink consumption were made using a one-way ANOVA. At post-drink consumption, comparisons were made using a mixed-effects model where significant fixed effects (drink) were analyzed using post hoc Sidak's test. ^{W}Different from Water ($P \leq 0.05$); ^{D}different from Diet ($P \leq 0.05$); Sdifferent from Sucrose (P = 0.04). P value columns are main effect of drink. All data except chloride were previously published by Chapman et al. (12). HFCS, high-fructose corn syrup.

sympathetic baroreflex sensitivity to a postprandial hyperinsulinemic state caused by sugar-sweetened soft drink consumption (22) may have countered, at least to some degree, reductions in cardiovagal baroreflex sensitivity observed in this study and may explain why we did not find changes in blood pressure or blood pressure variability. In addition, our findings may suggest that the operating point of the cardiovagal baroreflex curve is not shifted with sugar-sweetened soft drink consumption. Future studies may consider using pharmacological stimulation or neck suction techniques with muscle sympathetic nerve activity to generate baroreflex curves to further explore these associations.

Limitations

Our study has several limitations that warrant discussion. First, control of the baroreflex is dependent on both sympathetic and cardiovagal activity. Because sympathetic activity was not measured, such as with muscle sympathetic nerve activity, we cannot draw conclusions regarding the sympathetic arm of baroreflex sensitivity. Second, we did not investigate the response of the baroreflex across a broad range of arterial pressures, such as with the modified Oxford method (i.e., pharmacological stimulation of the arterial baroreflex). However, given that the cardiovagal baroreflex is mostly controlled parasympathetically and that large changes in blood pressure were not observed in this study, there is merit in using the sequence analysis of baroreflex sensitivity (11). Third, this study is limited by the small number of female subjects included in the study and that females were only studied during one phase of the menstrual cycle. In addition, female subjects were not taking oral contraceptive pills, which vary in their formulations (57) and have been reported to alter resting blood pressure and baroreflex sensitivity (58). Therefore, whether their use elicits similar modifications in cardiovascular control to sugar-sweetened soft drink consumption, as observed in this study, requires further investigation. Fourth, a noncaffeinated, HFCS-sweetened soft drink was not used in this study, and thus, the potential co-modulatory effect of caffeine could not be teased out. However, our findings indicate that the acute changes in cardiovascular control are not dependent on caffeine because the caffeine content was the same across the three experimental soft drinks. Fifth, we did not measure insulin, which would provide further insights into the mechanisms by which these drinks alter cardiovascular control. Sixth, it is not known whether the acute effects of soft drink consumption on cardiovascular function observed in this study are sustained with chronic consumption and if they share similar mechanisms. Seventh, we did not assess the cardiorespiratory fitness of our subjects. Recent evidence suggests that aerobic exercise is protective against vascular dysfunction induced by chronic sugar-sweetened beverage consumption (59).

Conclusions

This study offers several novel findings regarding the effects of soft drinks on cardiovascular function that occur within 30 min of drink consumption in young, healthy adults. We found that HFCS- and sucrose-sweetened soft drinks decreased spontaneous cardiovagal baroreflex sensitivity, and HFCS-sweetened soft drinks elicited greater reductions in the parasympathetic modulation of heart rate. Finally, we did not find differential increases in blood pressure variability with HFCS-sweetened soft drinks compared with artificially sweetened and sucrose-sweetened drinks and water.

Perspectives and Significance

The findings of our study indicate that sugar-sweetened soft drink consumption acutely influences autonomic control of the cardiovascular system in young, healthy adults. Although important, many recent investigations into the potential deleterious effects of soft drinks on cardiovascular health have been epidemiological studies that are unable to establish causality or included studies that use varying experimental models of sweetened water. The latter approach provides important mechanistic insight but may be limited in its external validity, given that soft drinks are composed of more ingredients than simply the sweetener used (e.g., caffeine and sodium content). Thus, our experimental approach provided insight into the acute cardiovascular effects of commercially available soft drinks, thereby enhancing the external validity of our study. Importantly, although this experiment provided intriguing findings, whether similar effects on the cardiovascular system would be found using a diet high in sugar-sweetened soft drinks or if a dose-response relation exists between the volume consumed and the extent of cardiovascular responses remains to be established. This study adds to the literature that a relatively moderate volume of sugar-sweetened soft drinks elicits relatively minor, but statistically significant, changes to spontaneous indices of cardiovascular function. Moreover, whether sugar-sweetened soft drink consumption elicits similar effects in populations with an exacerbated cardiovascular risk profile, such those with metabolic syndrome, hypertension, diabetes, or obesity, warrants further investigation.

ACKNOWLEDGMENTS

We thank the individuals who participated in this study.

GRANTS

This work was partially supported by the United States Centers for Disease Control and Prevention Grant R01-OH-011528.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

C.L.C., Z.J.S., and B.D.J. conceived and designed research; C.L.C., E.L.R., L.D.P., P.J.K., and A.C.B. performed experiments; C.L.C., E.L.R., M.L.W., L.D.P., P.J.K., and A.C.B. analyzed data; C.L.C., Z.J.S., and B.D.J. interpreted results of experiments; C.L.C. prepared figures; C.L.C. drafted manuscript; C.L.C., E.L.R., M.L.W., L.D.P., P.J.K., A.C.B., Z.J.S., and B.D.J. edited and revised manuscript; C.L.C., E.L.R., M.L.W., L.D.P., P.J.K., A.C.B., Z.J.S., and B.D.J. approved final version of manuscript.

REFERENCES

1. **Cheungpasitporn W**, **Thongprayoon C**, **O'Corragain OA**, **Edmonds PJ**, **Kittanamongkolchai W**, **Erickson SB.** Associations of sugar-sweetened and artificially sweetened soda with chronic kidney disease: a systematic review and meta-analysis. *Nephrology (Carlton)* 19: 791–797, 2014. doi:10.1111/nep.12343.
2. **Narain A**, **Kwok CS**, **Mamas MA.** Soft drinks and sweetened beverages and the risk of cardiovascular disease and mortality: a systematic review and meta-analysis. *Int J Clin Pract* 70: 791–805, 2016. doi:10.1111/ijcp.12841.
3. **Pacheco LS**, **Lacey JV Jr**, **Martinez ME**, **Lemus H**, **Araneta MRG**, **Sears DD**, **Talavera GA**, **Anderson CAM.** Sugar-sweetened beverage intake and cardiovascular disease risk in the California teachers study. *J Am Heart Assoc* 9: e014883, 2020.
4. **Parati G**, **Ochoa JE**, **Lombardi C**, **Bilo G.** Assessment and management of blood-pressure variability. *Nat Rev Cardiol* 10: 143–155, 2013 [Erratum in *Nat Rev Cardiol* 11: 314, 2014]. doi:10.1038/nrcardio.2013.1.
5. **Palatini P**, **Penzo M**, **Racioppa A**, **Zugno E**, **Guzzardi G**, **Anaclerio M**, **Pessina AC.** Clinical relevance of nighttime blood pressure and of daytime blood pressure variability. *Arch Intern Med* 152: 1855–1860, 1992.
6. **Mancia G**, **Bombelli M**, **Facchetti R**, **Madotto F**, **Corrao G**, **Trevano FQ**, **Grassi G**, **Sega R.** Long-term prognostic value of blood pressure variability in the general population. *Hypertension* 49: 1265–1270, 2007. doi:10.1161/HYPERTENSIONAHA.107.088708.
7. **Pringle E**, **Phillips C**, **Thijs L**, **Davidson C**, **Staessen JA**, **de Leeuw PW**, **Jaaskivi M**, **Nachev C**, **Parati G**, **O'Brien ET**, **Tuomilehto J**, **Webster J**, **Bulpitt CJ**, **Fagard RH**; **Syst-Eur Investigators.** Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. *J Hypertens* 21: 2251–2257, 2003. doi:10.1097/00004872-200312000-00012.
8. **Monahan KD.** Effect of aging on baroreflex function in humans. *Am J Physiol Regul Integr Comp Physiol* 293: R3–R12, 2007. doi:10.1152/ajpregu.00031.2007.
9. **Cowley AW**, **Liard JF**, **Guyton AC.** Role of the baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. *Circ Res* 32: 564–576, 1973. doi:10.1161/01.RES.32.5.564.
10. **Chapleau MW**, **Li Z**, **Meyrelles SS**, **Ma X**, **Abboud FM.** Mechanisms determining sensitivity of baroreceptor afferents in health and disease. *Ann NY Acad Sci* 940: 1–19, 2001. doi:10.1111/j.1749-6632.2001.tb03662.x.
11. **La Rovere MT**, **Pinna GD**, **Raczak G.** Baroreflex sensitivity: measurement and clinical implications. *Ann Noninvasive Electrocardiol* 13: 191–207, 2008. doi:10.1111/j.1542-474X.2008.00219.x.
12. **Camm AJ**, **Malik M**, **Bigger JT**, **Breithardt G**, **Cerutti S**, **Cohen RJ**, **Coumel P**, **Fallen EL**, **Kennedy HL**, **Kleiger R**; **Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.** Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 93: 1043–1065, 1996.doi:10.1161/01.CIR.93.5.1043.
13. **La Rovere MT**, **Bigger JT Jr**, **Marcus FI**, **Mortara A**, **Schwartz PJ.** Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 351: 478–484, 1998. doi:10.1016/S0140-6736(97)11144-8.
14. **La Rovere MT**, **Pinna GD**, **Maestri R**, **Mortara A**, **Capomolla S**, **Febo O**, **Ferrari R**, **Franchini M**, **Gnemmi M**, **Opasich C**, **Riccardi PG**, **Traversi E**, **Cobelli F.** Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation* 107: 565–570, 2003. doi:10.1161/01.CIR.0000047275.25795.17.
15. **Brown CM**, **Barberini L**, **Dulloo AG**, **Montani J-P.** Cardiovascular responses to water drinking: does osmolality play a role? *Am J Physiol Regul Integr Comp Physiol* 289: R1687–R1692, 2005. doi:10.1152/ajpregu.00205.2005.
16. **Brown CM**, **Dulloo AG**, **Yepuri G**, **Montani J-P.** Fructose ingestion acutely elevates blood pressure in healthy young humans. *Am J Physiol Regul Integr Comp Physiol* 294: R730–R737, 2008. doi:10.1152/ajpregu.00680.2007.
17. **Chou KH**, **Bell LN.** Caffeine content of prepackaged national-brand and private-label carbonated beverages. *J Food Sci* 72: C337–C342, 2007. doi:10.1111/j.1750-3841.2007.00414.x.
18. **Turnbull D**, **Rodricks JV**, **Mariano GF**, **Chowdhury F.** Caffeine and cardiovascular health. *Regul Toxicol Pharmacol* 89: 165–185, 2017. doi:10.1016/j.yrtph.2017.07.025.
19. **Chapman CL**, **Grigoryan T**, **Vargas NT**, **Reed EL**, **Kueck PJ**, **Pietrafesa LD**, **Bloomfield AC**, **Johnson BD**, **Schlader ZJ.** High-fructose corn syrup-sweetened soft drink consumption increases vascular resistance in the kidneys at rest and during sympathetic activation. *Am J Physiol Renal Physiol* 318: F1053–F1065, 2020. doi:10.1152/ajprenal.00374.2019.
20. **Babcock MC**, **Brian MS**, **Watso JC**, **Edwards DG**, **Stocker SD**, **Wenner MM**, **Farquhar WB.** Alterations in dietary sodium intake affect cardiovagal baroreflex sensitivity. *Am J Physiol Regul Integr Comp Physiol* 315: R688–R695, 2018. doi:10.1152/ajpregu.00002.2018.
21. **Hasser EM**, **Bishop VS**, **Hay M.** Interactions between vasopressin and baroreflex control of the sympathetic nervous system. *Clin Exp Pharmacol Physiol* 24: 102–108, 1997. doi:10.1111/j.1440-1681.1997.tb01791.x.
22. **Le MT**, **Frye RF**, **Rivard CJ**, **Cheng J**, **McFann KK**, **Segal MS**, **Johnson RJ**, **Johnson JA.** Effects of high-fructose corn syrup and sucrose on the pharmacokinetics of fructose and acute metabolic and hemodynamic responses in healthy subjects. *Metabolism* 61: 641–651, 2012. doi:10.1016/j.metabol.2011.09.013.
23. **Guelen I**, **Westerhof BE**, **van der Sar GL**, **van Montfrans GA**, **Kiemeneij F**, **Wesseling KH**, **Bos WJ.** Validation of brachial artery pressure reconstruction from finger arterial pressure. *J Hypertens* 26: 1321–1327, 2008. doi:10.1097/HJH.0b013e3282fe1d28.
24. **Walker RW**, **Dumke KA**, **Goran MI.** Fructose content in popular beverages made with and without high-fructose corn syrup. *Nutrition* 30: 928–935, 2014. doi:10.1016/j.nut.2014.04.003.
25. **Cheuvront SN**, **Ely BR**, **Kenefick RW**, **Sawka MN.** Biological variation and diagnostic accuracy of dehydration assessment markers. *Am J Clin Nutr* 92: 565–573, 2010. doi:10.3945/ajcn.2010.29490.
26. **Fontolliet T**, **Gianella P**, **Pichot V**, **Barthélémy JC**, **Gasche-Soccal P**, **Ferretti G**, **Lador F.** Heart rate variability and baroreflex sensitivity in bilateral lung transplant recipients. *Clin Physiol Funct Imaging* 38: 872–880, 2018. doi:10.1111/cpf.12499.

27. **Perini R**, **Veicsteinas A.** Heart rate variability and autonomic activity at rest and during exercise in various physiological conditions. *Eur J Appl Physiol* 90: 317–325, 2003. doi:10.1007/s00421-003-0953-9.
28. **Watso JC**, **Robinson AT**, **Babcock MC**, **Migdal KU**, **Wenner MM**, **Stocker SD**, **Farquhar WB.** Short-term water deprivation does not increase blood pressure variability or impair neurovascular function in healthy young adults. *Am J Physiol Regul Integr Comp Physiol* 318: R112–R121, 2020. doi:10.1152/ajpregu.00149.2019.
29. **Howard SC**, **Rothwell PM.** Reproducibility of measures of visit-to-visit variability in blood pressure after transient ischaemic attack or minor stroke. *Cerebrovasc Dis* 28: 331–340, 2009. doi:10.1159/000229551.
30. **Mena L**, **Pintos S**, **Queipo NV**, **Aizpúrua JA**, **Maestre G**, **Sulbarán T.** A reliable index for the prognostic significance of blood pressure variability. *J Hypertens* 23: 505–511, 2005. doi:10.1097/01.hjh.0000160205.81652.5a.
31. **Yong M**, **Diener HC**, **Kaste M**, **Mau J.** Characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke. *Stroke* 36: 2619–2625, 2005. doi:10.1161/01.STR.0000189998.74892.24.
32. **Bertinieri G**, **di Rienzo M**, **Cavallazzi A**, **Ferrari AU**, **Pedotti A**, **Mancia G.** A new approach to analysis of the arterial baroreflex. *J Hypertens Suppl* 3: S79–S81, 1985.
33. **Iellamo F**, **Hughson RL**, **Castrucci F**, **Legramante JM**, **Raimondi G**, **Peruzzi G**, **Tallarida G.** Evaluation of spontaneous baroreflex modulation of sinus node during isometric exercise in healthy humans. *Am J Physiol Heart Circ Physiol* 267: H994–H1001, 1994. doi:10.1152/ajpheart.1994.267.3.H994.
34. **Ebert TJ**, **Cowley Jr AW.** Baroreflex modulation of sympathetic outflow during physiological increases of vasopressin in humans. *Am J Physiol Heart Circ Physiol* 262: H1372–H1378, 1992. doi:10.1152/ajpheart.1992.262.5.H1372.
35. **Parati G**, **Di Rienzo M**, **Mancia G.** How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. *J Hypertens* 18: 7–19, 2000. doi:10.1097/00004872-200018010-00003.
36. **La Fountaine MF**, **Hohn AN**, **Testa AJ**, **Weir JP.** Attenuation of spontaneous baroreceptor sensitivity after concussion. *Med Sci Sports Exerc* 51: 792–797, 2019. doi:10.1249/MSS.0000000000001833.
37. **Maestri R**, **Raczak G**, **Torunski A**, **Sukiennik A**, **Kozlowski D**, **Rovere MTL**, **Pinna GD.** Day-by-day variability of spontaneous baroreflex sensitivity measurements: implications for their reliability in clinical and research applications. *J Hypertens* 27: 806–812, 2009. doi:10.1097/HJH.0b013e328322fe4b.
38. **Eckberg DL.** Sympathovagal balance: a critical appraisal. *Circulation* 96: 3224–3232, 1997. doi:10.1161/01.CIR.96.9.3224.
39. **Anderson EA**, **Hoffman RP**, **Balon TW**, **Sinkey CA**, **Mark AL.** Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J Clin Invest* 87: 2246–2252, 1991. doi:10.1172/JCI115260.
40. **Randin D**, **Vollenweider P**, **Tappy L**, **Jéquier E**, **Nicod P**, **Scherrer U.** Effects of adrenergic and cholinergic blockade on insulin-induced stimulation of calf blood flow in humans. *Am J Physiol Regul Integr Comp Physiol* 66: R809–R816, 1994. doi:10.1152/ajpregu.1994.266.3.R809.
41. **Vollenweider L**, **Tappy L**, **Owlya R**, **Jéquier E**, **Nicod P**, **Scherrer U.** Insulin-induced sympathetic activation and vasodilation in skeletal muscle. Effects of insulin resistance in lean subjects. *Diabetes* 44: 641–645, 1995. doi:10.2337/diab.44.6.641.
42. **Eringa EC**, **Stehouwer CD**, **Merlijn T**, **Westerhof N**, **Sipkema P.** Physiological concentrations of insulin induce endothelin-mediated vasoconstriction during inhibition of NOS or PI3-kinase in skeletal muscle arterioles. *Cardiovasc Res* 56: 464–471, 2002. doi:10.1016/S0008-6363(02)00593-X.
43. **Eringa EC**, **Stehouwer CD**, **Roos MH**, **Westerhof N**, **Sipkema P.** Selective resistance to vasoactive effects of insulin in muscle resistance arteries of obese Zucker (fa/fa) rats. *Am J Physiol Endocrinol Metab* 293: E1134–E1139, 2007. doi:10.1152/ajpendo.00516.2006.
44. **Kim JA**, **Montagnani M**, **Koh KK**, **Quon MJ.** Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation* 113: 1888–1904, 2006. doi:10.1161/CIRCULATIONAHA.105.563213.
45. **Young CN**, **Deo SH**, **Chaudhary K**, **Thyfault JP**, **Fadel PJ.** Insulin enhances the gain of arterial baroreflex control of muscle sympathetic nerve activity in humans. *J Physiol* 588: 3593–3603, 2010. doi:10.1113/jphysiol.2010.191866.
46. **Brand FN**, **McGee DL**, **Kannel WB**, **Stokes J 3rd**, **Castelli WP.** Hyperuricemia as a risk factor of coronary heart disease: the Framingham Study. *Am J Epidemiol* 121: 11–18, 1985. doi:10.1093/oxfordjournals.aje.a113972.
47. **Freedman DS**, **Williamson DF**, **Gunter EW**, **Byers T.** Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I epidemiologic follow-up study. *Am J Epidemiol* 141: 637–644, 1995. doi:10.1093/oxfordjournals.aje.a117479.
48. **Levine W**, **Dyer AR**, **Shekelle RB**, **Schoenberger JA**, **Stamler J.** Serum uric acid and 11.5-year mortality of middle-aged women: findings of the Chicago Heart Association Detection Project in Industry. *J Clin Epidemiol* 42: 257–267, 1989. doi:10.1016/0895-4356(89)90061-9.
49. **Waring WS**, **Adwani SH**, **Breukels O**, **Webb DJ**, **Maxwell SR.** Hyperuricaemia does not impair cardiovascular function in healthy adults. *Heart* 90: 155–159, 2004. doi:10.1136/hrt.2003.016121.
50. **Keyl C**, **Schneider A**, **Dambacher M**, **Bernardi L.** Time delay of vagally mediated cardiac baroreflex response varies with autonomic cardiovascular control. *J Appl Physiol* 91: 283–289, 2001. doi:10.1152/jappl.2001.91.1.283.
51. **Kollai M**, **Jokkel G**, **Bonyhay I**, **Tomcsanyi J**, **Naszlady A.** Relation between baroreflex sensitivity and cardiac vagal tone in humans. *Am J Physiol Heart Circ Physiol* 266: H21–H27, 1994. doi:10.1152/ajpheart.1994.266.1.H21.
52. **Rauh R**, **Burkert M**, **Siepmann M**, **Mueck-Weymann M.** Acute effects of caffeine on heart rate variability in habitual caffeine consumers. *Clin Physiol Funct Imaging* 26: 163–166, 2006. doi:10.1111/j.1475-097X.2006.00663.x.
53. **Chang CS**, **Ko CW**, **Lien HC**, **Chou MC.** Varying postprandial abdominovagal and cardiovagal activity in normal subjects. *Neurogastroenterol Motil* 22: 546–551, 2010.
54. **Rothberg LJ**, **Lees T**, **Clifton-Bligh R**, **Lal S.** Association between heart rate variability measures and blood glucose levels: implications for noninvasive glucose monitoring for diabetes. *Diabetes Technol Ther* 18: 366–376, 2016. doi:10.1089/dia.2016.0010.
55. **Ambarish V**, **Barde P**, **Vyas A**, **Deepak KK.** Comparison between pre-prandial and post-prandial heart rate variability (HRV). *Indian J Physiol Pharmacol* 49: 436–442, 2005.
56. **Grasser EK**, **Dulloo A**, **Montani JP.** Cardiovascular responses to the ingestion of sugary drinks using a randomised cross-over study design: does glucose attenuate the blood pressure-elevating effect of fructose? *Br J Nutr* 112: 183–192, 2014. doi:10.1017/S0007114514000622.
57. **Sims ST**, **Heather AK.** Myths and methodologies: reducing scientific design ambiguity in studies comparing sexes and/or menstrual cycle phases. *Exp Physiol* 103: 1309–1317, 2018. doi:10.1113/EP086797.
58. **Minson CT**, **Halliwill JR**, **Young TM**, **Joyner MJ.** Sympathetic activity and baroreflex sensitivity in young women taking oral contraceptives. *Circulation* 102: 1473–1476, 2000. doi:10.1161/01.CIR.102.13.1473.
59. **Bock JM**, **Iwamoto E**, **Horak JG**, **Feider AJ**, **Hanada S**, **Casey DP.** Aerobic exercise offsets endothelial dysfunction induced by repetitive consumption of sugar-sweetened beverages in young healthy men. *Am J Physiol Regul Integr Comp Physiol* 319: R11–R18, 2020. doi:10.1152/ajpregu.00055.2020.