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Synergistic effect of energy drinks and overweight/obesity on cardiac autonomic testing using the Valsalva maneuver in university students

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BACKGROUND: Obesity and caffeine consumption may lead to autonomic disturbances that can result in a wide range of cardiovascular disorders.

OBJECTIVES: To determine autonomic disturbances produced by the synergistic effects of overweight or obesity (OW/OB) and energy drinks.

DESIGN: Cross-sectional, analytical.

SETTING: Physiology department at a university in Saudi Arabia.

SUBJECTS AND METHODS: University students, 18-22 years of age, of normal weight (NW) and OW/OB were recruited by convenience sampling. Autonomic testing by the Valsalva ratio (VR) along with systolic and diastolic blood pressure, pulse pressure, and mean arterial blood pressure were measured at baseline (0 minute) and 60 minutes after energy drink consumption.

MAIN OUTCOME MEASURE(S): Autonomic disturbance, hemodynamic changes.

RESULTS: In 50 (27 males and 23 females) subjects, 21 NW and 29 OW/OB, a significant decrease in VR was observed in OW/OB subjects and in NW and OW/OB females at 60 minutes after energy drink consumption. Values of systolic and diastolic blood pressure, pulse pressure and mean arterial blood pressure were also significantly higher in OW/OB and in females as compared to NW and males. BMI was negatively correlated with VR and diastolic blood pressure at 60 minutes.

CONCLUSION: Obesity and energy drinks alter autonomic functions. In some individuals, OW/OB may augment these effects.

LIMITATIONS: Due to time and resource restraints, only the acute effects of energy drinks were examined.

Altered autonomic nervous system (ANS) regulation is thought to be a major mechanism in the genesis of various cardiovascular ailments manifested by increased sympathetic nervous system (SNS) or decreased parasympathetic nervous system (PNS) activity, manifested as reduced R–R interval, decreased baroreflex sensitivity (BRS), and enhanced SNS vasomotor tone.[1,2] Autonomic testing is widely used in clinics and research to assess autonomic disturbance in diabetes mellitus, multiple sclerosis, cancer and diverse cardiovascular illnesses.[1,3-5] Various epidemiological studies support the association between cardiac autonomic disturbance and mortality risk in previously asymptomatic subjects.[6-9] Wulsin et al revealed that autonomic dysfunction is associated with a risk of developing coronary heart disease.[6] Wellens et al also found altered autonomic response as an atherosclerotic risk that might lead to sudden cardiac death.[7] Therefore, autonomic testing is not only used to identify abnormal autonomic function for secondary prevention, but is also important for primary prevention. Autonomic measurements offer significant additional prognostic information over that offered by assessment of traditional cardiovascular risk factors like age, gender and others.[10] Various procedures have been described as diagnostic tools to monitor autonomic dysfunctions like tilt table

testing, traditional neurophysiologic measurements of sudomotor function, and Valsalva ratio (VR).[11,12] The VR is a simple, economical, non-invasive and reproducible method to diagnose or investigate ANS dysfunction. VR measures parasympathetic afferent (baroreceptor) and efferent (parasympathetic and sympathetic) autonomic nervous system functions.[13]

Obesity inflicts a considerable health burden on the community and individual, increasing morbidity and mortality. In the Middle East, the pandemic of obesity predominantly affects Saudi Arabia.[14] As per the WHO report, the worldwide incidence of obesity has doubled since 1980, affecting more than 1.9 billion adults 18 years and older and alarmingly, 41 million children under the age of 5 were overweight or obese.[15] In Saudi Arabia, the prevalence of overweight and obesity in young males and females was 23% and 30%, respectively.[16] Furthermore the incidence of obesity is highest in the eastern region of Saudi Arabia.[17]

Energy drinks, contemporary substitutes for cola, hold dangerously high doses of caffeine along with taurine and other carbohydrates.[18] With a reported 34.5 million consumers worldwide, there is hefty use in Saudi Arabia, predominantly in younger individuals.[19,20] These drinks provide an energy boost, wakefulness, alertness, and cognitive and mood enhancement at the cost of increasing the risk of atrial fibrillation, palpitations, headaches and seizure.[21,22] Energy drinks are banned for younger individuals and athletes in many countries after incidents of cardiac failure purportedly linked to consumption of energy drinks.[23,24] Since March 2014, the Saudi government has banned the sale of energy drinks at all government, health and education facilities.[25]

Both obesity and caffeinated drinks initiate reversible autonomic dysfunction that might become permanent and lethal if untreated.[26-29] Many studies have observed autonomic dysfunction but few have attempted to examine possible relationships with body weight and other variables such as gender.[30] Therefore, we aimed to assess whether there are synergistic effects of obesity with energy drink consumption in otherwise healthy male/female college students. We planned to study the effects of any autonomic dysfunction by noninvasive, easily accessible autonomic testing using the Valsalva maneuver and calculating a Valsalva ratio (VR).

SUBJECTS AND METHODS

The study was carried out at the Department of Physiology, College of Medicine, University of Dammam, Saudi Arabia from December 2014 to December 2015. Ethical permission for the project was obtained from the ethical committee deanship of Scientific Research, University of Dammam. This cross-sectional study used convenience sampling to select healthy Saudi male and female university students 18 to 22 years of age by advertisement in the colleges. Based on an earlier report by Alsunni et al, we decided on a sample size of 30 in each group.[30] Subjects were divided into two groups: normal weight (NW) (BMI=18.5 to 24.9 kg/m²) and overweight and obese (OW/OB) (BMI >25 kg/m²). Subjects were excluded if they had liver, kidney or cardiovascular disease, diabetes mellitus, anemia, electrocardiogram (ECG) abnormalities at baseline, smoked tobacco, or used any kind of medication or herbal supplements. Subjects were excluded if they had a known sensitivity to taurine or caffeine, were trained athletes or were regularly exercising, were pregnant or menstruating females, or regular users of energy drinks. Subjects were instructed to abstain from caffeine for at least 3 days prior to the testing. The subjects were also instructed not to eat or drink anything except water after 12 midnight before the day of the session. Written informed consent was taken from all the volunteers.

Upon arrival at the laboratory, the subjects were briefed about the protocol. Waist circumference (WC) and hip circumference were measured with a non-stretchable plastic tape to get the waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-stature ratio (WSR). Subjects were wired for recording of an ECG with a Power Lab 8/30 system (AD Instruments, Australia). while seated in a comfortable position. A single-lead recording was done with the ECG electrodes placed on the right and left shoulders (equivalent to limb lead I) with an earth electrode at the back. The wires were connected through the ECG box to a bioamplifier (ML132-AdInstruments) connected to the PowerLab. Blood pressure was monitored with a Welch Allyn SPOT vital sign monitoring device. Baseline data (0 minute) was recorded while subjects were breathing spontaneously for at least 7 minutes. The subjects were then provided with 5 mL/kg body weight of energy drink (Red Bull, Red Bull GmbH, Thailand). A can of Red Bull contains taurine 100 mg, glucuronolactone 600 mg, caffeine 80 mg, vitamin B5 6 mg, sucrose 21.5 g and glucose 5.25 g. An additional recording was done at 60 minutes after energy drink consumption. The whole session took approximately 1 hour and 30 minutes for each individual.

The Valsalva maneuver was performed in the sitting position and the procedure was repeated three times with three minute gaps. Each subject practiced the procedure until he/she was comfortable with it. Subjects

were instructed to take a deep breath and then blow into a 10-mL syringe by keeping the pressure at 40 mm Hg for 15 seconds.[31] The Valsalva ratio (VR) was obtained from the ECG by dividing the minimum heart rate during the Valsalva maneuver (longest R-R interval) with the maximum heart rate after the Valsalva maneuver (shortest R-R interval); a ratio greater than 1.45 was considered normal.[11]

Data was entered into IBM SPSS statistics version 20.0 (Armonk, NY, USA). Means and standard deviations were calculated. The unpaired t test was used to compare the VR values and cardiovascular variables between groups (normal weight and overweight/ obese and male and female). The paired t test with 95% confidence intervals was used to compare within-group differences at 0 and 60 minutes after consumption of an energy drink. The Spearman rank correlation coefficient or Spearman's rho was used to assess correlation between BMI versus VR and cardiovascular variables. For all tests, the level of statistical significance was set at $P<.05$.

RESULTS

Sixty-five subjects met the inclusion criteria, but 15 were unavailable or withdrew during the course of the study. Of the 50 participants (27 males and 23 females) who completed the study (21 NW and 29 OW/ OB), OW/OB subjects had a higher BMI ($P=.001$), WC ($P=.001$), HC ($P=.001$) and WSR ($P=.001$) as compared to NW subjects (**Table 1**). Males had higher values for WC ($P=.001$), HC ($P=.001$), systolic blood pressure ($P=.001$), PP ($P=.001$) and MABP ($P=.05$) compared to females. Mean (SD) VR in females was lower than in males at 60 minutes ($P<.003$), while there were no changes in VR within gender groups (**Table 2a**). For NW subjects, there was no difference between 0 and 60 minute values in VR, but for OW/OB subjects there was a borderline significant difference at 60 minutes as compared to 0 minutes (**Table 2b**).

No significant differences were found between the NW and OW/OB groups in hemodynamic variables, but comparison of values within the group found significant increases in OW/OB group at 60 minutes as compared to 0 minute in systolic blood pressure, diastolic blood pressure and MABP (**Table 3**). Significant changes over 60 minutes were also observed in the NW group in systolic blood pressure and MABP at 60 minutes as compared to 0 minute.

Comparison of various hemodynamic variables in males and females found significant differences in systolic blood pressure and pulse pressure at 0 and 60 minutes ($P=.001$) (**Table 4**). There were significant changes in hemodynamic variables over 60 minutes within the groups. In males systolic blood pressure at 60 minutes increased significantly from 0 minutes. In females, there were significant changes in systolic blood pressure, diastolic blood pressure and MABP at 60 minutes as compared to 0 minute.

Negative correlations were observed at 60 minutes after consumption of an energy drink between BMI

Table 1. Baseline characteristics of study participants.

Variables	Normal weight (n=21)	Overweight/obese (n=29)	Male (n=27)	Female (n=23)
Mean age (years)	20.5 (0.59)	20.6 (0.67)	20.7 (0.60)	20.5 (0.66)
BMI (kg/m²)	21.9 (2.06)	32.7 (6.09)[a]	29.3 (7.64)	26.9 (6.62)
WC (cm)	75.4 (8.92)	97.0 (14.53)[a]	94.7 (16.17)	79.9 (12.8)[a]
HC (cm)	94.6 (6.74)	118.1 (12.85)[a]	111.2 (15.19)	104.7 (16.17)[a]
WHR (cm)	.79 (.06)	.82 (.09)	.85 (.06)	.76 (.07)
WSR (cm)	45.7 (4.05)	58.7 (6.95)[a]	55.3 (9.11)	50.8 (7.75)
SBP (mm Hg)	122.3 (19.16)	120.3 (16.53)	130.1 (18.6)	110.6 (7.81)
DBP (mm Hg)	74.9 (12.53)	71.6 (7.95)	72.8 (12.74)	73.3 (6.09)
PP (mm Hg)	47.4 (13.72)	48.6 (15.72)	57.2 (13.50)	37.3 (6.97)[a]
MABP (mm Hg)	90.7 (13.63)	87.9 (8.82)	91.9 (13.54)	85.8 (5.85)[b]
VR0	1.67 (.23)	1.61 (.24)	1.68 (.18)	1.59 (.29)

Values are mean (standard deviation). BMI: body mass index, WC: waist circumference, HC: hip circumference, WHR: waist to hip ratio, WSR: waist to stature ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, MABP: mean arterial blood pressure, VR0: Valsalva ratio at 0 minute; [a]$P<.001$, [b]$P=.05$

Table 2a. Valsalva ratio at 0 and 60 minutes by gender with statistical significance indicated in the margins (values are mean and standard deviation).

	Male (n=27)	Female (n=23)	
Valsalva ratio 0 minute	1.68 (0.19)	1.59 (0.29)	.371
Valsalva ratio 60 minutes	1.67 (.16)	1.48 (.21)	<.003[a]
	.900	.066	

[a]95% confidence interval for difference in means: -.35 to -0.0. Two-tailed paired (within group) or unpaired *t* test (between groups).

Table 2b. Valsalva ratio at 0 and 60 minutes by weight with statistical significance indicated in the margins (values are mean and standard deviation).

	Normal weight (n=21)	Overweight/ obese (n=29)
Valsalva ratio 0 minute	1.68 (0.23)	1.61 (0.25)
Valsalva ratio 60 minutes	1.69 (0.15)	1.51 (0.23)
	.843	<.058[b]

[b]95% confidence interval for difference in means: -0.004 to 0.216). Two-tailed paired (within group) or unpaired *t* test (between groups).

versus VR (r=-.30, *P*=.035) (**Figure 1** left) and diastolic blood pressure (r=-.30, *P*=.037) (**Figure 1** right). Other correlations were insignificant.

DISCUSSION

We examined the possibility of a relationship between obesity and energy drink consumption on various hemodynamic parameters and autonomic test using the Valsalva ratio in young Saudi male and female university students. Consumption of energy drinks in obese individuals with autonomic dysfunction may be dangerous, especially to the cardiovascular system. To our knowledge this is the only reported study that has examined energy drink consumption in the overweight/obese and possible effects on autonomic system specifically using the VR. We found autonomic dysfunction manifested as a decreased VR after 60 minutes of consumption of an energy drink, particularly in the OW/OB group. Different hemodynamic parameters were also significantly altered by energy drink consumption, predominantly in the OW/OB group, but substantial changes were detected at 60 minutes in both the NW and OW/OB groups in both genders.

Our results are comparable to results witnessed by other researchers.[32-34] Al Sunni et al found autonomic imbalances in OW/OB subjects as compared to normal weight subjects using QTc and heart rate variability for

Table 3. Comparison of systolic blood pressure, diastolic blood pressure, pulse pressure and mean arterial blood pressure between normal weight and overweight and obese subjects at different time points.

Variables	Normal weight (n=21)	Overweight/ obese (n=29)
Systolic blood pressure (mm Hg)		
0 minute	122.3 (19.1)	120.3 (16.5)
60 minute	131.9 (23.4)[a]	129.1 (16.7)[b]
Diastolic blood pressure (mm Hg)		
0 minute	74.9 (12.5)	71.6 (7.9)
60 minute	79.0 (13.9)	77.2 (10.5)[c]
Pulse pressure (mm Hg)		
0 minute	47.6 (13.7)	48.6 (15.7)
60 minute	52.8 (22.3)	51.8 (17.1)
Mean arterial blood pressure (mm Hg)		
0 minute	90.7 (13.6)	87.9 (8.8)
60 minute	96.7 (14.0)[d]	94.4 (10.0)[e]

Values are mean (standard deviation).
95% confidence interval for within-group differences from 0 to 60 minutes and *P* value:
[a]15.07-4.05; *P*=.002
[b]13.4-4.43, *P*=001
[c]3.15-9.94; *P*=.003
[d]2.36-9.60; *P*=.003
[e]4.05-15.07, *P*=001

autonomic testing.[30] Prior et al found a dose-dependent increase in sympathetic excitation and arterial pressure in response to leptin that was more pronounced in OW/OB subjects.[32] They believed that the impairment of autonomic cardiac control seen in OW/OB subjects is associated with leptin levels, insulin resistance, increased oxidative stress and inflammation that mainly originated from adipose tissue. Along with that, activation of the sympathetic nervous system may also play a significant role in increasing renal sodium reabsorption, impairing pressure natriuresis that might lead to altered kidney function and hypertension in obese subjects.[33]

Contrary to our observations, Hursh et al found no significant difference in cardiac autonomic testing between normal and obese subjects, although they discovered high levels of C-reactive protein, an inflammatory marker in obese subjects, suggesting a possible link between development of metabolic syndrome and cardiovascular diseases.[34] Autonomic disturbance was

correlated in our study with obesity that originated from increased sympathetic and decreased parasympathetic activity as witnessed by augmented systolic blood pressure, diastolic blood pressure and mean arterial blood pressure in the OW/OB subjects. Autonomic imbalance may alter hemodynamics by affecting peripheral vascular resistance, adrenal medullary activity, sinoatrial nodal discharge and myocardial contractility.[35,36] Our observations are supported by Johncy et al, who found increased sympathetic and decreased parasympathetic activity in OW/OB subjects with a family history of hypertension.[37]

We observed marked autonomic disturbance in females compared to males. In addition to cardiovascular ailments, ANS dysfunction in females generates hormonal imbalances, polycystic ovarian disease and infertility.[38-40] Saleem et al found low autonomic response in females as compared to males, which reflected sympathetic dominance in the women in their study population.[41] In contrast to our study Sharma et al observed relatively higher parasympathetic activity and lesser sympathetic activity in females as compared to males (age group 12 to 17 years).[42] They noted that testosterone in males increases sympathetic activity, while estrogen decreases sympathetic activity in females. This idea is backed by Sookan et al, who considered this a cardioprotective mechanism in premenopausal females compared to males.[43] This suggestion is further reinforced by Zhao et al who noticed that younger women have better autonomic activity than age-matched men; they further concluded that this gender difference decreased above the age of 30 years until there was no difference above 50 years between the two groups.[44] The mechanism of gender disparity in changes of au-

Table 4. Comparison of systolic blood pressure, diastolic blood pressure, pulse pressure and mean arterial blood pressure between males and females at 0 and 60 minutes after consumption of an energy drink.

Variable	Males (n=27)	Females (n=23)
Systolic blood pressure (mm Hg)		
0 minute	130.1 (18.6)	110.6 (7.8)
60 minute	138.9 (21.6)[a]	120.1 (10.1)[b]
Diastolic blood pressure (mm Hg)		
0 minute	72.8 (12.7)	73.3 (6.0)
60 minute	75.7 (14.3)	80.6 (7.9)[c]
Pulse pressure (mm Hg)		
0 minute	57.2 (13.5)	37.3 (6.9)
60 minute	63.2 (19.6)[d]	39.4 (7.3)
Mean arterial blood pressure (mm Hg)		
0 minute	91.9 (13.5)	85.8 (5.8)
60 minute	96.8 (14.2)	93.8 (8.1)[e]

Values are mean and standard deviation. 95% confidence interval for within-group differences.
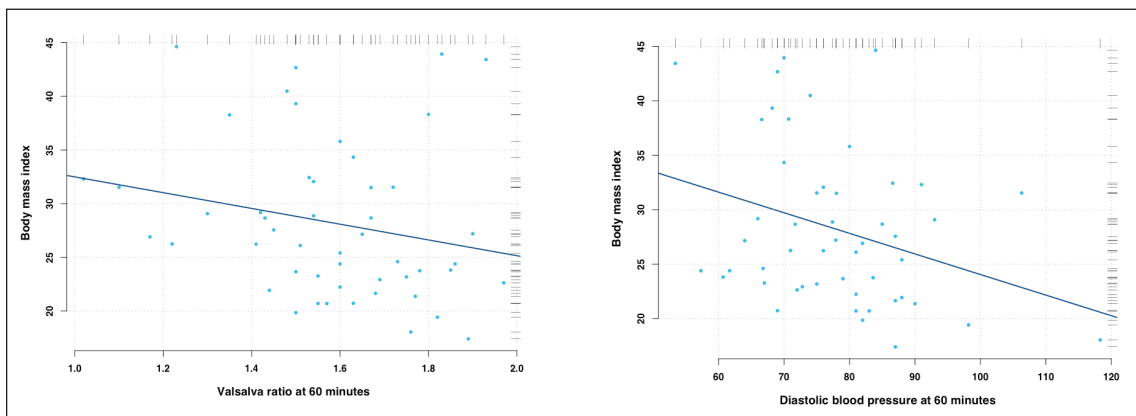[a] 0 vs 60 minutes: 3.16-14.52; *P*=.004
[b] 0 vs 60 minutes: 6.17-12.69, *P*<.001
[c] 4.19-10.49, *P*=.001
[d] 0 vs 60 minutes: -12.1 to 0.20, *P*=.057
[e] 0 vs 60 minutes: 5.17-10.83, *P*<.001

tonomic cardiac function is not clear; estrogen and cytokine expression may play a role in the different autonomic modulation.[45] Men have been reported to have higher sympathetic tone with an increased number of

Figure 1. Correlation of BMI with Valsalva ratio 60 minutes after consumption of energy drink (left) (Spearman correlation coefficient rho=-0.30, *P*=.035, n=50) and diastolic blood pressure (right). (Spearman correlation coefficient rho = -0.30, *P*=.037, n=50).

neurons in the sympathetic ganglion and higher muscular sympathetic activity.[46]

In contrast to our study, Jain et al found no difference in VR in between normal weight and obese individuals, but observed increased diastolic blood pressure in obese subjects after stress-like exercise.[47] The possible reason for this disparity is that they used a cut off value for BMI between normal and obese of 23 kg/m^2 (new WHO criteria for an Indian population). In support of our study, Tonhajzerova et al observed a lower VR in OW/OB as compared to a control group in a study of OW/OB children.[48]

Energy drinks contain a large amount of caffeine with other energy promoting ingredients like glucose, taurine, vitamins, minerals and some herbal extracts. The combination of caffeine with these substance can further enhance its effects.[18] A can of energy drink possesses approximately 25-40 g of glucose, an amount sufficient to cause to hyperglycemia. Hyperglycemia is considered to be cardiotoxic and an important risk factor for various cardiovascular diseases.[49] The absorption time of caffeine is also important. The variation from 30 to 60 minutes might reflect the peak of caffeine levels around that time in our participants.[50] Many studies have shown that caffeine or caffeinated drinks alter autonomic activities, but the precise underlying mechanisms remain poorly understood.[51-54] Bunsawat et al found altered autonomic function with caffeinated drinks along with delayed autonomic recovery after exercise in their subjects. They believed that caffeine increased catecholamine release, elevated blood pressure, inhibited baroreflex function, prolonged the QT interval and decreased heart rate by stimulating sympathetic nerve activity.[51] Similar results were also presented by Flueck et al,[52] Gomar et al[53] and

Chrysant et al.[54] They observed that caffeine increased sympathetic activity and produced autonomic modulation by acting on adenosine receptors on heart muscle cells, which initiates a second messenger system with cyclic adenosine monophosphate within the cells, mimicking the effects of epinephrine to increase heart rate and cardiac contractility at the same time enhancing the release of cortisol and increasing peripheral vascular resistance and blood pressure. Another study by Monda et al found increased parasympathetic and decreased sympathetic response after consumption of caffeinated drink in a case-control study of 20 subjects.[55]

One of the limitations of this study is that we only examined the acute effects of energy drink on our participants. Further assessment of habitual consumers is needed to evaluate chronic effects on health. Also, we were unable to propose a primary culprit among the components of the energy drink that might be involved in autonomic disturbance.

Energy drinks are very popular among our Saudi youth, but awareness of potential health hazards is limited.[56,57] We found that reduced parasympathetic drive and/or increased sympathetic outflow in females and particularly in OW/OB subject is further augmented by energy drinks. The VR is an effective, cheap and widely accepted method that can be conveniently used for the detection of autonomic dysfunction. Early detection of such autonomic changes by VR may be important in management of obesity and energy drink habits. Awareness of the effects of consumption can lead to a safer and healthier life.

Conflict of interest

The authors report no conflict of interest.

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