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Hemodynamic and Autonomic Reactivity to Mental and Physical Stress in Lean, Overweight and Obese Subjects

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Abstract

Objective: There could be progressive changes in hemodynamic and autonomic parameters causing cardiovascular damage from lean to morbid obesity. We aim to study resting and reactivity of hemodynamic and autonomic parameters to physical and mental stress in lean, overweight and obese subjects of the Oman Family Study (OFS).

Materials and Methods: Normal subjects from OFS, grouped as lean (N=437; Males=194), overweight (N=366; Males=172) and obese (N=214; Males=90) based on WHO classification of BMI underwent impedance cardiography and spectral analysis to estimate hemodynamic and autonomic parameters at rest and during 3min of word conflict test (WCT) and cold pressor test (CPT).

Results: At rest, overweight had high BP compared to lean, similar BP in overweight and obese and lowest stroke index (SI) in obese and low power spectral density ($P<0.05$) in obese compared to overweight. The changes (Δ) in HR, mean BP, cardiac and peripheral resistance index were similar in 3 groups during WCT. Autonomic responses to WCT and CPT were similar in 3 groups. Obesity measures (BMI, % fat) showed monotonic correlations with resting hemodynamic and autonomic parameters and with ΔWCT and CPT HR and SI.

Conclusion: The Hemodynamic and autonomic alterations and reactivity are inconsistent in 3 groups. The question arises whether clinically overweight are different from obese ones.

Keywords: Obesity; Hemodynamic reactivity; Autonomic reactivity; Mental stress; Physical stress

Abbreviations: Δchange: Magnitude of the response to the stress; BMI: Body mass index; BP: Blood pressure; BRS: Baroreceptor sensitivity; CI: Cardiac index; CO: Cardiac output; CPT: Clod Pressor Test; DBP: Diastolic blood pressure; HDL: High density lipoprotein; HFnu: High frequency normalized units; HOMAiR: Insulin resistance; HR: Heart rate; HRV: Heart rate variability; LDL: Low density lipoprotein; LF/HF: Sympathovagal balance; LFnu: Low frequency normalized units; LVET: Left ventricular ejection time; MSNA: Muscle sympathetic nerve activity; OFS: Oman Family Study; PSD: Power spectral density; RRI: R-R interval; SBP: Systolic blood pressure; SI: Stroke index; SV: Stroke volume; TFM: Task Force Monitor; TG: Triglycerides; TPRI: Total peripheral resistance index; WC: Waist circumference; WCT: Word Conflict Test; WHO: World Health Organization; WHR: Waist-to-hip ratio

Introduction

Obesity is a known risk for cardio-metabolic diseases such as hypertension, ischemic heart disease [1,2], type-2 diabetes mellitus [3] and comorbidities like obstructive sleep apnea [4]. Previous studies showed hemodynamic and autonomic alterations in lean compared to obese [5,6] such as increased resting heart rate (HR), blood pressure (BP) [5,7], muscle sympathetic nerve activity (MSNA) [5,7,8], left ventricular mass index [9] and low frequency spectrum of heart rate variability (HRV) [6]. Contrary to this, autonomic activity was also shown to decrease with obesity [10,11] and had inverse relationship with body fat percentage [1].

Mental and physical laboratory stress tests in humans are known to expose hemodynamic and autonomic abnormalities that are not evident during resting states [12,13]. Reactivity to mental stress using the word conflict test (WCT) [5,14] or physical stress using the cold pressor test (CPT) [5,8,15,16] showed different responses in lean, overweight and obese subjects. A study in children showed higher resting BP and lower forearm vascular resistance in obese compared to lean children [17]. Obese children also showed significantly higher BP and lower forearm vascular response to WCT and to hand grip test.

It has been postulated that, in the clinical course, there would be progression of sympathetic excitation leading to cardiovascular, renal and target organ damage as obesity progresses from lean to overweight and morbid obesity [18]. Many studies have compared hemodynamic and autonomic reactivity during laboratory stress tests in lean with either overweight or obese subjects. We are not aware of any studies that compared baseline hemodynamic and autonomic parameters and their reactivity in lean, overweight and obese subjects simultaneously. We hypothesize that resting and reactivity of hemodynamic and autonomic parameters would show successive impairment from lean to overweight to obese subjects. This study therefore aims to compare baseline, hemodynamic and autonomic parameters' reactivity to physical and mental stress in lean, overweight and obese subjects of the Oman Family Study (OFS).

Materials and Methods

Study area and Pedigrees

The OFS included voluntarily participation of 1277 (age 16-80years) subjects from at least three generations of 5 large families living in separate villages within a perimeter of 20 km around the city of Nizwa, the capital of the interior province of Oman. They represented about 10-15% of total number of individuals of these families. They appeared healthy and had no clinical complaints. A more detailed description of the stratification of the cohort and OFS was reported elsewhere [19,20].

Subjects (N=1149) from OFS aged 18-50 years were invited to participate. A written, explained, signed or thumb rubber stamped consent was obtained from each subject. Out of invited, 1017 (88.5%) subjects took part in the study. They were divided into lean (N=437; Males=194), overweight (N=366; Males=172) and obese (N=214; Males=90) defined according to the World Health Organization (WHO) criteria as described below. The remaining 132 subjects were unable to participate in the study because they work outside Nizwa. The study was approved by Sultan Qaboos University Ethics Committee (Project ID: SR/med/phys/04/01).

Anthropometric measurements

Weight and height were measured using standard methods. Body fat percentage (% fat) was assessed using electrical impedance (Tanita, Japan). Body mass index (BMI Kg/m^2) was estimated by dividing weight (Kg) with the square of height in meters. Obesity groups were defined according to WHO criteria as lean (BMI 18.9-24.9Kg/m^2); Overweight (BMI 25.0-34.9Kg/m^2) and Obese (BMI >35Kg/m^2) [21].

Waist circumference (WC, cm) was measured by a soft tape at the highest point of the iliac crest at minimal respiration to the nearest 0.1cm and hip circumference around the widest circumference of the buttocks, with the tape parallel to the floor [21]. Waist-to-hip ratio (WHR) was calculated by dividing WC by hip circumference.

Hemodynamic and autonomic measurements

The hemodynamic and autonomic parameters were acquired using the Task Force Monitor (TFM, CNsystems, Austria) [22]. The HR was calculated from the 6-lead electrocardiogram and BP from beat-to-beat BP using the vascular unloading technique [22]. Beat-to-beat BP was automatically corrected every minute by the oscillometric BP measurements recorded from the contra-lateral upper arm. The impedance signal was obtained with a small constant sinusoidal alternating current passing between an electrode placed around the neck and two others placed at the mid-axillary line at the lower end of the sternum. The voltage between the electrodes is proportional to the thorax impedance. Left ventricular ejection time (LVET), the time between points 'B' and 'X' (opening and closure of aortic valve, respectively) of the impedance signal, is considered in further calculations of hemodynamic parameters [22] and were indexed for body surface area as stroke index (SI), cardiac index (CI) and total peripheral resistance index (TPRI).

Autonomic parameters were computed using adaptive autoregressive model from beat-to-beat R-R-interval (RRI) using frequency domain spectral analysis of the HRV. The TFM calculated absolute and normalized units (nu) of the low frequency (LF: 0.05-0.15Hz) (RRI-LFnu) and high frequency (HF: 0.15-0.40Hz) (RRI-HFnu) bands of HRV and for 0.05-0.15Hz band of systolic BP variability (SBP-LFnu) [23]. The RRI-HFnu represented parasympathetic modulation of the sinoatrial node and sympathetic modulation of vasomotor tone was represented by RRI-LFnu and SBP-LFnu. Sympathovagal balance (LF/HF) was calculated as the ratio of SBP-LFnu and RRI-HFnu. Baroreceptor reflex sensitivity (BRS) was automatically assessed using the sequence technique [24,25].

Laboratory stress tests

The word conflict test (WCT) involving sensory rejection and components of decision-making is a validated psycho-physiological indicator of stress reactivity [26]. The incongruence of verbal narration of the conflict of words and colors shown in this test invokes cardiovascular responses. There is no learning effect or tolerance with repeated testing and response is not affected by gender [12,27]. The original English names of colors were translated into *Arabic*. This Arabic chart where names of colors are written in different colors (e.g. Colour Blue written in red) was displayed on a monitor. The observer selected words at a constant speed of one word/sec. The subject was asked to narrate the color of the word and not read the word. Subjects were encouraged to respond faster and to concentrate fully throughout the test.

Out of the 1017 subjects a total of 436 (lean: N=246, males=51%; overweight: N=114, males=53%; and obese: N=76, males=46%) completed the WCT. This is due to illiteracy especially of females.

The cold pressor test (CPT) involves immersion of the hand/foot in ice-cold water. This stimulates a local cold sensation which turns into pain sensation within 30 seconds triggering cardiovascular reactivity [13,28]. The left foot of the subject was immersed in cold water with crushed ice (temperature 2-4°) up to the ankle joint for 3 minutes. The foot was used as both hands were connected to the TFM for BP measurements. At the end of the test, the foot was wrapped in a towel.

The CPT was completed by 900/1017 subjects (lean: N=396, M 44%; overweight: N=316, M 47%; and obese: N=188, M 43%). Some subjects refused the test (57%) and few could not tolerate the pain during CPT (34%).

Biochemical measurements

Biochemical tests included fasting and 2-hour blood glucose and serum insulin levels, total serum cholesterol, low-density lipoprotein (LDL), high density lipoprotein (HDL) cholesterol and triglycerides (TGs). Insulin resistance was indicated by HOMAiR as [FPG(millimolar)*fasting insulin(microunits/milliliter)/22.5]. All sera for biochemical tests were processed the same day of sample collection at the University Hospital laboratories using modern automated equipment (Synchron 7, Access II and Image; Beckman Coulter, Fullerton, CA). Further details of methodology of biochemical analysis and quality assurance are described elsewhere [29].

Experimental Protocol

All experiments were conducted in a quiet room in the field research centre from 07:00 to 12.00 hours with a comfortable room temperature of 24-26 °C. Subjects were transported to the center after an overnight fast and blood was withdrawn for biochemical tests. Subjects were then connected to the TFM. After 10 minutes of supine rest, hemodynamic and autonomic parameters were recorded as follows: 10minutes- rest, 3minutes- WCT, 3-5minutes- recovery or until parameters retuned to baseline, followed by 3minutes- CPT.

Tests were administered by the same male/female technician for the respective gender. Quality assurance of all work was ascertained by duplicate measurements from randomly allocated subjects and restricting all measurements to maximally 2 matched observers for anthropometric, and biochemical parameters.

Statistics

Descriptive and comparative analyses were performed using SPSS package (version-21). Parametric data were expressed as means+SD/SEM. Probability value of <0.05 was considered statistically significant.

Anthropometric measurements of the 3 BMI groups were compared using one way analysis of variance with Scheffe's *post-hoc* test for group differences. Univariate analysis adjusted for age and gender with obesity as fixed factors was used to test differences in biochemical and baseline hemodynamic and autonomic parameters among 3 BMI groups.

Beat-to-beat measurements obtained with TFM were averaged for time periods of 10 minutes of rest, and 3 minutes of WCT and CPT. A two-way repeated-measure ANOVA adjusted for age and gender was used to test possible differences within and between three obesity groups for hemodynamic and autonomic reactivity to both physiological challenges. Repeated measure analysis was considered eligible for interpretation when the overall F-test was significant [30]. The P value is given for the group and time interaction estimated using this two-way repeated-measure ANOVA adjusted for age and gender. Bonferroni adjustment was used to check *post-hoc* group differences.

For all subjects, weight, BMI, waist and WHR were correlated with biochemical measures using Spearman's correlation test. Spearman's correlation test was also used to correlate hemodynamic and autonomic measures at rest and during WCT and CPT stress.

Results

Anthropometric and biochemical parameters

Table 1 - shows the characteristics of the 3 obesity groups. Lean subjects were significantly younger than overweight and obese who were of similar age. Waist circumference and % fat showed significant linear increase from lean to obese.

Fasting and 2-H glucose were similar in the 3 groups. Fasting insulin was significantly higher in the overweight and obese compared to the lean one and significantly higher in the obese compared to the overweight group. However, 2-H insulin was significantly higher in the obese compared to the lean and overweight. The HOMAiR and serum leptin showed significant linear increase from lean to obese groups. The HDL and LDL were similar amongst 3 groups, but TGs was significantly higher in overweight and obese compared to lean (Table 1).

	Lean (Ln)	Overweight (Ow)	Obese (Ob)	P (Ln–Ow)	P (Ln-Ob)	P (Ow-Ob)
Age	32.8 (16.3)	38.0 (15.4)	38.1 (3.7)	0.0001	0.0001	0.43
Weight	56.6 (7.5)	68.5 (8.6)	83.4 (12.0)	0.0001	0.0001	0.0001
BMI	22.6 (1.4)	27.3 (1.5)	34.0 (3.8)	0.0001	0.0001	0.0001
WC	73.2 (0.7)	85.4 (0.7)	98.8 (0.9)	0.0001	0.0001	0.0001
WHR	0.87 (0.1)	0.92 (0.1)	0.96 (0.1)	0.0001	0.0001	0.007
Body fat	20.1 (6.8)	28.3 (7.0)	35.4 (7.3)	0.0001	0.0001	0.0001
Sugar 0-H	5.3 (0.1)	5.6 (0.1)	5.7 (0.1)	0.184	0.068	0.489
Sugar 2-H	6.4 (0.2)	6.7 (0.2)	7.3 (0.3)	0.316	0.330	0.211
Insulin 0-H	3.7 (0.3)	4.5 (0.3)	6.2 (0.4)	0.005	0.0001	0.0001
Insulin 2-H	19.5 (1.7)	22.2 (1.8)	33.2 (2.3)	0.171	0.0001	0.0001
HOMAir	0.9 (0.1)	1.1 (0.1)	1.6 (1.0)	0.007	0.0001	0.0001
TG	0.9 (0.1)	1.2 (0.1)	1.4 (0.1)	0.019	0.0001	0.103
HDL	1.1 (0.03)	0.9 (0.03)	0.9 (0.04)	0.816	0.042	0.364
LDL	3.1 (0.1)	3.3 (0.1)	3.4 (0.1)	0.910	0.310	0.361
Leptin	17.4 (1.2)	31.8 (1.3)	50.4 (1.8)	0.0001	0.0001	0.0001
HR	69.0 (0.7)	68.0 (0.8)	71.4 (1.0)	0.585	0.025	0.007
SBP	111.0 (1.3)	116.0 (1.4)	115.0 (1.7)	0.011	0.055	0.809
DBP	69.0 (1.0)	75.0 (1.0)	74.0 (1.3)	0.002	0.110	0.295
MBP	81.7 (1.1)	87.5 (1.2)	85.2 (1.5)	0.006	0.160	0.353
SI	49.6 (0.8)	44.2 (0.8)	40.1 (1.1)	0.002	0.0001	0.028
CI	3.5 (0.1)	2.9 (0.1)	2.8 (0.08)	0.003	0.002	0.577
TPRI	1938.9 (52.6)	2420.6 (56.4)	2441.6 (72.9)	0.0001	0.001	0.854
LFnu	48.3 (1.5)	52.0 (1.6)	48.4 (2.1)	0.109	0.789	0.027
HFnu	51.7 (1.5)	47.9 (1.6)	51.5 (2.1)	0.109	0.789	0.274
LF/HF	1.2 (0.1)	1.4 (0.1)	1.3 (0.1)	0.08	0.262	0.0944
PSD	11.9 (0.1)	11.9 (0.1)	11.4 (0.1)	0.944	0.020	0.017
BRS	18.2 (1.1)	18.4 (1.1)	14.9 (1.5)	0.262	0.622	0.150

Age yr; Weight kg; BMI- Body mass index kg/m^2; WC- waist circumference cm; WHR- waist to hip ratio; body fat %; Sugar mM; Insulin IU; HOMAiR: Insulin resistance; TG- Triglycerides mM; HDL- High density lipoprotein mM; LDL- Low density lipoprotein mM; Leptin ng/mL; HR- Heart rate bpm; SBP- Systolic BP mmHg; DBP- Diastolic BP mmHg; MBP- Mean BP mmHg; SI- Stroke index ml/m^2; CI- cardiac index L/min*m^2; TPRI- Total peripheral resistance index dyne*s*m^2/cm^2; LFnu- Low frequency normalized units; HFnu- High frequency normalized units; LF/HF-Sympatho-vagal balance; PSD- Power spectral density ms^2; BRS- baroreceptor sensitivity ms/mmHg

Table 1: Age and gender adjusted baseline characteristics of biochemical, hemodynamic and autonomic parameters in lean, overweight and obese subjects. Values are expressed in mean (SD)

Resting hemodynamic and autonomic parameters

Table 1 - shows similar HR in the lean and overweight but significantly higher in the obese than the other two groups. Systolic BP, DBP and MBP were significantly higher in the overweight than in the lean. It is important to note that SBP, DBP and MBP (Mean BP) were similar between the lean and obese and between the overweight and obese groups. The lean had significantly higher SI and CI and lower TPRI compared to the overweight (SI: P=0.002; CI: P-0.003; TPRI: P=0.0001) and the obese (SI: P=0.0001; CI: P-0.002; TPRI: P=0.001). However, SI was significantly lower in the obese compared to other two groups (Lean P=0.0001; Overweight P=0.028) and CI and TPRI were similar in the overweight and obese groups.

The resting LFnu, LF/HF and BRS were not different in the 3 groups. Interestingly, LFnu was not different between the obese and lean groups but was significantly higher in overweight compared to obese (P=0.027). Total PSD (Power spectral density) which reflects HRV was lower in the obese compared to the lean (P=0.02) and the overweight groups (P=0.017).

Reactivity to the WCT

In Table 2 the magnitude of the response (Δchange) during WCT was analyzed by the interaction of groups and time using repeated measure analyses. It showed that HR increased during WCT in these 3 groups with no change in ΔHR. The SBP increased

during WCT in all three groups. The lean had higher ΔSBP (9.6+0.9mmHg) than the overweight (4.6+1.1mmHg; P=0.019) and lower than the obese groups (10.5+1.7mmHg; P=0.001). The ΔWCT-SBP was similar between the overweight and obese. Diastolic BP, MBP and TPRI though increased during WCT; their Δchanges were similar in 3 groups. The ΔSI was significantly different amongst the 3 groups (P=0.007). The SI significantly reduced in lean (-1.54+0.4ml/sqm) and overweight (-0.35+0.6ml/sqm) and increased in the obese (1.83+0.9 ml/sqm) (lean-vs-overweight: P=0.001; lean-*vs*-obese: P=0.0001; overweight-*vs*-obese P=0.001). Although WCT-CI was significantly increased in 3 groups, ΔCI was similar in all.

	Lean		Overweight		Obese		P*
	Rest	Stress	Rest	Stress	Rest	Stress	
WCT							
HR	72.1 (10.8)	80.2 (12.2)	70.2 (11.5)	75.5 (12.1)	73.6 (10.9)	79.1 (12.0)	0.430
SBP	110.9 (14.3)	119.9 (15.0)	115.7 (14.7)	122.1 (15.2)	116.9 (12.3)	126.3 (14.4)	0.012
DBP	69.2 (11.6)	76.5 (12.6)	72.4 (11.8)	78.3 (13.2)	72.1 (9.4)	78.3 (11.3)	0.112
MBP	81.8 (13.1)	90.4 (14.1)	85.5 (12.8)	92.0 (13.9)	85.4 (10.3)	93.2 (12.3)	0.057
SI	52.9 (9.8)	51.5 (9.4)	47.6 (9.5)	47.5 (8.8)	42.1 (7.9)	42.9 (8.4)	0.007
CI	3.8 (0.9)	4.1 (0.9)	3.3 (0.8)	3.6 (0.9)	3.1 (0.7)	3.4 (0.9)	0.266
TPRI	1729.2 (532.5)	1798.8 (507.3)	1967.6 (792.1)	2104.9 (581.9)	2128.3 (712.5)	2249.0 (574.1)	0.577
LFnu	52.5 (21.2)	54.0 (13.8)	55.7 (21.9)	54.3 (13.8)	54.4 (20.9)	56.6 (14.9)	0.299
HFnu	49.1 (16.5)	46.1 (13.1)	47.8 (16.9)	45.2 (13.9)	46.8 (18.8)	43.9 (14.7)	0.983
LF/HF	1.3 (0.8)	1.5 (1.2)	1.3 (0.8)	1.3 (1.1)	1.5 (1.3)	1.8 (2.5)	0.687
PSD	12.0 (1.2)	11.5 (1.1)	12.0 (1.2)	11.7 (1.1)	11.7 (1.2)	11.4 (1.1)	0.056
BRS	19.1 (13.1)	13.9 (8.7)	20.9 (14.8)	15.5 (11.9)	18.2 (13.6)	14.9 (10.1)	0.078
CPT							
HR	71.1 (10.3)	77.3 (12.1)	69.7 (10.5)	75. 3 (11.9)	72.4 (10.7)	76.9 (11.3)	0.073
SBP	109.7 (14.9)	124.7 (17.6)	114.8 (15.5)	130.3 (17.7)	116.9 (14.2)	131. 9 (15.8)	0.933
DBP	69.8 (11.7)	83.3 (14.5)	74.2 (12.5)	87.2 (13.9)	73.8 (10.7)	86.3 (12.3)	0.783
MBP	81.5 (13.1)	96.7 (16.0)	85.9 (13.4)	100.5 (15.5)	85.8 (11.6)	99.8 (13.4)	0.733
SI	48.8 (10.8)	46.6 (9.8)	42.9 (10.1)	41.8 (8.7)	38.4 (8.4)	37.5 (8.0)	0.071
CI	3.5 (0.9)	3.6 (0.9)	2.9 (0.8)	3.1 (0.8)	2.8 (0.7)	2.9 (0.7)	0.336
TPRI	1248.9 (393.9)	2237.4 (714.9)	1407.9 (442.5)	2653.1 (767.1)	1381.0 (370.4)	2869.9 (764.7)	0.229
LFnu	52.2 (20.7)	58.7 (16.3)	52.3 (21.1)	59.0 (15.6)	52.7 (20.6)	61.0 (16.6)	0.499
HFnu	78.9(222.9)	41.4 (16.3)	133.1 (420.4)	40.9 (15.8)	106.5 (351.2)	38.9 (16.6)	0.287
LF/HF	1.38 (0.9)	2.1 (1.8)	1.3 (1.1)	2.4 (4.6)	1.4 (1.4)	2.4 (2.4)	0.273
PSD	11.8 (1.2)	11.8 (1.2)	11.6 (1.3)	11.7 (1.3)	11.4 (1.2)	11.4 (1.3)	0.858
BRS	17.4 (12.4)	13.6 (10.1)	16.3 (12.5)	13.9 (13.4)	14.8 (10.7)	11.7 (10.3)	0.798

*P values is for group and time interaction for 3 groups using two way repeated-measure ANOVA adjusted for age and gender
HR- Heart rate bpm; SBP- Systolic BP mmHg; DBP- Diastolic BP mmHg; MBP- Mean BP mmHg; SI- Stroke index ml/m^2; CI- cardiac index L/min*m^2; TPRI- Total peripheral resistance index dyne*s*m^2/cm^2; LFnu- Low frequency normalized units; HFnu- High frequency normalized units; LF/HF-Sympatho-vagal balance; PSD- Power spectral density ms^2; BRS- baroreceptor sensitivity ms/mmHg

Table 2: Age and gender adjusted hemodynamic and autonomic reactivity to WCT and CPT in lean, overweight and obese groups. Values are expressed as mean (SEM)

During WCT, the increase in LFnu and LF/HF and decrease in HFnu and PSD which indicated sympathetic activation were similar in the 3 groups. During WCT, the BRS reduced in the 3 groups (P=0.001) but ΔBRS was not different.

Reactivity to the CPT

Table 2 - Although HR, BP and TPRI were increased (P=0.0001) and SI and CI reduced (P=0.008, P=0.0001) during CPT, there was no difference in their Δchanges in 3 groups.

Autonomic parameters; LFnu, HFnu, LF/HF, PSD and BRS and their Δchanges were similar to those of the WCT.

Correlations of obesity parameters with hemodynamic parameters

Table 3 - Resting HR showed a significant inverse correlation with weight and positive relationship with % fat. Resting BP and TPRI showed significant positive correlation with weight, WC, WHR and BMI. The TPRI had stronger correlation with obesity parameters compared to BP. Both resting SI and CI showed significant decrease with the increase in all obesity parameters. Correla-

tions between absolute values of hemodynamic parameters during WCT and CPT and obesity parameters were identical to those obtained with resting values.

	Weight	WC	BMI	WHR	% Fat
Rest					
HR	-0.177*	0.034	0.022	-0.045	0.179*
SBP	0.411*	0.212*	0.251*	0.100*	-0.056
DBP	0.354*	0.261*	0.221*	0.229*	-0.037
MBP	0.388*	0.204*	0.208*	0.138*	-0.085*
SI	-0.261*	-0.521*	-0.421*	-0.466*	-0.405*
CI	-0.300*	-0.454*	-0.369*	-0.448*	-0.266*
TPRI	0.413*	0.463*	0.383*	0.437*	0.155*
LFnu	0.110*	0.038	0.029	0.019	-0.048
HFnu	-0.117*	-0.035	-0.03	-0.020	0.045
PSD	0.063	-0.220*	-0.128*	-0.253*	-0.297*
LF/HF	0.041	-0.046	-0.024	-0.056	-0.054
BRS	-0.042	-0.292*	-0.170*	-0.259*	-0.251*
WCT					
HR	-0.170*	-0.067	-0.107*	-0.143*	0.059
SBP	0.422*	0.223*	0.183*	0.145*	-0.209*
DBP	0.319*	0.191*	0.110*	0.153*	-0.188
MBP	0.371*	0.200*	0.127*	0.162*	-0.243*
SI	-0.286*	-0.338*	-0.348*	-0.229*	-0.244*
CI	-0.336*	-0.315*	-0.339*	-0.289*	-0.146*
TPRI	0.494*	0.384*	0.372*	0.330*	0.017
LFnu	0.168*	0.106	0.086	0.099*	-0.056
HFnu	-0.168*	-0.106	0.086	-0.099*	-0.056
PSD	0.118*	-0.046	-0.001	0.014	-0.146*
LF/HF	0.167*	0.98*	0.086	0.101	-0.052
BRS	0.043	-0.030	-0.003	0.023	-0.052
CPT					
HR	-0.209*	-0.052	-0.048	-0.113*	0.136*
SBP	0.319*	0.217*	0.222*	0.082*	0.006
DBP	0.247*	0.204*	0.161*	0.163*	-0.025
MBP	0.273*	0.163*	0.151*	0.086*	-0.073*
SI	-0.280*	-0.472*	-0.415*	-0.423*	-0.380*
CI	-0.353*	-0.426*	-0.372*	-0.429*	-0.228*
TPRI	0.432*	0.435*	0.389*	0.393*	0.153*
LFnu	0.108*	0.028	0.069*	-0.009	-0.042
HFnu	0.016	-0.89	-0.070*	-0.034	0.039
PSD	0.083*	-0.173*	-0.110*	-0.199*	-0.278*
LF/HF	0.106*	0.034	0.072*	-0.006	-0.038*
BRS	0.032	-0.166*	-0.081*	-0.180*	-0.157*

Weight kg; BMI- Body mass index kg/m^2; WC- waist circumference cm; WHR- waist to hip ratio; body fat %; Sugar mM; Insulin IU; HOMAiR: Insulin resistance; TG- Triglycerides mM; HDL- High density lipoprotein mM; LDL- Low density lipoprotein mM; Leptin ng/mL; HR- Heart rate bpm; SBP- Systolic BP mmHg; DBP- Diastolic BP mmHg; MBP- Mean BP mmHg; SI- Stroke index ml/m^2; CI- cardiac index L/min*m^2; TPRI- Total peripheral resistance index dyne*s*m^2/cm^2; LFnu- Low frequency normalized units; HFnu- High frequency normalized units; LF/HF-Sympatho-vagal balance; PSD- Power spectral density ms^2; BRS- baroreceptor sensitivity ms/mmHg

Table 3: Spearman's rho correlations of weight, WC, BMI, WHR and % fat with resting hemodynamic and autonomic parameters and absolute values of hemodynamic and autonomic parameters during WCT and CPT (*P<0.05)

For reactivity scores, only ΔHR and ΔSI were correlated with obesity measures. The ΔWCT-HR had significant negative correlation with WC (r=-0.176; P<0.05), BMI (r=-0.178; P<0.05), WHR (r=-0.153; P<0.05) and % fat (r=-0.245; P<0.05). The ΔWCT-SI showed a positive correlation with all obesity parameters except for weight (WC 0.167; BMI 0.179; WHR 0.132; and % fat 0.185; P<0.05 for all). The ΔCPT-HR were similar to those obtained with WCT except for % fat (Weight: r=-0.154; WC -0.120; BMI -0.089; and WHR -0.125; P<0.05 for all). The ΔCPT-SI showed positive correlation with all obesity measures (Weight: r=0.076; WC 0.244; BMI 0.146; and WHR 0.223; and % fat 0.177; P<0.05 for all).

Correlations of obesity parameters with autonomic parameters

Table 3 - Resting WCT and CPT LFnu showed significant increase with increase in weight. No other obesity measures showed any correlation with LFnu at rest or during both stress tests. The Rest and WCT-HFnu showed significant negative correlation with weight. The CPT-HFnu showed significant negative correlation with BMI and WCT-HFnu with WHR. Resting and CPT-PSD were significantly negatively correlated with waist, BMI, WHR and % fat; and WCT-PSD was correlated with weight (r: 0.118; P<0.05) and % fat (r: -0.146; P<0.05) only. None of the obesity parameters showed any correlation with resting LF/HF. Both, WCT (r: 0.167; P<0.05) and CPT LF/HF (r: 0.106; P<0.05) were correlated with weight. Resting BRS was significantly reduced with increasing WC, BMI, WHR and % fat. There were significant negative relationships between resting BRS and obesity parameters during CPT but not WCT.

None of obesity parameters showed correlation with Δchange in autonomic parameters during CPT and WCT.

Discussion

To our knowledge, this is the first study comparing beat-to-beat hemodynamic and autonomic parameters at rest and during mental and physical stress in 3 BMI groups in normal homogeneous population.

The main outcomes of the study were- 1) Significantly higher resting BP in overweight compared to lean; significantly higher resting SI and CI and low TPRI in the lean compared to the overweight and obese groups with the lowest SI in obese. 2) Significantly low resting PSD in obese compared to overweight with similar LF/HF and BRS in the 3 groups (Table 1); 3) Similar ΔWCT-HR, DBP, MBP, TPR and CI in all 3 groups; 4) Similar hemodynamic responses to CPT in 3 groups; 5) Similar autonomic response to WCT and CPT in 3 groups 6) Monotonic non-linear correlation of obesity measures with resting hemodynamic and autonomic parameters and only ΔWCT and CPT HR and SI showed correlations with obesity measures.

Baseline hemodynamic and autonomic parameters

We found similar resting HR in lean and overweight groups, but higher in the obese and higher BP in overweight compared to the lean one. The study showed similar BP between the lean and obese and between overweight and obese groups. Few studies reported similar BP and HR between obese and lean women [5], middle age obese men and women [15] and also in overweight compared to lean subjects [8]. In contrast, other studies have reported higher SBP, DBP and MBP but similar HR in obese compared to lean subjects [7,17,31,32]. Fornitano et al reported higher HR and BP in obese compared to overweight subjects [33]. Literature has not been convincing about higher BP and HR in overweight and obese subjects.

Increased muscle and adipose tissue mass of obese subjects may have high metabolic requirements leading to high SI and CI and low TPRI [32]. A study reported ethnicity and total fat mass adjusted high resting stroke volume (SV) and cardiac output (CO) in obese subjects compared to lean [34]. In comparison, we found significantly lower SI and CI and higher TPRI in overweight and obese with SI being the lowest in obese. The significantly positive Pearson's correlations of obesity parameters with resting BP and TPRI (Table 3) and negative correlation with resting SI and CI support these findings. Although resting TPRI was similar between overweight and obese; it revealed stronger positive correlation with obesity parameters than BP. Our findings are similar to a recent study in obese school children which showed significantly positive correlation of BMI with BP, SV and CO adjusted for waist, WHR, % fat, glucose and lipids [35]. Ribeiro et al also showed significant positive correlation of BMI with BP and MSNA [7]. The BP control will not be understood without understanding the interactions of its determinants such as SI, CI and TPRI. Available literature is not conclusive about low or high SI, CI and TPRI in overweight and obese subjects. Differences in the above studies could be due to the different age groups studied.

The low PSD, a marker of HRV in obese compared to lean and overweight may suggest impaired sympathetic activity in the obese. However, LFnu, the indicator of sympathetic activity was significantly higher in the overweight compared to obese. We expected consistent increase in sympathetic activity from lean to obese groups [18]. The overweight increase in sympathetic activity (LFnu, LF/HF) compared to the lean but it was not significant. Previous studies have shown similar baseline MSNA in lean and overweight [8] but higher in obese ones [5,7,31]. Rodríguez-Colón et al showed reduced HRV in obese children and adolescents [36]. We found similar BRS and LF/HF in 3 groups and negative non-linear correlation of HRV, vagal activity and BRS with body weight (Table-3). Our findings are consistent with Laederach *et al* who showed negative correlation of BMI, WHR and WC with sympathetic and parasympathetic activity and BRS [10]. Hyperleptinemia and hyperinsulinemia, the potential mechanisms of impaired autonomic activity in obese individuals [16] were also found in overweight and obese groups compared to the lean in our study (Table 1).

Our study suggested impaired resting hemodynamic and autonomic parameters in normotensive and non-diabetic obese and overweight subjects which are indications of early pathophysiological changes preceding the future cardiovascular diseases.

Hemodynamic and autonomic reactivity during WCT

Our study showed similar Δchange in HR, DBP, MBP, TPR and CI and Autonomic reactivity to WCT in these 3 groups. The WCT-ΔSBP was similar between the overweight and obese. Our findings are in agreement with Kuniyoshi et al who found no differences in HR, BP, MSNA forearm blood flow and vascular resistance during WCT in lean and obese subjects of similar age to our subjects [5]. Similar HR but augmented BP responses to WCT were shown in obese compared to lean children [17] and in obese hypertensives compared to lean hypertensives [14]. We cannot offer explanation for decrease in WCT-SI in lean and opposite response in obese. Reactivity to mental and physical stress is shown to be influenced by gender [37]. However, in our study, similar gender distribution in all 3 BMI groups and also repeated measure analyses controlled for age and gender may have nullified the gender effect if any on the reactivity in these 3 groups.

This is the first study showing negative correlations of ΔWCT-HR and positive correlation of ΔWCT-SI with obesity parameters indicating less change in HR and more in SI with obesity in response to stressors. The Δchanges of other hemodynamic and autonomic parameters during WCT were independent of obesity. Only one paper reported negative correlation of BMI with change in mid frequency band of HRV in response to mental stress [10]. An 18-year follow up study showed that, nor-epinephrine spillover in response to mental stress was negative predictor of the future BMI and WC [38].

In summary, our study showed that mental stress provoked similar hemodynamic and autonomic reactivity in 3 study groups. We did not find enough evidence to confirm increased BP, peripheral and cardiac autonomic responses to mental stress in 3 obesity groups.

Hemodynamic and autonomic reactivity during CPT

During the CPT, increased MSNA with no change in HR and BP was shown in overweight compared to lean [8] and also in obese compared to lean subjects [5,15]. Similar hemodynamic and autonomic reactivity to CPT in 3 obesity groups in our study confirms this finding. Our study is the first to report the lack of correlation between the obesity measures and all hemodynamic and autonomic reactivity measures to CPT except for ΔCPT-HR and SI.

Strengths and Limitations

Strength of this study is that gradual changes in the baseline hemodynamic and autonomic parameters with progress of obesity were studied using 3 groups as lean, overweight and obese subjects. The study also enriches science with hemodynamic and autonomic responses of these 3 groups to physiological stresses using very simple mental and physical tests which are laboratory simulations of the real life events. In conclusion, our study suggested impairment in resting hemodynamic and autonomic parameters in normal obese and overweight subjects but not in a linear fashion from lean to overweight to obese as expected. Hemodynamic and autonomic reactivity to mental and physical stress is similar in overweight and obese. The novelty of this study is that, it showed non-linear correlations of resting hemodynamic and autonomic parameters with obesity measures and also that except for ΔHR and ΔSI, reactivity to mental and physical stress is independent of the obesity measures. These above hemodynamic and autonomic alterations may prove to be precedence to cardiovascular diseases and associated comorbidities. However, the question arises whether clinically overweight are different from obese ones.

Non-invasive estimation of HRV has its limitations [24]. Due to lack of facilities we did not measure MSNA and noradrenalin spillover in the 3 obesity groups. This would have added more information to our results. Additional stress test with handgrip could have given more understanding on metaboreceptor role in these 3 groups.

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