A STUDY TO ASSESS SYMPATHETIC RESPONSE CHANGES IN CAROTID FEMORAL PULSE WAVE VELOCITY USING COLD PRESSOR TEST IN NORMAL BMI, OVERWEIGHT AND OBESE SUBJECTS

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Abstracts

Background & objectives: Obesity, known to be a disease of developed world, has hit the developing world equally in last few decades, and hence the cardiovascular (CV) morbidity. As the therapeutic interventions employed with clinical disease, early prediction of the future cardiovascular events has been a must, especially in the susceptible groups, as in positive family history or obesity. In the light of variable data available worldwide, the comparison of vascular status and the sympathetic reactivity of different Body Mass Index (BMI) individuals can be employed as predictive and objectifying tool, for early life style interventions at subclinical stage.**Methods:** 105 normotensive individuals from general population were selected, after screening and following exclusion criteria, 35 each in normal BMI, Overweight and Obese groups (WHO Classification). The vascular stiffness reflected by carotid femoral Pulse Wave Velocity (cf-PWV) was recorded before, during and after application of Cold Pressor Test (CPT). **Results:** The baseline cf-PWV is directly proportional to the BMI. Though sympathetic response changes were highest in the Normal BMI group, the augmentation was statistically significant in the overweight and obese group during CPT application.

Interpretation & conclusion: CPT can be employed as a preliminary test in the early stages in the susceptible individuals to cardiovascular risks, after establishing their cardiovascular fitness, knowing their sympathetic reactivity.

Key Words: carotid femoral pulse wave velocity, cold pressor test, body mass index, obesity, sympathetic response

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Introduction: In the modern world obesity, has reached a global epidemic emerging as ` new world syndrome' reflection of massive social, economic and cultural problems affecting all age groups, all populations of developing and developed countries.[1]

The World Health Organization (WHO) has declared obesity as the largest global chronic health problem in adults which is increasingly turning into a more serious problem than malnutrition.[2] In 2014, more than 1.9 billion adults (18 years and older) were overweight. Of these over 600 million were obese. It has been further projected that 60% of the world's population, i.e. 3.3 billion people, could be overweight (2.2billion) or obese (1.1 billion) by 2030 if recent trends continue.[3] India had 0.4 million obese men, or 1.3% of the global obese population in 1975, but in 2014, it zoomed into the fifth position with 9.8 million obese men, or 3.7% of the global population. Among women, India has jumped to the third rank with 20 million obese women (5.3% of global population). These findings are alarming and require the attention of all us to prevent drastic consequences in days to come.

Obesity is a result of chronic imbalance between energy intake and energy expenditure. Energy balance is regulated by various neural and hormonal mechanisms. Due to hemodynamic and metabolic derangements it is implicated in pathogenesis of various diseases particularly cardiovascular diseases, diabetes mellitus type 2 and certain types of cancer.[4]

It is associated with a much worse arterial profile, as an increased carotid lumen size was accompanied by higher blood pressure, greater arterial stiffness, and greater carotid intima media thickness as compared to overweight or normal-weight individuals and such remodelling is also accompanied by reduced arterial function and increased cardiovascular risk.[5]

The autonomic nervous system (ANS) of obese individuals is chronically altered.[6, 7] The excess

weight induces ANS dysfunction, which may be involved in the haemodynamic and metabolic alterations that increase the cardiovascular risk of obese individuals. Regulation of energy homeostasis, Leptin and its multiple interactions with neuropeptides may link excess weight gain with increased sympathetic activity. Long-term leptin infusion at rates that mimic plasma concentrations found in obesity raises arterial pressure and heart rate via adrenergic activation in non-obese rodents.[8]

In young overweight individuals, SNS activity is directly related to the degree of cardiac, renal, and vascular dysfunction, suggesting that sympathetic neural drive may be a major player in CV risk development .[9]

As the mechanical and structural properties of the arterial wall may change before the occurrence of clinical symptoms of cardiovascular disease, pule wave velocity (PWV) and its changes to the sympatho-excitatory stimulus in relation to BMI can help identifying normotensive individuals who should be targeted for the implementation of interventions aimed at preventing or delaying the progression of subclinical arterial stiffening and the onset of hypertension and cardiovascular diseases with weight gain.

Material and Methods: The study was approved by the institutional ethics committee of the Uttar Pradesh University of Medical Sciences (UPUMS) Saifai, Etawah and has been conducted in the research laboratory of Department of Physiology UPUMS, Saifai, Etawah. Ethical clearance from the Institutional Ethical Committee was taken. The present study was carried out on the 105 normotensive volunteers subjects, 25 to 35 year of age. The subjects were divided into three BMI groups as per the WHO classification viz. BMI 18.5 to 24.9 as Normal, BMI 25.0 to 29.9 as Overweight and BMI >30 as obese individuals.

All the presenting subjects were screened clinically as well as were investigated to rule out any comorbidities and persons with history of smoking, history of diabetes mellitus, hypertension, angina, arrhythmia, myocardial ischemia, peripheral ischemic disease with documented claudication, respiratory system diseases, neurological diseases, female in menstrual phase, persons with Haemoglobin (Hb) < 10 gm% and deranged thyroid profile, were excluded from the study.

CPT was employed as the sympatho excitatory tool to see the changes in the baseline carotid femoral pulse wave velocity in all the groups.

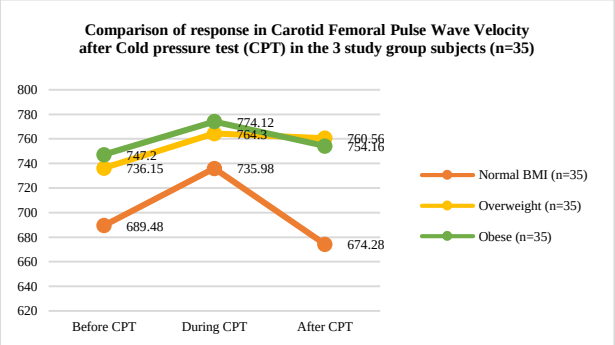
The cf-PWV was measured using PeriScope, (developed by Genesis Medical Systems, Hyderabad, India) an 8-channel real-time PC based simultaneous acquisition and analysis system. It is estimated from the composite brachial ankle pulse wave velocity (ba-PWV) found out by averaging left and right ba- PWV. The regression analysis between ba-PWV and cf-PWV yields the following equation: Estimated carotid femoral PWV = 0.8333 * (Avg. ba-PWV)- 233.33. * $p < 0.01$

cf-PWV was recorded with the subject seated comfortably. The subject was asked to immerse his / her hand in cold water and the temperature was maintained at 4°C throughout the procedure described by Le Blanc et al. The subject's hand then was immersed in lukewarm water for half a minute and he / she was allowed to rest. All the parameters were again recorded at an interval of five minutes after CPT.

Result:

The mean cf-PWV before CPT was 689.48±225.21 cm/sec, 736.15±199.41 cm/sec and 747.20±105.99 cm/sec respectively, during CPT was 735.98±317.60 cm/sec, 764.30±195.24cm/sec and 774.12±101.98 cm/sec respectively and after CPT was 674.28±250.43 cm/sec, 760.56±218.71cm/sec and 754.16±126.10 cm/sec respectively **(Chart-1)**.

Chart-1: Comparison of response in Carotid Femoral Pulse Wave Velocity after Cold pressure test (CPT)



Two sample t- test with equal variance was conducted to determine the difference between the

mean value of cf-PWV between normal BMI, Overweight and Obese groups. None of the comparision groups show statistically significant differences **(Table-1)**.

Table 1: Difference between the mean value of cf-PWV between normal BMI, Overweight and Obese groups

Mean ± S.E. of difference in cf-PWV (95% C.I.) (cm/sec)			
Test protocol	Normal BMI vs Overweight	Normal BMI vs Obese	Overweight vs Obese
Before cold pressor test	46.67±50.84 (-54.78 – 148.13) p=0.361	57.72±42.07 (-26.23- 141.68) p=0.174	11.05±38.17 (-65.12- 87.22) p=0.77
During cold pressor test	28.31±63.01 (-97.43 – 154.06) p=0.654	38.14±56.38 (-74.37 - 150.65) p=0.501	9.82±37.23 (-64.47 – 84.12) p=0.270
After cold pressor test	86.28±56.20 (-25.86 – 198.43) p= 0.129	79.87±47.39 (-14.69 – 174.45) p=0.096	-6.405±42.67 (-91.56 – 78.75) p=0.881

Paired t- Test was used to analyse differences of means to determine if cf-PWV was different during CPT and after CPT in the different BMI groups. Data is difference of means ± standard error **(Table-2)**.

Table-2: Difference of mean cf-PWV within a group

Difference of mean cf-PWV within a group (Paired t-Test) (cm/sec)				
BMI Groups	Before CPT- during CPT (Mean ± SE)		Before CPT- after CPT (Mean ± SE)	
Normal	-46.50±50.8	p=0.36	15.19±46.3	p=0.74
BMI (n=35)	7 (-149.88 – 56.88)	7	4 (-78.98 – 109.38)	4
Overweight (n=35)	-28.14±4.34 (-36.96- -19.32)	p=0.000	-24.41±38.80 (-103.27 – 54.44)	P=0.533
Obese (n=35)	-26.91±5.84 (-38.78- -15.04)	p=0.000	-19.96±8.74 (-24.73 – 10.85)	P=0.074

The Normal BMI group had statistically indifferent values during and after CPT, both (p>0.05), despite the greatest net increase in the cf-PWV during the CPT. Whereas overweight and obese group have statistically significant increase in the cf-PWV during the CPT (<0.05) and statistically insignificant increase in the cf-PWV after CPT (p>0.05).

Discussion: Sympathetic nervous system plays an important role in the metabolic homeostasis. It has been related to numerous metabolic and cardiovascular disorders. There are evidences of obesity associated sympathetic activation as a potential mechanism to increase cardiovascular events. Landsberg hypothesised that the increase in the sympathetic activity is homeostatic response, for stimulating thermogenesis, with weight gain.[10] There has been considerable controversy regarding the effects of obesity on sympathetic system behaviour.

The correlation of arterial stiffness and obesity is multifactorial. Visceral adipocytes have an elevated lipolytic activity that results in increased free fatty acids release in the portal vein with an accumulation and contributes to insulin resistance, circulation of proinflammatory cytokines and high levels of leptin have been found to be correlated with reduction in arterial distensibility. Leptin can exert receptor-mediated influence on vessel tone and growth and, stimulate vascular smooth muscle proliferation and migration. Leptin induces oxidative stress in endothelial cells, triggering the

transcription of oxidant-sensitive genes that participate in atherogenesis. Leptin increases sympathetic nervous activity.[11]

To establish the relation, we evaluated carotid femoral pulse wave velocity (cf-PWV) in our study, and found that the cf-PWV was directly proportional to the BMI of the subject groups 689.48±225.21, 736.15±199.41and 747.20±105.99 cm/sec respectively, though it was not statistically significant. The application of the CPT caused significant increase in cf-PWV of the overweight and obese group and the net change in the obese group was subnormal to the overweight group. After the test ambiguous changes were seen in the three different groups. Similar results were proposed by Wildman et al who evaluated less obese African-American and whites and found strong correlation of PWV to the BMI, waist circumference and waist hip ratio.[12] Rider et al evaluated baseline data from a longitudinal study and postulated direct correlation between PWV and BMI, total fat mass but not visceral obesity, assessed by MRI.[13] On the contrary, Desamericq et al concluded that the PWV was not associated with obesity.[14]

Recio-Rodriguez et al found that an increase of BMI of 1kg/m^2 led to an increase of 0.052 m/s in PWV, corresponding to about six months of vascular aging.[15] Cecelja et al reviewed all articles relating PWV to cardiovascular risk factors up to December 2008 and report that a relationship between BMI and PWV was found in only 13% of the studies.[16] Desamericq evaluated relationship between BMI and carotid–femoral PWV. Only 10 of the total of 62 studies (16%) found a positive association between BMI and PWV. Nordstrand et al concluded that the PEV was positively correlated to BMI in female gender but negatively in male.[17]

Borner et al applied CPT to see the effect on baseline PWV of healthy subjects and found significant increase in the PWV.[18]

In the view of the available data and our study it was found that that the application of the CPT as a contributory factor to augmentation of the cf-PWV in higher BMI groups.

Conclusion: Even the modest weight gain causes increase in the cf-PWV and arterial stiffness (may be due to inflammatory and neuro humoral changes). Though proportionately smaller increase in cf-PWV, hence arterial stiffness, in higher BMI groups, exposure to cold may cause unsafe zone of arterial stiffness and vasoconstriction.

CPT can be employed as a preliminary test in the subclinical early stages in the susceptible individuals to cardiovascular risks, after establishing their cardiovascular fitness, to know their sympathetic reactivity.

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