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Metaboreflex activation by rhythmic exercise as a cardiovascular risk in metabolic syndrome and obesity

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Abstract

Introduction: There is increasing prevalence of metabolic syndrome (MS) and obesity. Dysregulation in a mechanism causing cardiovascular adjustments during exercise (Metaboreflex; a feed-back mechanism originating in skeletal muscle due to local metabolites) has been studied in MS and obesity.

Aims & objective: To see the effect of metaboreflex by rhythmic handgrip exercise on hemodynamic parameters (Blood pressure (BP), cardiac output(CO), stroke volume(SV), pulse rate (PR), systemic vascular resistance(SVR)) in subjects with MS & obesity.

Method & materials: 46 subjects, aged 25 to 45 years of both sex were enrolled & classified into a) subjects without MS with normal or overweight BMI b) subjects without MS with obese BMI c) subjects with MS with obese BMI and d) subjects with MS with morbid obese BMI. Hemodynamic parameters were evaluated by impedance cardiovasography in supine position. Maximum Voluntary Contraction was measured by Handgrip Dynamometer. Rhythmic handgrip exercise was done at 30% of the subjects' MVC (for 2 mins), followed by post exercise cuff occlusion to enhance metaboreflex, for 2 mins (20 mm Hg above systolic). The parameters were assessed post-rhythmic exercise.

Results & conclusion: Following exercise, there was vasoconstriction mediated pressor response (statistically significant increase in diastolic BP) and flow mediated pressor response (statistically significant increase in systolic BP) in normal or overweight subjects without MS. In subjects without MS with obese BMI and subjects with MS with obese BMI, statistically significant decrease in SVR was found. In subjects with metabolic syndrome with morbid obese BMI, decrease in SV and statistically significant increase in PR was found.

Keywords: metabolic syndrome, obesity, hemodynamics, metaboreflex, rhythmic exercise.

1. Introduction

Cardiovascular diseases are the most frequent causes of morbidity and mortality. There is a need for better understanding of their pathophysiology. During exercise, appropriate cardiovascular adjustments are necessary to meet the metabolic demands of active skeletal muscle. Autonomic alterations play a major role in ensuring these adjustments. Several neural mechanisms working in concert are responsible for regulating this autonomic activity, like Central command, the ergoreflex/exercise pressor reflex (EPR), the arterial baroreflex, and the cardiopulmonary baroreflex. Some dysregulation in these mechanisms has been demonstrated in various circulatory and metabolic diseases [1,2].

Metabolic syndrome (MS) is driven largely by obesity exacerbated by sedentary lifestyles. Obesity is a major public health issue [3,4]. Further investigation in this field is warranted. Metaboreflex (subset of ergoreflex) can be used as a tool for SNS evaluation, and thus for cardiovascular risks in such subjects. Moreover, it is important that future studies take into account the possible effects of drugs/ therapy on the correction of the dysregulation of these reflexes [5].

1.1 Metaboreflex (MR)

Receptors within muscles gather information concerning the metabolic (metabolites accumulation such as lactic acid, potassium [6-8]) conditions of the muscles involved in the exercise being performed. This information is then provided to nucleus tractus solitaries [6,9], through groups III and IV muscle afferents. Cardiovascular controlling areas then operate the hemodynamic adjustments in order to regulate blood flow.

In order to know the effect of individual components of MS (i.e. hypertension, obesity, dyslipidemia) on EPR, many studies were conducted [9-18]. However, the studies were conflicting.

The present study was done to find the role of Body Mass Index (BMI) and MS on effect of metaboreflex on central hemodynamics and cardiac parameters in adults.

1.1 Aim and objectives

To evaluate the effect of metaboreflex by rhythmic handgrip forearm exercise on hemodynamic parameters in subjects with MS and subjects with obesity, by measuring Blood pressure, Cardiac output and Systemic vascular resistance before and after rhythmic handgrip exercise

2. Material and method

2.1 Selection of subjects and ethical clearance

The study was conducted in Department of physiology after approval from the Institutional ethical committee of KGMU, Lucknow.46 subjects aged 25 to 45 years enrolled after proper consent, according to

a) NCEP: ATP III 2001 criteria for MS[16,19]
b) WHO criteria for BMI[17,20]

They were divided into:

1. Subjects without MS with normal or overweight BMI----- 18 subjects
2. Subjects without MS with obese BMI ----- 8 subjects
3. Subjects with MS with obese BMI ----- 12 subjects
4. Subjects with MS with morbidly obese BMI --- 8 subjects

2.2 Inclusion/exclusion criteria

Subjects aged 25 to 45 years with or without MS or obesity was included in the study. Subjects with systemic diseases, Cardiac Vascular and Respiratory abnormalities or history of smoking, heavy exercise within 12 hrs, hypertension, and drug intake interfering with exercise response like beta blockers were excluded from the study.

2.3 Parameters measured

Weight, height, Body Mass Index (BMI), Systolic and diastolic Blood Pressure were calculated by conventional methods. MVC (maximum voluntary contraction) was calculated using handgrip dynamometer. Cardiac Parameters, (Pulse Rate, Stroke Volume, stroke volume index, Cardiac Output, cardiac index) and hemodynamic Parameters (Systemic vascular resistance (Total Peripheral Resistance), Systemic vascular resistance index) were measured using Impedance cardiovasography.

Impedance cardiovasography[18,22]:

Non invasive procedure, where small change in the impedance of the body segment caused by physiological processes like blood circulation is obtained as waveforms and different variables are measured. It has most often acceptable accuracy, precision and responsiveness in a wide range of circulatory situation [19,23].

In Department of biochemistry, Blood sample (3 ml before exercise) was drawn from antecubital vein. Fasting Blood Sugar/Glucose (FBS), Serum High Density Lipoprotien (HDL) and Serum triglycerides were analyzed on vitros 250 dry chemistry full autoanalyzer.

2.4 Method

1) Anthropometry (weight and height) to classify individuals according to BMI.
2) Anthropometry (waist circumference) and biochemical parameters (Blood lactate, serum potassium, FBS, serum HDL, and serum Triglycerides) measured to classify into subjects with and without MS.
3) Individuals made to lie supine and comfortable.
4) Individuals rested for 5 mins.
5) Pre exercise measurement of cardiac and hemodynamic parameters of the subjects.
6) Subjects' Maximum Voluntary Contraction recorded by Handgrip Dynamometer.
7) Rhythmic handgrip exercise (forearm exercise) at 30% of MVC [20,24] (for 2 mins), followed by Post Exercise Cuff Occlusion (PECO[24,25]) 20 mm Hg above systolic blood pressure, to isolate metaboreflex from other reflexes.
8) Post rhythmic exercise measurement of cardiac and hemodynamic parameters of the subjects (Vasoconstriction mediated pressor response and flow mediated pressor response due to metaboreflex activation).

2.5 Statistics

2.5.1 Type of study

Experimental Longitudinal study.

2.5.2 Statistical analysis

Student paired t test was done for comparison between pre and post exercise parameters.

2.5.3 Required sample size

The sample was calculated by using the following formula [21,33].

$n=Z_{1-\alpha/2}^2 \times SD^2/d^2$

$Z_{1-\alpha/2}$=Power of the study

SD: Standard deviation of the study variable

d: Absolute error

In a study [22,34], there was an exaggerated increase in systemic vascular resistance from baseline during the metaboreflex in subjects with MS and obesity 0.52 ± 177.6. Assuming 80% power, 5% significance level with 95% confidence interval as well as absolute error being 40, the total sample size calculated was 38.

3. Result

Table 1: Vasoconstriction mediated pressor response: Change in SVR, SVRI, and DBP due to metaboreflex activation [23,26].

	(-) MS with normal or overweight BMI			(-) MS with obese BMI		
Parameters	**Pre exercise**	**Post exercise**	**P value**	**Pre exercise**	**Post exercise**	**P value**
DBP (mmHg)	74.11±8.87	80.89±10.18	0.0001*	79.00±6.84	83.75±5.70	0.002*
SVR (dynes sec/cm5)	1456.56±360.50	1463.78±308.56	0.15	1422.75±329.18	1281.25±387.10	0.001*
SVRI(dynes sec/cm^5/m^2)	2354.17±407.41	2406.78±379.94	0.19	2493.00±590.91	2232.25±633.20	0.0001*
	(+) MS with obese BMI			(+) MS with morbid obese BMI		
DBP (mmHg)	82.00±7.18	88.83±14.25	0.01*	81.50±8.12	86.25 ±10.92	0.001*
SVR (dynes sec/cm5)	1426.08±361.96	1327.75 ±347.27	0.0001*	1019.62±129.01	1032.25±169.40	0.14
SVRI(dynes sec/cm^5/m^2)	2644.25±640.98	2445.17±592.70	0.0001*	2118.88±239.21	2105.12±322.09	0.14

Decrease in SVR is statistically significant (p<0.001*) in groups: 1. (-) MS with obese BMI and 2.(+) MS with obese BMI

Table 2: Flow mediated pressor response: Change in SV, SVI, PR, CO, CI, and SBP due to metaboreflex activation [20,24]

	(-) MS with normal or overweight BMI			(-) MS with obese BMI		
Parameters	**Pre exercise**	**Post exercise**	**P value**	**Pre exercise**	**Post exercise**	**P value**
SBP (mm Hg)	119.33±10.35	124.33±13.63	0.001*	119.00±7.78	129.75±9.34	0.0001*
CO (l/min)	4.87±1.36	5.07±1.06	0.11	5.08±1.10	5.57±1.44	0.10
CI (l/min/m^2)	2.91±0.59	3.06±0.40	0.09	2.88±0.55	3.15±0.65	0.08
SV (ml/beat)	61.22±17.77	61.71±16.28	0.13	66.90±8.40	73.58±12.28	0.06
SVI (ml/beat/m^2)	36.63±8.04	36.75±7.45	0.14	38.27±5.91	42.00±6.83	0.05*
PR (beats/min)	79.78±9.68	81.28±12.83	0.11	75.62±10.37	80.50±14.27	0.003*
	(+) MS with obese BMI			(+) MS with morbid obese BMI		
SBP (mm Hg)	125.83±11.00	138.00±19.85	0.0001*	131.00±8.14	139.25±12.27	0.0001*
CO (l/min)	5.51±1.53	6.15±1.70	0.03*	7.38±0.77	7.87±1.14	0.13
CI (l/min/m^2)	2.91±0.67	3.24±0.75	0.08	3.53±0.39	3.79±0.56	0.14
SV (ml/beat)	73.58±16.90	76.07±17.09	0.07	89.13±16.92	86.57±14.29	0.06
SVI (ml/beat/m^2)	38.13±6.48	39.53±6.79	0.15	43.07±7.75	41.94±7.24	0.10
PR (beats/min)	75.92±12.01	75.58±11.01	0.11	83.25±8.81	87.75±7.97	0.03*

Changes in CVS parameters are statistically more significant (*) in groups: 1. (-) MS with obese BMI 2. (+) MS with obese BMI. SV decreased and PR increased in group: (+) MS with morbid obese BMI.

4. Discussion

Obesity is characterized by SNS predominance in the basal state and *reduced SNS responsiveness after various sympathetic stimuli* [24,25]. This is shown in the present study.

4.1 Subjects without metabolic syndrome (MS)

4.1 a) Vasoconstriction mediated pressor response

Systemic Vascular Resistance (SVR) and Systemic Vascular Resistance Index (SVRI):

Preexercise: SVRI was higher in subjects with high BMI, though insignificantly. This could be due to increased SNA in obese, as stated above.

Post-exercise: In subject with lower BMI, SVR and SVRI were increased, although insignificantly. This could be due to vasoconstriction which is mediated by pressor response following exercise induced metaboreceptor stimulation [24,25]. In subjects with higher BMI following exercise SVR and SVRI were decreased significantly. In subjects with higher BMI, the increased fat content in the skeletal muscle of obese individuals may desensitize the metaboreceptors[25,29], reducing the metaboreflex-mediated Muscle Sympathetic Nerve Activity. This would have caused impairment of vasoconstriction mediated pressor response.

DBP

Preexercise: Preexercise values were similar in subjects with higher BMI and in subjects with lower BMI.

Post-exercise: DBP increased in both groups significantly, more in subjects with lower BMI. Decreased vasoconstriction mediated response in subjects with higher BMI reduced the SVR and ultimately prevented DBP from excessive rise.

Thus we found that vasoconstriction mediated pressor response is decreased in subjects with higher BMI.A study [12,15] by Negrão et al showed similar results. It is unlikely that the exercise force performed during handgrip exercise explains the reduction in response in higher BMI individuals. The exercise force was adjusted to the percentage of the MVC in both groups. Besides, the MVC was similar between the two groups.

4.1 b) Flow mediated pressor response

Stroke Volume(SV), Stroke Volume Index(SVI)*:*

Preexercise: SV was higher in subjects with higher BMI, due to difference in BSA.

Post exercise: SVI showed significant increase in subjects with higher BMI due to decreased afterload.

SBP, Cardiac Output (CO), Cardiac Index (CI), and Pulse Rate (PR)*:*

Preexercise: No significant differences were present in any parameter (SBP, CO, CI and PR) between subjects with higher BMI and subjects with lower BMI.

Post-exercise: All parameters (SBP, CO, CI and PR) showed a more significant increase after exercise in subjects with higher BMI compared to subjects lower BMI.

Thus, the present study found enhanced flow mediated pressor response in subjects with higher BMI which can be explained due to decreased afterload in subjects with higher BMI.

4.2 Subjects with MS

4.2 a) Vasoconstriction mediatedpressor response

Systemic Vascular Resistance (SVR), Systemic Vascular Resistance Index (SVRI)*:*

Preexercise: The significant difference in SVR between subjects with higher BMI and subjects with lower BMI could be due to difference in BSA.

Post-exercise: In MS, following exercise, SVR and SVRI were decreased significantly in subjects with lower BMI i.e., obese subjects, which could be due to Insulin resistance [26,30]. This reduces glycolysis in skeletal muscle, which attenuates muscle acidosis during exercise. Thus, the metaboreceptors underwent less stimulation during exercise. On the other hand, SVR and SVRI showed no change in post exercise values, in subjects with higher BMI. The difference between these two groups, subjects with higher BMI and subjects with lower BMI, was significant. This could be due to impaired NO release due to decreased Endothelial Nitric Oxide Synthase (eNOS)[26,30] and Neuronal Nitric Oxide Synthase (nNOS)[27,31] activity, and therefore impaired vasodilatation, in MS at higher BMI, causing vasoconstriction.

Thus the present study found unimpaired vasoconstriction in subjects with MS with higher BMI.

DBP*:*

Preexercise: There was no difference in prexercise DBP in MS, as hypertensive patients were excluded from the study.

Post-exercise: There is an increase in DBP, more in subjects with higher BMI. i.e., vasoconstriction mediated pressor response is enhanced in subjects with MS with higher BMI, compare to subjects with MS with lower BMI.

Thus, it can be said that endothelial dysfunction [26,30] and altered nNOS[27,31] activity in NTS is found in subjects with MS with higher BMI. Similar findings were reported by **Trombetta et al** [15] and **Dipla et al**[10].

4.2 b) Flow mediated pressor response:

Stroke Volume (SV), Stroke Volume Index (SVI), and Pulse Rate(PR)*:*

Preexercise: Significant differences were present in SV due to higher BSA in subjects with higher BMI.

*Post-exercise:*In subjects with MS with higher BMI, SV and SVI decreased after exercise (due to significant increase in PR). This could be due to increased afterload at a higher BMI.

SBP, Cardiac Output (CO), Cardiac Index (CI)*:*

Preexercise: Findings were similar but insignificant.

Post-exercise: In subjects with MS with lower BMI, increase in CO was significant, but not in subjects with MS with higher BMI. This implies that afterload is lower due to vasodilatation, in subjects with MS with lower BMI compared to subjects with MS with higher BMI.

Ichinose et al [28] also did not find an important increase in CO during activation of the muscle metaboreflex due to significant tachycardia in MS, and the lack of an increase in CO was explained to be due to a small reduction in SV, which was most likely caused by an increase in left ventricular afterload. They also found that, the increase in left ventricular contractility is not enough to sustain SV in the face of a substantial increase in afterload.

Thus, it can be said that in subjects with MS with higher BMI, decreased flow mediated pressor response is due to increase in after load, as contractility is not decreased. Similarly, a study by Limberg et al[24] suggests mechanisms playing an important role in exaggerated blood pressure responses to exercise in MS adults. Thus, the present study findings show increased vasoconstriction mediated pressor response due to metaboreflex activation in subjects with MS with higher BMI compared to subjects with MS with lower BMI.

Therefore, earlier studies reporting on the effect of individual components of MS (i.e. hypertension, obesity, dyslipidemia) were conflicting.

It was concluded that

a) In normal subjects, vasoconstriction mediated pressor response and flow mediated pressor response occur during exercise due to metaboreflex activation.
b) In subjects without MS, impaired vasoconstriction mediated pressor response at higher BMI could be due to increased fat content [25] in the skeletal muscle of obese individuals.
c) In subjects with MS, impaired vasoconstriction mediated pressor response at lower BMI could be due to increased fat content [25] and insulin resistance [26].
d) In subjects with MS, unimpaired vasoconstriction mediated pressor response at higher BMI, compared to lower BMI, could be due to impaired NO release[26,27].
e) SV and SVI decrease in MS with higher BMI, which could be due to increased after load, without any change in contractility [27].

Thus, metaboreflex assessment can act as a non invasive tool for prediction of cardiovascular risks.

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