International Journal of Applied Research 2016; 2(1): 354-358

ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2016; 2(1): 354-358
www.allresearchjournal.com
Received: 13-11-2015
Accepted: 15-12-2015

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Effect of rhythmic handgrip exercise on cardiovascular system in otherwise healthy obese subjects

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Abstract
Introduction: Obesity is a topic of increasing concern and is associated with decreased physical activity. Some dysregulation in a mechanism causing cardiovascular, and hemodynamic adjustments during exercise (Meta boreflex; a feed-back mechanism originating in skeletal muscle due to local metabolites) has been demonstrated in obese subjects.
Aims and objective: The purpose of this study is to see the effect of metaboreflex by rhythmic handgrip exercise on hemodynamic parameters (Blood pressure(BP), cardiac output(CO)/index(CI), stroke volume(SV)/index(SVI), pulse rate(PR), systemic vascular resistance(SVR)/index(SVRI)) in subjects with obesity.
Method and Materials: A total of 26 subjects, aged between 25 to 45 years were enrolled in this study and classified into a) subjects(18 in number) with normal or overweight BMI, and b) subjects(8 in number) with obese BMI. Hemodynamic parameters were evaluated by impedance cardiovasography in supine position, after 5 minutes of rest. 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). Parameters were assessed post rhythmic exercise.
Results: 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 subjects. In subjects with obese BMI, there was a statistically significant reduction in SVR and therefore a reduction in vasoconstriction mediated pressor response. Decrease in SVR also caused an increased flow mediated response (CO).
Conclusion: In this study, it can be concluded that obese BMI decreases vasoconstriction response due to Metaboreflex and therefore Metaboreflex can act as a predictor of cardiovascular risks in obesity.

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

Introduction
Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure [1]. The emergence of obesity as a major public health issue has prompted efforts to understand the contributions of both energy intake and expenditure [2].
Exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective of improvement or maintenance of physical fitness [1].
During exercise, appropriate cardiovascular, and hemodynamic adjustments are necessary to meet the metabolic demands of active skeletal muscle. Autonomic alterations in sympathetic and parasympathetic nerve activities play a major role in ensuring these adjustments. Several neural mechanisms working in concert are responsible for regulating this autonomic activity. Central command (a feed-forward mechanism originating from higher brain centers), the ergoreflex/exercise pressor reflex (EPR; a feed-back mechanism originating in skeletal muscle), the arterial baroreflex (a negative feed-back mechanism originating from the carotid sinus and aortic arch), and the cardiopulmonary baroreflex (a negative feed-back mechanism originating from the heart, and blood vessels of the lungs) are all known to contribute to the neural cardiovascular adjustments to physical activity [3].

In healthy individuals, sympathetic activity to cardiovascular apparatus augments and prevails over parasympathetic tone, thereby increasing HR and myocardial contractility and constricting the vascular beds of organs and tissues not involved in exercise. Some dysregulation in these mechanisms has been demonstrated in various diseases, mainly circulatory and metabolic diseases. Further investigation in this field is warranted. 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, 3].

Metaboreflex (MR)

Alam and Smirk [4, 5] for the first time demonstrated that metabolic reflex originating in skeletal muscle can mediate cardiovascular adjustments to exercise, the so called "metaboreflex".

The first mention of the possibility of existence of muscle metaboreceptors was by Zuntz and Geppart in 1886 [6].

Receptors within muscles gather information concerning the metabolic (amount of metabolites accumulation) conditions of the muscles involved in the exercise being performed. This information is then provided to the cardiovascular controlling areas located in the medulla oblongata (nucleus tractus solitaries) [7], through groups III and IV muscle afferents that project to the dorsal horn of the spinal cord. Cardiovascular controlling areas then operate the hemodynamic adjustments in order to regulate blood flow on the basis of the status of contracting muscle. The metaboreceptors are thought to be sensitive to several substances such as lactic acid, potassium, bradykinin, arachidonic acid products, Adenosine Triphosphate (ATP), diprotonated phosphate, and adenosine [7-9].

Cardiovascular diseases are the most frequent causes of morbidity and mortality around the world. There is a need for better understanding of their pathophysiology. Among neurohormonal systems, SNS (sympathetic nervous system) plays a central role in cardiovascular regulation in both health and disease. The MR can be used as a tool for SNS evaluation, and thus evaluation of cardiovascular risks.

This study shows how metaboreflex affects cardiovascular system in subjects of obesity.

In order to know the effect of obesity on MR, many studies were conducted [10-16]. Trombetta I.C., *et al*. (2003) [15] reported that weight loss improves neurovascular and muscle metaboreflex control in obesity. Negrão C.E., *et al*. (2001) [13] found that Muscle metaboreflex control is diminished in normotensive obese women. Thus the studies were conflicting.

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

Aim

To evaluate the effect of muscle metaboreflex activation on central hemodynamics and cardiac functions in adult obese population.

Objectives

1) To record the anthropometric measurements (wt/weight, ht/height) of the study and control group.
2) To assess the hemodynamic parameters (SBP/systolic blood pressure, DBP/diastolic blood pressure, PR/pulse rate, CO/cardiac output, CI/cardiac index, SV/stroke volume, SVI/stroke volume index, SVR/systemic vascular resistance, and SVRI/systemic vascular resistance index) before and after rhythmic/intermittent exercise.
3) To assess the biochemical status before exercise (FBS/fasting blood sugar, HDL/high density lipoprotein, and serum Triglycerides).

The study was conducted in Department of physiology in Impedance Cardio Vaso Graphy Laboratory, K.G.M.U., Lucknow.

Selection of subjects and ethical clearance

An approval from the Institutional ethical committee of KGMU, Lucknow was taken for conducting the research before the start of this study.

26 subjects were enrolled, and categorized into:

- Otherwise healthy, normal and overweight BMI (18 in number).
- Otherwise healthy, obese BMI (8 in number).

Inclusion and Exclusion Criteria

Inclusion Criteria

- Normal healthy subjects of age 25 to 45 yrs.
- Otherwise healthy, overweight or obese subjects of age 25 to 45 yrs.

Exclusion Criteria

- Subjects with metabolic syndrome (NCEP: ATP III 2001 criteria [17]).
- Subjects with systemic diseases, Cardiac Vascular and Respiratory abnormalities.

History of smoking, heavy exercise within 12 hrs, hypertension, Drug intake interfering with exercise response like beta blockers, vasodilators, ACE inhibitors, Ca channel antagonist, digitalis, antiarrhythmic agents and diuretics, hyperkalemia and hypokalemia.

BMI range (kg/m^2) classification [18]

<22.5 Normal
22.55-24.9 Overweight
>=25 Obese

Informed consent was taken from each subject for anthropometry, rhythmic handgrip exercise, impedance cardiovasography and blood sampling for mentioned biochemical analysis before and after exercise.

Parameters to be measured

1. Anthropometric Assessment

- Weight and height was measured according to techniques proposed by Jelliffe [19].
- Body Mass Index (BMI) was calculated according to formulae. BMI = weight/height^2 expressed in kilogram per meter square.

Cardiac and Hemodynamic assessment

Via Handgrip Dynamometer

- MVC (maximum voluntary contraction)

Via Mercury Sphygmomanometer and stethoscope

- Blood Pressure: systolic and diastolic

Via Impedance cardiovasography from Larsen & Tourbo *(Department of physiology)*

Cardiac Parameters
- Pulse Rate
- Stroke Volume, stroke volume index
- Cardiac Output, cardiac index

Hemodynamic Parameters
- Systemic vascular resistance (Total Peripheral Resistance), Systemic vascular resistance index

Impedance cardiovasography [20]

Noninvasive measurement of impedance requires using surface electrodes. Constant amplitude sinusoidal current is passed through the body segment or the calibration network through a relay with the help of current electrodes I1 and I2. Voltage sensing electrodes V1 and V2 are applied at desired location on the body segment along the current path. The amplitude of sensed sinusoidal signal is directly proportional to the instantaneous Z (Impedance) of the body segment between the sensing electrodes. Z is processed yielding basal impedance Z_o, $\Delta Z(t)$ and dZ/dt waveform which are read through an interface. Small change in the impedance of the body segment caused by physiological processes like blood circulation is obtained as waveforms. Measurement of these physiological processes from these impedance signals is known as Impedance Cardiovasography (ICVG).

It has most often acceptable accuracy, precision and responsiveness in a wide range of circulatory situation [21].

Biochemical measurement

In Department of biochemistry

Blood sample (3 ml before exercise) was drawn from antecubital vein. Biochemical parameters were analyzed on vitros 250 dry chemistry full autoanalyzer. Following biochemical parameters were measured:
- Fasting Blood Sugar/Glucose (FBS)
- Serum High Density Lipoprotien (HDL)
- Serum triglycerides

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 exclude subjects with metabolic syndrome.
3) Individuals made to lie supine in bed and made 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 [22] (for 2 mins), followed by Post Exercise Cuff Occlusion (PECO [23]) 20 mm Hg above systolic.
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).

It was an experimental longitudinal study design. Paired t test was applied to compare the differences between Preexercise and post rhythmic exercise values as well as compare the differences between the groups.

Result

Vasoconstriction mediated presser response: Change in SVR, SVRI, and DBP due to metaboreflex activation [24].

	Normal or Overweight			obese		
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*

Decrease in SVR is statistically significant (p<0.001*) in obese group

Flow mediated presser response: Change in SV, SVI, PR, CO, CI, and SBP due to metaboreflex activation [24].

	Normal or Overweight			Obese		
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()	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()	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*

Changes in CVS parameters are statistically more significant (*) in obese group

Discussion

Obesity is a very common disease worldwide, resulting from a disturbance in the energy balance. The major concerns of obesity are the co-morbidities, such as cardiovascular disease, stroke, and other life threatening conditions [25].

Sympathetic Nervous System (SNS) activity is associated with energy balance. Most of the data suggest that *obesity* is characterized by SNS predominance in the basal state and *reduced SNS responsiveness after various sympathetic stimuli*. This study was planned with an aim to study if obesity are having any effect on metaboreflex, to see if it contributes to cardiovascular risks [23].

All these subjects performed handgrip rhythmic exercises as per the protocol [23, 26].

Vasoconstriction mediated presser 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 [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 [27], reducing the metaboreflex-mediated Muscle Sympathetic Nerve Activity. This would have caused impairment of vasoconstriction mediated pressor response.

Diastolic Blood Pressure (DBP): Changes due to change in SVR and SVRI were found in 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 [13] by Negrão C.E., *et al.* (2001) showed similar findings and stated that muscle metaboreflex control is diminished in normotensive obese women. The response observed in this study was following static exercise and only vasoconstriction mediated pressor response was noted. It suggested that the increased fat content in the skeletal muscle of obese individuals may desensitize the metaboreceptors, reducing the metaboreflex-mediated MSNA.

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, in the study by Negrão CE. *et al*. (2001) [13], the maximal voluntary force was similar between the two groups.

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. In SVI, no significant differences were present between subjects with higher BMI and subjects with lower BMI.

Post exercise: Contrary to vasoconstriction mediated pressor response, SVI showed significant increase in subjects with higher BMI due to decreased afterload, and not in lower BMI subjects.

Systolic Blood Pressure (SBP), Cardiac Output (CO), Cardiac Index (CI), and Pulse Rate (PR) Changes due to change in SVI were observed in SBP, CO, CI and 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. Metaboreflex assessment can thus acts as a noninvasive tool for prediction of cardiovascular risks.

Through the present study we found that in apparently healthy obese subjects, higher BMI caused diminished vasoconstriction mediated pressor response and therefore increased flow mediated pressor response.

Thus we can conclude that:

a) In normal subjects, vasoconstriction mediated pressor response and flow mediated pressor response occur during exercise due to metaboreflex activation.
b) Impaired vasoconstriction mediated pressor response at higher BMI could be due to increased fat content[27] in the skeletal muscle of obese individuals which would desensitize the metaboreceptors, reducing the metaboreflex-mediated response.
c) Metaboreflex assessment can act as a noninvasive tool for prediction of cardiovascular risks.

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