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RESEARCH ARTICLE

Mean recovery heart rate during ergoreflex in adult male cancer patients

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ABSTRACT

Background: Cancer is a disease characterized by unregulated growth of the cell. Cachexia is one of the most common syndromes in cancer patients, seen in almost half of the patients, characterized by weight loss and can occur in a number of conditions. **Aims and Objective:** The present study was aimed to analyze mean recovery heart rate during ergoreflex in adult male cancer patients. **Materials and Methods:** A study group comprised 30 cancer patients between the age group of 45 and 60 years, who were selected from the cancer outpatient department of Himalayan Institute of Medical Sciences, Dehradun, with primary diagnosis of cancer. The patients were confirmed for cancer histologically and were included before the start of the treatment and after follow-up of 3 months of treatment. **Results:** The results indicated a significant increase in heart rate and respiratory rate during sustained hand grip (SHG) exercise and were maintained during venous occlusion and immediately after SHG. There was a significant increase in heart rate and respiratory rate during SHG exercise, which was maintained during venous occlusion and immediately after SHG. **Conclusion:** This reflex exerts positive feedback action favoring exercising muscle metabolism in conditions of elevated energetic demands by increasing ventilatory drive, blood pressure, sympathetic activation, and vasoconstriction of exercising limb.

KEY WORDS: Cancer; Ergoreflex; Cachexia

INTRODUCTION

Cancer is a disease characterized by unregulated growth of the cell. Cachexia is one of the most common syndromes in cancer patients, seen in almost half of the patients. Cachexia is characterized by weight loss involving depletion of host adipose tissue and skeletal muscle mass.[1] Cachexia occurs in a number of diseases such as chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), acquired immune deficiency syndrome, and anorexia nervosa. Weight loss in anorexia nervosa is predominantly from fat tissue, the muscle mass being mainly preserved. In cancer patients, weight loss is equally from fat and lean tissue with significant loss of muscle tissue.[2] Although anorexia is common in cancer patients, the body composition changes suggest that anorexia alone is not responsible for cachexia. In cancer patients, loss of both muscle and adipose tissue has been reported to precede the fall in food intake.[3]

A number of cytokines including tumor necrosis factor-α, interleukin (IL)-1, IL-6, and interferon-γ have been proposed as a mediator of cachectic process.[1] Loss of muscle tissue in cancer patients is reflected in functional changes of various reflexes arising from them, for example, ergoreflex.

Ergoreflex is a peripheral reflex originating in skeletal muscles. Nerve endings that are sensitive to metabolites exist in skeletal muscles and have been named ergoreceptors.[4] Ergoreceptors are intramuscular afferents and are functionally differentiated into mechanoreceptors and chemoreceptors. The mechanoreceptors are finely myelinated Group III afferents, and they respond mainly to mechanical stimuli.

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Chemoreceptors are Group IV afferents which are sensitive not only to acid metabolites in muscles but also to prostaglandins and bradykinin. Once the ergoreceptors are stimulated, they cause sympathetic drive and increase in blood pressure and ventilation. This combined effect is beneficial in diverting more oxygenated blood to the working skeletal muscles.[5] Ergoreceptors activation has been subject of several recent studies in heart failure syndrome, where metabolic abnormalities in skeletal muscles with early acidosis and accumulation of catabolites on exercise have been shown to be responsible for their enhanced activity.[6]

The muscle wasting maybe associated with reduced muscle strength and fatigue on physical exertion. These functional changes are accompanied by increased sympathetic activity, manifested as reflex increase in heart rate, respiratory minute volume, and constriction of peripheral blood vessels and increased blood pressure. This is well established as one of the factors contributing to fatigue and dyspnea in heart failure patients. In patients with CHF, there is evidence of a significant association between peripheral muscle wasting and enhanced ergoreflex.[7]

The depletion of lean tissue in cancer patients might contribute to the functional changes in skeletal muscles and ergoreflex. The study was undertaken to test the hypothesis that ergoreflex is hyperactive in cancer patients and it contributes to early fatigue, breathlessness, and exercise limitations.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Physiology, Himalayan Institute of Medical Sciences (HIMS), Swami Ram Nagar, Dehradun, over 12 months. Study group comprised 30 cancer patients between the age group of 45–60 years, who were selected from the COPD of HIMS Dehradun with a primary diagnosis of cancer. The patients were confirmed for cancer histologically and were included before the start of the treatment and after follow-up of 3 months of treatment.

The patients were excluded for the other cachetic conditions such as CHF, COPD, anorexia nervosa, tuberculosis, liver diseases, and thyrotoxicosis. The study protocol was approved by the institutional ethics committee. Written informed consent was obtained from the subjects after explanation of the study. Control subjects were selected from the people working in HIMS belonging to the age group of 45–60 years.

Method of Testing Ergoreflex

Subjects were asked to avoid strenuous physical activity for at least 24 h before assessment test and to refrain from smoking and having caffeinated beverages for at least 3 h before test. The subjects were briefed and familiarized with the process so as to remove apprehension regarding the test. The environment in the laboratory was quiet, with dimmed lighting, and the subject was asked to rest for 15 min before any data collection. Tests were performed in the morning from 8 am to 10 am in thermoneutral zone to avoid the effect of diurnal variation and temperature. Data were recorded, with subject in seated position in chair. To evaluate ergoreflex in forearm, post-exercise regional circulatory occlusion method was used.[5]

The protocol included two exercise bouts which were performed in random order: The test consisted of following steps: There was a period of rest of at least 30 min between two bouts of exercise to minimize the effect of muscle fatigue.

Briefly, the test consisted of following steps:

Determination of maximum voluntary contraction (MVC) of hand muscles using handgrip dynamometer. Subject was asked to perform sustained hand grip (SHG) at 50% MVC for 3 min. From 10 s before the end of exercise, 3 min of circulatory (venous) occlusion was done at 40 mmHg. Recovery phase started with release of pressure at the end of occlusion period. Data were recorded for 10 min during recovery phase. The degree of activation of ergoreflex was assessed during recovery phase as the difference in the parameters between recovery with occlusion and non-occlusion. Recording of pulmonary function tests by spirometry.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (version 16). Repeated measures analysis of variance (ANOVA) was used to compare the differences of mean of heart rate and respiratory rate during recovery periods in both the groups and to compare the differences in means in occlusion versus non-occlusion protocol for the estimation of activation of ergoreflex.

RESULTS

The present study was conducted with an aim to study the ergoreflex in adult male cancer patients and to find association, if any between body composition changes and ergoreflex in adult male cancer patients. A total of 60 volunteers were studied and analyzed. They were divided into two groups: Control and experimental subjects. Each group was studied according to two protocols (I - without occlusion after SHG and II - with occlusion after SHG).

Table 1 shows the results of analysis of mean recovery heart rate using repeated measures ANOVA during protocol I (non-occlusion) in control and experimental groups. In control group, recovery heart rate decreased from a mean value of 87.9 ± 1.4 (beats/min) during SHG to mean value of 81.7 ± 1.5 (beats/min) at last minute of recovery phase. In experimental group, recovery heart rate decreased during

Table 1: Analysis of mean recovery heart rate during protocol I (non-occlusion) using repeated measures ANOVA in control and experimental group

Variable (heart rate during recovery)	Control group Mean±SE (*n*=30)	Experimental group Mean±SE (*n*=30)	ANOVA
HR SHG	87.9±1.4	110.5±1.2	*P*=0.001 *F*=107.2
HR Rec1	89.5±1.6	106.6±1.5	
HR Rec2	85.7±1.6	104.5±1.6	
HR Rec3	83.5±1.4	100.5±1.7	
HR Rec4	82.6±1.4	99.6±1.4	
HR Rec5	81.9±1.5	98.8±1.3	
HR Rec6	81.7±1.5	98.9±1.4	

*Statistically significant if $P<0.05$. HR SHG: Heart rate during sustained hand grip, Rec1: 1st min of recovery phase, Rec2: 2nd min of recovery phase, Rec3: 3rd min of recovery phase, Rec4: Mean of 4th and 5th min of recovery phase, Rec5: Mean of 6th and 7th min of recovery phase, Rec6: Mean of 8th and 9th min of recovery phase, ANOVA: Analysis of variance, SE: Standard error

SHG in the last phase of recovery, from 110.5 ± 1.2 (beats/min) to 98.9 ± 1.4 (beats/min). Comparison of both showed that heart rate at the end of recovery period was significantly higher in experimental group than control group. The difference between the two groups was statistically significant ($P < 0.001$ and $F = 107.2$).

Table 2 shows the results of analysis of mean recovery heart rate during recovery in protocol II (occlusion) control and experimental groups. In control group, recovery heart rate decreased from mean value of 95.1 ± 1.6 (beats/min) during occlusion to mean value of 82.3 ± 1.2 (beats/min) at the last minute of recovery phase. In the experimental group, recovery heart rate decreased during occlusion in the last phase of recovery, from 122 ± 1.4 (beats/min) to 102.8 ± 1.3 (beats/min). On comparing these two groups, it was observed that recovery heart rate was delayed in experimental group and there was statistically significant difference in recovery rate of control and experimental groups ($P < 0.001$ and $F = 160.4$).

Table 3 shows a comparison of differences of means of recovery heart rate between protocol I (non-occlusion) and protocol II (occlusion) in both control and experimental groups using repeated measures ANOVA. On comparison of the two groups, it was inferred that there was activation of ergoreflex to a higher degree in experimental group in comparison to that of control group ($P < 0.000$; $F = 10.5$).

Table 4 shows the heart rate during various phases of recovery, with and without occlusion protocol (protocol I and protocol II). The differences (Δ^1 and Δ^2) in the protocols were taken as the index of ergoreflex activation. These were compared in control and experimental group. The experimental group had significantly higher activation of ergoreflex.

DISCUSSION

In our study, baseline heart rate and respiratory rate were significantly elevated in cancer patients. This finding is also most consistent with cardiac sympathetic activation in COPD patients.[8]

We observed a significant increase in heart rate and respiratory rate during SHG exercise, which was maintained during venous occlusion and immediately after SHG. Possible mechanism may be metaboreflex mediated sympathetic activation in cancer patients, i.e., ergoreflex.[9] This reflex exerts positive feedback action favoring exercising muscle metabolism in conditions of elevated energetic demands by increasing ventilatory drive, blood pressure, sympathetic activation, and vasoconstriction of exercising limb.[10]

Alam and Smirk[10] gave the concept of a chemical (metabolic) reflex arising from muscle, by showing that blood pressure and heart rate remained elevated when metabolites produced during exercise were trapped in muscle by occlusion of the leg blood flow immediately following exercise. The link between sympathetic nerve activity and activation of metaboreflex during exercise has been confirmed from studies revealing a latent onset of efferent neural discharge that coincides with an increase in muscle metabolites measured by P^{31} magnetic resonance spectroscopy. Using P^{31} magnetic resonance spectroscopy, Wilson *et al.*[11] demonstrated excessive demonstrated excessive depletion of phosphocreatine and greater acidosis in forearm muscle during submaximal exercise in CHF patients compared with normal subjects. These findings were later confirmed by Massie *et al.*,[12] who found a relationship between degree of skeletal muscle alterations in the forearm during exercise and clinical severity of CHF.

Voluntary isometric exercise in man is accompanied by a marked increase in blood pressure, cardiac output, heart rate (Lind *et al.*),[13] and pulmonary ventilation (Wiley and Lind),[14] (Myhre and Andersen).[15]It is possible that some of the ventilatory response mediated by the muscle afferents was due to an increase in peripheral chemoreceptor drive. It is known that sympathetic nervous activity can increase the discharge rate of peripheral arterial chemoreceptors (Lee *et al.*),[16] (Biscoe and Purves).[17] However, Parida *et al.*[18]

Table 2: Analysis of mean recovery heart rate during protocol II (occlusion) using repeated measures ANOVA in control and experimental group

Variable (heart rate during recovery)	Control group Mean±SE (*n*=30)	Experimental group Mean±SE (*n*=30)	ANOVA
HR SHG	95.1±1.6	122.0±1.4	*P*=0.001 *F*=160.4
HR Rec1	89.2±1.5	116.0±1.7	
HR Rec2	87.6±1.6	111.0±1.8	
HR Rec3	85.2±1.5	107.3±2.0	
HR Rec4	84.1±1.5	106.6±1.6	
HR Rec5	83.3±1.2	104.7±1.5	
HR Rec6	82.3±1.2	102.8±1.3	

*Statistically significant if $P<0.05$. HR SHG: Heart rate during sustained hand grip, Rec1: 1st min of recovery phase, Rec2: 2nd min of recovery phase, Rec3: 3rd min of recovery phase, Rec4: Mean of 4th and 5th min of recovery phase, Rec5: Mean of 6th and 7th min of recovery phase, Rec6: Mean of 8th and 9th min of recovery phase, ANOVA: Analysis of variance, SE: Standard error

Table 3: Activation of ergoreflex by comparison of differences of means of recovery heart rate during occlusion and non-occlusion protocols by repeated measures in control and experimental group

Variable HR (beats/min)	Differences of means during occ and non occ		ANOVA
	Control group Mean±SE (*n*=30)	Experimental group Mean±SE (*n*=30)	
HR SHG	9.2	12.4	*P*=0.002 *F*=10.5
HR Rec1	5.3	9.9	
HR Rec2	6.2	9.5	
HR Rec3	4.4	10.6	
HR Rec4	4.7	9.1	
HR Rec5	5.2	7.2	
HR Rec6	5.1	6.8	

*Statistically significant if $P<0.05$. HR SHG: Heart rate during sustained hand grip, Rec1: 1st min of recovery phase, Rec2: 2nd min of recovery phase, Rec3: 3rd min of recovery phase, Rec4: Mean of 4th and 5th min of recovery phase, Rec5: Mean of 6th and 7th min of recovery phase, Rec6: Mean of 8th and 9th min of recovery phase, ANOVA: Analysis of variance, SE: Standard error

Table 4: Shows the values of recovery HR in control and experimental group (cancer patients), using repeated measures ANOVA. The differences were used for computing the degree of activation of ergoreflex

Recovery HR	Control group Means±SEM (*n*=30)			Experimental group Means±SEM (*n*=30)		
	Without occlusion	Occlusion	Δ^1	Without occlusion	Occlusion	Δ^2
HRSHG	87.9±1.4	95.1±1.6	9.2	110.5±1.2	122.0±1.4	12.4
HR Rec1	89.5±1.6	89.2±1.5	5.3	106.6±1.5	116.0±1.7	9.9
HR Rec2	85.7±1.6	87.6±1.6	6.2	104.5±1.6	111.0±1.8	9.5
HR Rec3	83.5±1.4	85.2±1.5	4.4	100.5±1.7	107.3±2.0	10.6
HR Rec4	82.6±1.4	84.1±1.5	4.7	99.6±1.4	106.6±1.6	9.1
HR Rec5	81.9±1.5	83.3±1.2	5.2	98.8±1.3	104.7±1.5	7.2
HR Rec6	81.7±1.5	82.3±1.2	5.1	98.9±1.4	102.8±1.3	6.8
	P=0.252 *F*=1.34			*P*=0.001 *F*=15.26		

*Statistically significant if $P<0.05$. Δ^1: Differences of mean in control group, Δ^2: Differences of mean in experimental group, HR SHG: Heart rate during sustained hand grip, Rec1: 1st min of recovery phase, Rec2: 2nd min of recovery phase, Rec3: 3rd min of recovery phase, Rec4: Mean of 4th and 5th min of recovery phase, Rec5: Mean of 6th and 7th min of recovery phase, Rec6: Mean of 8th and 9th min of recovery phase, ANOVA: Analysis of variance, SEM: Standard error of mean

showed that ventilatory response to exercise was unaffected by denervation of carotid body chemoreceptor.

The above findings could be confirmed by taking more sample size. Although the sample size is less, we have performed detailed procedure to get opt conclusion which is the strength of the study.

CONCLUSION

There was a significant increase in heart rate and respiratory rate during SHG exercise, which was maintained during venous occlusion and immediately after SHG. Overactivation of the ergoreflex is associated with abnormal cardiorespiratory

reflex control, independently of clinical severity. Among impaired reflexes, overactivation of the ergoreflex is an important determinant of exercise hyperventilation and reduced exercise tolerance.

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