

Ventilatory Response to Interval Workload Exercise Protocol and Inhaled β_2 -agonists in Patients with Exercise-Induced Bronchospasm.

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ABSTRACT

Study objectives: The purposes of this study were to determine the effect of interval workload exercise protocol on selected pulmonary functions in asthmatic subjects with exercise-induced bronchospasm (EIB), and to demonstrate the difference between using interval exercise protocol alone and the combination of it with administration of short-acting bronchodilator β_2 -agonists on pulmonary functions for the same subjects.

Participants: Twenty-six asthmatic subjects, fifteen males and eleven females aged 35.61 ± 2.5 years with a history of EIB participated in the study. They were in stable clinical and physiological conditions. Subjects did not administer any medicines 24 hours prior to each intervention.

Interventions: All subjects were enrolled in two interventions study procedures. In the first intervention, they practice interval workload exercise protocol of 60% - 40% of their maximum work rate (MWR), which is determined previously by using symptom-limited exercise test, for 30 minutes by bicycle ergometer. While in the second intervention, short-acting bronchodilator β_2 -agonists was administered through pressurized metered-dose inhaler and after 10-minutes, they practice the same exercise protocol as in the first intervention. Selected pulmonary function measures of FVC, FEV₁, FEV₁%pred., MVV and RR were recorded pre, during and immediately after cessation of exercise and after 15 minutes rest by using computerized spirometry.

Results: On comparing during exercise parameters between the first and second interventions, it was found a significant ($P < 0.05$) decrease in RR (26.2 ± 3.2 vs. 20.9 ± 2.1 C/M) in the second intervention. While on comparing the two interventions immediately after cessation of exercise, it was found a significant ($P < 0.05$) increase in FEV₁%pred. (69.4 ± 7.5 vs. 80.5 ± 6.8 %), in PEFR (5.5 ± 1.4 vs. 6.9 ± 1.5 L/S) and in MVV (95.1 ± 20.0 vs. 98.4 ± 19.0 L/M), while RR showed significant ($P < 0.05$) decrease (28.7 ± 3.2 vs. 21.8 ± 1.8 C/M) in the second intervention. On comparing the pulmonary function parameters for both interventions after 15 minutes rest, it was found a significant increase ($P < 0.05$) in FVC (2.5 ± 0.6 vs. 3.0 ± 0.4 L), in FEV₁ (2.4 ± 0.6 vs. 2.9 ± 0.5 L), in FEV₁%pred. (68.6 ± 5.7 vs. 76.8 ± 3.3 %) and in MVV (95.8 ± 14.2 vs. 102.6 ± 20.1 LM).

Conclusions: Interval workload exercise protocol is efficient in asthmatic subjects with a history of EIB and it can be used in pulmonary rehabilitation and during carrying out their daily activities. Short-acting bronchodilator β_2 -agonists that are used in occasions before exertion can be replaced by practicing the exercise or the daily activities as an interval exercise workload protocol, to improve the cardiopulmonary fitness and to avoid the adverse reactions of β -agonists.

INTRODUCTION

Asthma is a chronic inflammatory lung disease, affects about 5-10% of the population worldwide and as much as a major health care issue in most countries. The prevalence of asthma is increasing, despite better understanding of its pathogenesis and improved treatments. During the past 10 years, the perception of asthma has shifted from a disease primarily characterized by altered bronchial smooth muscle function to one mainly characterized by chronic inflammation.¹

About 80% of asthmatic patients have exercise induced bronchospasm (EIB). EIB is defined as a decrease in lung function following vigorous exercise. Bronchospasm usually occurs 1 to 15 minutes following exercise intense enough to elicit 85% or more of maximal oxygen consumption for 4 to 10 minutes. EIB affects up to 35% of athletes and up to 90% of asthmatics. Asthma morbidity and mortality have increased over the past several decades. It is possible that a simple free running test for EIB may serve as a tool to study the factors contributing to recent trends in asthma, and to screen for asthma in athletes².

Peripheral airway resistance (PAR) has been shown to be increased in asymptomatic asthmatic patients with normal spirometric values. In a study to investigate whether PAR in asthmatics with EIB would rise in response to cool, dry air by using wedged bronchoscope technique. It was found that asthmatics but not normal subjects, had a significant absolute maximal increase in PAR following exposure to cool, dry air and it was correlated with airways hyperresponsiveness to exercise and may play an important role in EIB. At high ventilation level, as during heavy exercise, the direct airway effects of cold air may also

contribute to the bronchoconstriction in susceptible individuals due to the evaporative water loss from airway mucosa leading to airway hyperosmolarity, which triggers bronchospasm.^{3,4}

In patients with asthma, improvement in lung mechanics, alleviation of dyspnea and increased activity levels are desirable therapeutic goals. Studies that are designed to evaluate the impact of interventions, such as bronchodilator therapy, increasingly incorporate these important clinical outcome measures. Relief of exertional dyspnea following both β_2 -agonists and anticholinergic therapy has been shown to correlate well with reduction of dynamic lung hyperinflation, as measured by serial expiratory capacity measurements during exercise.^{5,6}

Measurements of functional ability are important for assessment and management of chronic lung disease. Functional ability reflects the individuals' capacity to meet the needs of daily living.⁷

Patients with asthma are limited in their exercise tolerance by; dyspnea, peripheral muscle weakness and lactic acidosis at low levels of exercise. The factors that contribute to dyspnea in these patients are related to a combination of high ventilatory requirement coupled with low ventilatory capacity. The rehabilitation strategy was a comprehensive program that included modalities of exercise training, breathing control techniques, disease education and instruction in the use of medication.⁸

Lung function is a strong predictor of overall mortality in asthma and COPD. Forced expiratory volume in the first second (FEV1) is considered to be the "gold standard", whereas peak expiratory flow (PEF) is mostly used in absence of FEV1 measurements. In asthma, best FEV1 seemed to be a better predictor of mortality than best PEF. While in

COPD, best PEF provides independent prognostic information^{9,10}.

FEV₁ decline in patients with mild airflow obstruction receiving continuous bronchodilator treatment (β_2 -agonists) was significantly larger than in those symptomatically treated. So that regular inhaled β_2 -agonists should not be used to treat EIB. However, inhaled short-acting β_2 -agonists used immediately before exercise remains an extremely effective way of preventing EIB. So that long-acting β_2 -agonists may be required as a maintenance treatment of asthma and prevention of bronchospasm in patients who require regular treatment, as it decreases airway responsiveness consistently to direct bronchoconstrictors (allergen, exercise and hypertonic solution) and inconsistently to direct bronchoconstrictors (histamine and methacholine). Adverse reactions of inhaled short-acting β_2 -agonists are tachycardia, tremor, dizziness, insomnia and abdominal pain^{11,12}.

The standard therapy of asthma consists of; anti-inflammatory control including corticosteroids, β_2 -agonists and anticholinergic agents. Long acting β_2 -agonists

improve clinical indices of asthma but have no effect on the underlying inflammatory process. These findings strengthen guideline recommendations that they should not be prescribed as a sole antiasthma medication^{13,14}. A pulmonary rehabilitation program performed twice weekly with moderate exercise workloads can lead to a physiologic training response irrespective of the degree of airflow limitation^{15,16}.

The intensity of aerobic training is limited in asthmatics by dyspnea. Improving strength of inspiratory muscles could enhance aerobic training by reducing exercise-related

SUBJECTS, MATERIAL AND METHODS

Subjects

Twenty-six asthmatic subjects (fifteen males and eleven females), with mean age of 35.61 ± 2.5 years, weight 69.0 ± 9.4 kilograms, height 179.3 ± 9.0 centimeters and with a history of EIB were participated in this study.

All participants were non-smokers, asymptomatic at the time of the study and in stable clinical and physiological conditions. They had no known coronary, orthopaedic, neurological or endocrinial disorders and without a recent history of upper respiratory tract infection. There was no clinical evidence of exercise-limiting cardiovascular or neuromuscular diseases.

Subjects did not receive any medications and β_2 -agonists inhalers were withheld for 24 hours prior to each study day. Female subjects were instructed to participate in the study after the end of menstrual cycle. Written informed consent was obtained from each subject before the study.

Material

- Bicycle ergometer (Monark 818 E).
- Computerized spirometer (Super Spiro Discm 21 FX).
- Pressurized metered-dose inhaler of short-acting bronchodilator β_2 -agonists (Salbutamol).

Methods

Subjects were instructed to have the last meal 2 hours before starting the exercise protocol and to have a rest for half an hour. Exercise challenge was performed in an air-conditioned room with constant temperature and humidity. The study procedures were

dyspnea^{17,18,19}.

carried out a day after day interval.

The first initial procedure was performed to determine the maximum work rate (MWR) for participants by using symptom-limited exercise test by the bicycle ergometer and was always preceded by a familiarization test. The subject pedaled at work rate of 20-30 Watt (W) for 3 minutes as a warm up. The work rate increased 20-30 W. every minute until the subject was unable to continue due to either leg fatigue or shortness of breath. MWR was calculated according to the conversion table and its mean value for all participants was 220.0 ± 40.2 W.

The first intervention; during which interval workload exercise protocol was done for all participants, at first the subject seated on the bicycle ergometer and breathed though the mouthpiece of the spirometer with a nose clip in place and the following spirometer measures were taken as pre-parameters; forced vital capacity (FVC) in liters (L), forced expiratory volume in the first second (FEV1) in liters (L), forced expiratory volume in one second percent predicted (FEV1%pred.), peak expiratory flow rate (PEFR) in liters/second (L/S), maximal voluntary ventilation (MVV) in liters/minute (L/M) and respiratory rate (RR) in cycle/minute (C/M).

The interval workload exercise protocol was performed by asking the subject to pedal for 2-3 minutes as a warm-up period at a work rate of 20-30W, to prepare the cardiopulmonary system for exercise. Then the work rate increased to 60% of the subject's MWR, then reduced to 40% of MWR and increased again to 60%. This alteration was carried out every 5 minutes for a total exercise

period of 30 minutes.

The previous spirometry measures were taken during exercise, immediately after cessation of exercise and 15 minutes after exercise.

The second intervention; during which interval workload exercise protocol with administration of short-acting bronchodilator β_2 -agonists were applied. Firstly, the subject received the β_2 -agonists Salbutamol 100 μ g in a pressurized metered-dose inhaler, 10 minutes before starting the exercise protocol that was done as in the first day of the study. Spirometry measures were also taken during, immediately after cessation of exercise and 15 minutes after exercise.

Statistics

Data were collected and statistically analyzed by using mean, standard deviation and paired t-test to compare between during, immediately after exercise and after 15 minutes rest in the first intervention (exercise) and their corresponding measures in the second intervention (short-acting bronchodilator and exercise) with a level of significance at $P < 0.05$.

RESULTS

The pre parameters are just the same in the first and second interventions, where FVC was 2.8 ± 0.5 (L), FEV1 was 2.6 ± 0.5 L, FEV1%pred. was 74.7 ± 1.9 %, PEFR was 6.5 ± 1.4 (L/S), MVV was 104.1 ± 20.1 (L/M) and RR was 15.8 ± 1.7 (C/M), table (1).

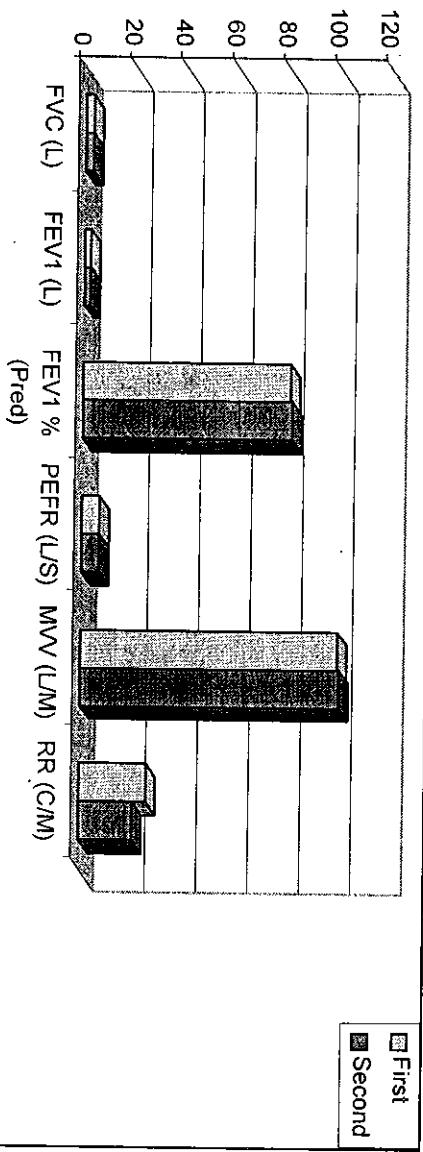
Table (1): Differences of measured pulmonary functions between the first and second interventions.

Variables	Intervention	Pre	During	Immediately after	After 15 min. rest
FVC (L)	First	2.8 ± 0.5	3.0 ± 0.6	2.6 ± 0.6	2.5 ± 0.6
	Second				
FEV1 (L)	First	2.6 ± 0.5	3.1 ± 0.3	2.8 ± 0.6	2.4 ± 0.6
	Second				
FEV1% Pred.	First	74.7 ± 1.9	80.9 ± 5.4	69.4 ± 7.5	68.6 ± 5.7
	Second				
PEFR (L/S)	First	6.5 ± 1.4	7.0 ± 1.5	5.5 ± 1.4	6.3 ± 1.5
	Second				
MVV (L/M)	First	104.1 ± 20.1	100.5 ± 20.4	95.1 ± 20.0	95.8 ± 14.2
	Second				
RR (C/M)	First	15.8 ± 1.7	20.9 ± 2.1	21.8 ± 1.8	17.7 ± 4.3
	Second				

*Significant P<0.05

On comparing during interval workload protocol between the first and interventions, it was found a significant ($P<0.05$) decrease in RR in the second intervention (26.2 ± 3.2 vs. 20.9 ± 2.1 C/M), while there was insignificant ($P>0.05$) increase in FVC (3.0 ± 0.6 vs. 2.8 ± 0.4 L), in FEV1% pred. (80.9 ± 5.4 vs. 82.3 ± 4.1 %),

in PEFR (7.0 ± 1.5 vs. 7.2 ± 1.3 L/S) and in MVV (100.5 ± 20.4 vs. 101.3 ± 18.9 (L/M) in the second intervention. FEV1 showed no significant difference between the two interventions (2.8 ± 0.6 vs. 2.8 ± 0.4 L), figure 1, table 1.

*Fig. (1): Differences of measured pulmonary function parameters between the first and second interventions during exercise.*

On comparing the measured ventilatory parameters at cessation of exercise (immediately after exercise) between the first and second interventions, it was found in the second intervention, a significant ($P<0.05$) increase in FEV1%pred. (69.4±7.5 vs. 80.5±6.8 %), in PEFR (5.5±1.4 vs. 6.9±1.5

L/S) and in MVV (95.1±20.0 vs. 98.4±19.0 L/M), while RR showed a significant ($P<0.05$) decrease in the second intervention (28.7 ± 3.2 vs. 21.8 ± 1.8 C/M). FVC showed an insignificant increase in the second intervention (2.6 ± 0.6 vs. 2.8 ± 0.4 L) and also of FEV1 (2.4±0.6 vs. 2.7±0.5 L), figure 2, table 1.

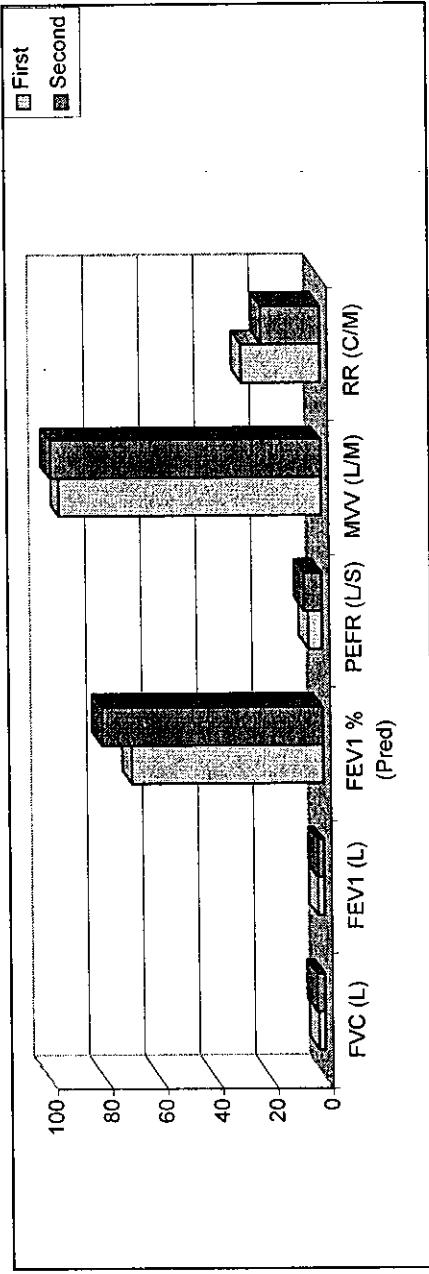


Fig. (2): Differences of measured pulmonary function parameters between the first and second interventions immediately after exercise.

On comparing the same parameters after 15 minutes of exercise, between the first and second interventions, it was found in the second intervention, a significant ($P<0.05$) increase in FVC (2.5 ± 0.06 vs. 3.0 ± 0.4 L), FEV1 (2.4 ± 0.6 vs. 2.9 ± 0.5 L) and in MVV

(89.8 ± 5.7 vs. 76.8 ± 3.3 %), while PEFR showed an insignificant increase in the second intervention (6.3 ± 1.5 vs. 6.7 ± 1.3 L/S) and finally RR showed insignificant decrease (19.8 ± 5.0 vs. 17.7 ± 4.3 C/M), figure 3, table 1.

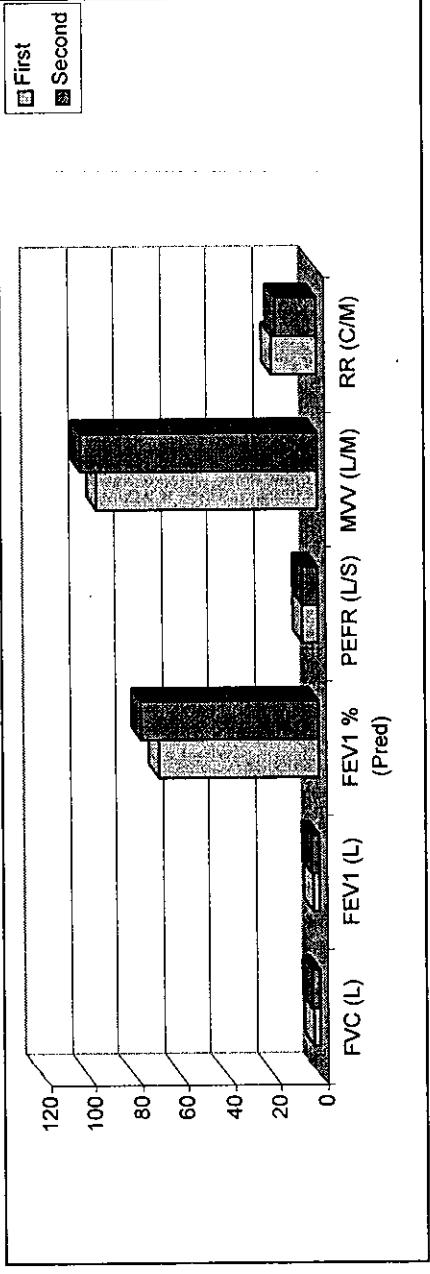


Fig. (3): Differences of measured pulmonary function parameters between the first and second interventions after 15 minutes rest.

DISCUSSION

Patients with asthma are limited in their exercise tolerance by dyspnea, peripheral muscle weakness and lactic acidosis at low levels of exercise. The factors that contribute to dyspnea in these patients are related to a combination of high ventilatory requirement coupled with low ventilatory capacity. The rehabilitation strategy was a comprehensive program that included modalities of exercise training, breathing control techniques, disease education and instruction in the use of medication.⁸

Measurements of functional ability are important for assessment and management of chronic lung disease. Functional ability reflects the individuals' capacity to meet the needs of daily living.⁷

In patients with asthma, improvement in lung mechanics, alleviation of dyspnea and increased activity levels are desirable therapeutic goals.

In asthma of moderate intensity, change in FEV₁ is possibly a better predictor of exercise performance after bronchodilators than in severe disease, but considerable intersubject variability remains.²⁰ However, improvement in FVC after bronchodilator therapy, which generally reflects a reduction in residual volume, is poorly predictive of improved dyspnea and exercise tolerance.¹⁵ Mass spiroometry in high-risk population is an effective and easy method for early detection of EIB and asthma.²¹

Clinical studies as well as experimental studies have shown that exposure to various air pollutants can increase bronchial responsiveness to allergen stimulation or bronchial reactivity.²²

Asthmatic females participated in this study after the end of menstrual cycle to avoid interaction with premenstrual exacerbation of

asthma symptoms. As premenstrual worsening of lung function begins 7-10 days before the onset of menstruation and peaks 2-3 days before the onset, this change in asthma in the latter half of luteal phase of menstrual cycle would be related to hormonal change.²³

In patients with symptomatic asthma, desirable therapeutic goals include improvement of ventilation mechanics, alleviation of dyspnea, increased activity levels and improved quality of life. Studies designed to evaluate the efficacy of interventions, such as bronchodilator therapy, increasingly incorporate these important clinical outcomes. Traditionally, the primary outcome measure for clinical trials has been the measurement of FEV₁. Recent studies have provided greater appreciation that symptomatic benefit with lung hyperinflation is clearly linked to effective pharmacological volume reduction.^{15,24}

Airway obstruction in EIB is considered a post-exercise phenomenon. However, many patients with EIB complain of respiratory distress during exercise. In short-term exercise (6 minutes), there was a little or no airway obstruction. While in long-term exercise (20 minutes), airway obstruction occurs during exercise and the manifestation of dyspnea is associated in the recovery period.²⁵

There is a different physiological response pattern to interval or continuous training in asthma. Interval exercise resembles the daily life activity pattern more closely than continuous exercise. One reason for anticipating enhanced exercise tolerance after interval training as compared to continuous work training relates to recent observations in peripheral skeletal muscle biopsies showing that baseline energy status can be altered, resulting in a shift towards a decreased aerobic enzyme capacity and an increased glycolytic capacity. In the interval training, leg pain at

peak workload was dramatically decreased; despite an increase in lactate concentration and peak workload, suggesting an enhanced exercise tolerance²⁶.

The evidence of bronchodilatation during interval exercise protocol can be explained by the increasing concentration of the circulating catecholamines during exercise, which is dependent on the workload and is modest at submaximal level³.

The results showed evidence of bronchodilatation during interval workload exercise protocol for 30 minutes in both interventions, while in other studies^{25,27}, it was found airway obstruction starting after 15 minutes of exercise, which was significant at 20 minutes. This may be attributed to the application of short exercise duration for less than 20 minutes.

In this study, it was found that there was non-significant bronchoconstriction immediately after cessation of exercise and after 15 minutes of rest in the first intervention which practice the interval exercise protocol only, while in the study of Vogiatzis & colleagues⁸ and Coppoole & co-workers²⁶, there was a significant bronchoconstriction, which was due to the use of either constant or incremental workloads exercise protocol which were responsible of inducing reflex bronchoconstriction as a result of strenuous activities.

The results show that there was non-significant difference of FVC, FEV₁, FEV₁%pred. and PEFR between the results of the first intervention group who practiced interval workload exercise protocol only and those of the second intervention who received the short-acting bronchodilator and practice the same exercise protocol. This will demonstrate the efficacy of practicing interval exercise as much as the short-acting bronchodilator. So it is advisable for asthmatic

patients to practice their exercise programs and achieving their activities of daily livings as an interval workload activity instead of using the short-acting bronchodilator to avoid their side effects.

The bronchodilatation response in the second intervention is due to the synergistic effect of both interval exercise and β 2-agonists on bronchial wall. While in the first intervention, the bronchial response after exercise demonstrates the cardiopulmonary fitness that is improved by engaging in pulmonary rehabilitation which improves the functional abilities of asthmatic patients to meet their needs for daily livings⁷, while the bronchodilatation effect of β 2-agonists reflects just a pharmacological state of temporary improvement¹².

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مدى استجابة الموظف الرؤية التشريعات ذات الشدة المتغيرة واستنشاق الفتاوى بغير سريعة المفعول

يعتبر مرض حساسية الصدر المصاحب بالاقياب الشعبي ناتج عن التربينات الرياضية من أكثر الأمراض انتشاراً وهو يهدى إلى الخفاض معدل قدرة الشخص على التنفس في أداء المجهود مما يعكس على كفاءة الشخص من الناحية العقلية والاجتماعية. تهافت هذه البراسة إلى بيان أنّه استخدم التربينات الرياضية ذات الشدة المتغيرة وتناول الأدوية المبسطة للإقناب الشعبي المصابة بالاقناب الشعبي الناتج عن التربينات الرياضية ذات الشدة في أداء المجهود مما يعكس على كفاءة الشخص من الناحية العقلية والاجتماعية. تهافت هذه البراسة إلى بيان أنّه استخدم التربينات الرياضية ذات الشدة المتغيرة وتناول الأدوية المبسطة للإقناب الشعبي المصابة بالاقناب الشعبي الناتج عن التربينات الرياضية ذات الشدة في أداء المجهود مما يعكس على كفاءة الشخص من الناحية العقلية والاجتماعية. تهافت هذه البراسة إلى بيان أنّه استخدم التربينات الرياضية ذات الشدة المتغيرة وتناول الأدوية المبسطة للإقناب الشعبي المصابة بالاقناب الشعبي الناتج عن التربينات الرياضية ذات الشدة في أداء المجهود مما يعكس على كفاءة الشخص من الناحية العقلية والاجتماعية.