The Protective Effects of Continuous and Interval Exercise on Athletes with Exercise Induced Asthma

Adesola, A. M.
Department of Physiology, Faculty of Basic Medical Sciences
Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria
E-mail: amadesola@lautech.edu.ng

ABSTRACT

The purpose of this experiment is to determine the effect of two forms of warm-up on post exercise bronchoconstriction in athletes with exercise-induced asthma. Twelve moderately trained persons with asthma were tested under three experimental conditions: continuous warm-up (CW), interval warm-up (IW), and control (C). CW consisted of 15 minutes of treadmill running at a velocity corresponding to 60% VO_2 max followed by an exercise challenge test (ET = 6 minutes at 90% VO_2 max). IW involved 8 x 30 seconds runs (1.5 minutes rest between bouts of exercise), at an intensity equivalent to 100% VO_2 max, followed by an ET. C consisted of only the ET. FEV_1, FVC, and MMEFR were measured prior to the experimental conditions, repeated before the ET, and every 2 minutes during a 25 – minute passive recovery period, using a Breon spirometer. Post-exercise changes in pulmonary function were recorded as the largest decrease in FEV, FVC, and MMEFR during the recovery period, and expressed as a percentage of baseline values. Significant differences were detected in % FEV_1, % FVC and %MMEFR, in comparing C, CW, and IW, respectively. Scheffe's test detected significance between C and CW for all three dependent variables, no statistical significance between C and IW or IW and CW occurred. These data indicate that a continuous warm-up of 15 minutes at 60% VO_2 max can significantly decrease post exercise bronchoconstriction in moderately trained athletes.

Keywords: *Exercise – induced asthma, refractory period, warm-up*

INTRODUCTION

During an exercise challenge the most intense symptoms of exercise-induced asthma (EIA) occur after 6-8 minutes of exercise; beyond this time the severity may begin to decrease and this has led to the observation that some patients can "run through" their asthma (Fitch and Godfry, 1976). After exercise, 40-50% of persons with EIA will be refractory to an exercise task performed within 2 hours of the initial challenge (Bar-Yishay and Godfry, 1984). The mechanisms responsible for this refractory period are not completely understood and may be related to increase circulating levels of catacholamines (Barnes, Brown and Silverman, 1981) or to depletion of mediators from mast cells (Edmunds and Godfry, 1978; Eggleston, 1986). EIA is precipitated by cold, dry air and inhibited by inspiring warm, humid air (Chen and Horton, 1977). It has been suggested that Respiratory Heat Loss (RHL) acts as a stimulus to EIA (Anderson *et al.*, 1982; Deal, McFadden, Ingram

and Jaeger, 1979; Deal et al., 1979; Mcfadden, 1983). The type of exercise that will induce a refractory period has not been well established, nor has the effect of previous exercise on RHL. A warm-up period prior to vigorous exercise is widely recommended and is considered to offer physiological, psychological, and injury preventing benefits (Morton, Fitch and Davis, 1979). However, the effect of warm-up exercise on EIA has not been extensively investigated. Schnall and Landau (1980) have reported that seven, repeated, 30 – seconds, high intensity runs, preceding a 6 minutes exercise challenge resulted in significantly less bronchoconstriction. Morton, Fitch and Davis, (1979) limit their warm up period to 3 minutes at an intensity equivalent to 60% VO_2 max. They were unable to demonstrate a significant difference in post exercise bronchoconstriction and suggested that the duration of exercise should be increased. As these two types of warm-up exercises are frequently chosen by athletes in preparation for more vigorous activities, this study is designed to compare the severity of bronchoconstriction, following a 6 minute exercise challenge test, in athletes with exercise induced asthma who were exposed to 15 minutes of continuous, moderate intensity exercise, 8 x 30 seconds, high intensity, interval running immediately prior to the challenge test.

METHOD

Subjects: *T*welve moderately trained athletes, nine females and three males, (age = 26.5 ± 2.2 years, height = 169.2 ± 2.6 kg; VO_2 max = 52.5 ± 1.3 ml.kg-^{1}.min-^{1}) with EIA volunteered for the study. The study was approved by the clinical screening committee for research and other studies involving human subjects, written informed consent was obtained from all participants. All subjects were receiving â-agonists in aerosol form (Salbutamol) and/or cromolyn sodium to control their disease. The criteria for inclusion in the study were a maximal oxygen update (VO_2max) of >45ml.kg^{-1}.min^{-1}, a positive histamine challenge tests, and a >15% fall in FEV_1 following an exercise challenge test. The subjects were nonsmokers and did not have any additional pulmonary function abnormalities. Prior to treadmill testing they did not participate in any form of physical activity nor ingest caffeine for 4 hours.

Fitness Assessment (FA): Prior to the maximal exercise test, a prescribed dose of the subjects' bronchodilator was self administered. Maximal oxygen uptake (VO_2max) was determined during a progressive continuous treadmill run. Following a 5 minute warm-up at 2.22m.s^{-1}, the treadmill speed was automatically increased to 0.22m.s^{-1} each minute until volitional fatigue. Heart rate was monitored by direct electrocardiography (Avionics 4000 Electrocardigraph). Expired gases were continuously sampled and respiratory gas exchange variables were measured with a Beckman metabolic measurement Cart interfaced to a Hewlett Packard 3052, a data acquisition system. The mean for the four highest consecutive 15-s values for oxygen consumption was taken as the maximal oxygen consumption.

Pulmonary Function (PF): These were measured at rest using a Collins spirometer prior to beginning the study. Forced Expiratory Volume in 1 second (FEV_1), Maximal Mid-expiratory Flow Rate (MMEFR), and forced vital capacity (FVC) were measured. The highest of three trials was recorded. Each subject completed a histamine challenge test to assess the degree of bronchial reactivity. A continuous breathing method was used; this involved inhalation of increasing concentrations of histamine during tidal volume breathing for 2 minutes interval. Saline inhalation is used as control. The maximum dose of histamine given was 16mg.ml^{-1} (Juniper, Cockroft and Hargreave, 1991). Pulmonary function was measured after each concentration of histamine until a fall in FEV_1 of 20% or more occurred. A 20% or greater fall in FEV_1 with a histamine concentration (PC_{20}) less than 8.0mg.ml^{-1} was considered to be a positive test (indicative of bronchial hyper reactivity (Cockroft, Murdock, Berscheid and Gore , 1992).

Exercise Challenge Test (ECT): Each subject underwent an exercise challenge test that consisted of a 6 minute treadmill run at a velocity corresponding to 90% VO_2 max for confirmation of the diagnosis and to act as a control for the study. The treadmill speed was prescribed using the values determined during the fitness assessment. Pulmonary function measures were determined using a Breon spirometer (Model 2400) prior to the test and every 2 minutes during a 25 minute passive recovery following the test. Post exercise changes were recorded as the largest decrease in FEV_1, FVC, and MMEFR during recovery, expressed as a percentage of baseline values. A >15% fall in FEV_1 following the exercise challenge test representing the criteria for a positive test.

Peak Expiratory Flow Rate (PEFR): This rate is the maximum of peak rate (or velocity), in liters per minute, with which air is expelled with maximum force after a deep inspiration. The peak expiratory rate is the maximum flow rate or peak flow rate of air, during a single forced expiration. This estimation is useful in distinguishing reversible (e.g. asthma) from irreversible (e.g. emphysema) diseases. The peak flow meter, which measures PEFR, is of special value in cases of asthma where the effectiveness of treatment with a bronchodilator can be quickly evaluated. For example, a PEFR of, say, 150 liters/min may improve to 300 liters/min. within a short time of inhalation of the drug. But the meter is not useful for assessing the degree of disability of patients with lung fibrosis and other restrictive conditions because they may have normal expiratory flow rate. The measurement of the effect of training in athletes is yet another application of the Wright peak flow meter.

Timed Vital Capacity (FEV_1): It is the largest volume of air a person can expel from the lungs with maximum effort after first filling the lungs fully by a deepest possible inspiration. It amounts to 3.5 liters. The FEV_1 is a dynamic capacity. In a normal person, a single forced expiration takes about 3 seconds, and the tracing thus obtained is called an "expiratory spirogram" The fractions of FVC are: 80% in

1 second (FEV_1), 93% in 2 seconds, and 98% in 3 seconds. The FEV_1 is called the "first expiratory volume at 1 second (FEV_1)" or "forced expiratory volume in 1 second". In addition to FVC and FEV_1, the average expiratory flow rate during the middle 50% of FVC, also called "maximal mid-expiratory flow rate" (MMEFR; OR FEF 25-50%) can also be calculated

Respiratory Heat Loss (RHL): During the exercise testing the ambient temperature and pressure, relative humidity, and the expired gas volume and temperature were recorded and used to calculate the respiratory heat and water loss according to the equation of Strauss, Jagger and Mc Fadden (1986).

$$RHL = VE (HC[Ti – Te + Hv (Wci-Wce)],$$

Where

RHL = respiratory heat loss ($Kcal.min^{-1}$)
VE = ventilation ($l.min^{-1}$ BTPS),
HC = specific density of air (0.304×10^{-3} $Kcal.l^{-1}. {}^{o}C^{-1}$),
Ti = inspired temperature ^{o}C,
Te = expired temperature ^{o}C,
Hv = heat of vapourization of water (0.58 $Kcal.g^{-1}$).
Wci = water content of inspired air ($mg.l^{-1}$),
Wce = water content of expired air ($mg.l^{-1}$).

After completing baseline testing, each subject then participated in three experimental sessions. Each session included a treatment intervention, a 2 – minute rest period, an exercise challenge test and a passive recovery. The control (C) condition involved no activity during the treatment intervention period. Continuous warm-up consisted of a 15 – minute continuous treadmill run at a velocity equivalent to 60% VO_2 max. Interval warm-up consisted of 8 x 30 seconds runs on the treadmill with 1.5 minute rest between sprints. The intensity of the sprints was a treadmill velocity corresponding to 100% VO_2 max calculated from the initial fitness assessment. These conditions were followed by a 2 minute rest period to allow for pulmonary function measurements and a change in treadmill velocity. The exercise challenge test followed immediately. A baseline measure of pulmonary function was taken prior to treatment intervention. A pre exercise challenge value was taken 1 minute prior to the exercise challenge test. Eleven post exercise challenge measures were recorded during the recovery phase at the following times: 0.5, 2, 4, 6, 8, 10, 12, 14, 16, 20, and 25 minutes. Percent fall in FEV_1, MMERF, and FVC were calculated using the lowest values obtained during recovery. The pulmonary function data and RHL were analysed using four separate ANOVAs. When significant differences were found a post-hoc Scheffe's test was used to determine differences between treatments. Statistical significance was inferred for $P < 0.01$ for all ANOVAs to offset possible á-error due to multiple comparisons, and $P < 0.05$ for post-hoc analyses.

RESULTS AND DISCUSSION

Subjects: Table 1 presents the individual physical characteristics of the subjects. These athletes were moderately trained having a range of maximal oxygen consumption of 45 – 60ml.kg^{-1}min^{-1} (mean ±SD = 52.7 ± 4.6). Each subject was confirmed as having bronchial hyperreactivity by a >20% fall in FEV_1 at a PC_{20} of <8.0 mg.ml^{-1} during the histamine challenge test. EIA was also confirmed by a >15% fall in FEV_1 following the exercise challenge test. In this study each subject satisfied the criteria for both increased bronchial reactivity and EIA.

Pulmonary Function Measures: The baseline pulmonary function measures that were taken prior to each experimental session were within 10% of the values obtained during the preliminary pulmonary function testing (Table 2). Following the treatment intervention, the pre exercise challenge measures, taken 1 minute prior to exercise challenge, confirmed that bronchoconstriction was not induced by the treatment intervention. These measures were within a 15% decrease in baseline values. The mean challenges in FEV_1, MMEFR, and FVC for each treatment are presented in figure 1. There was a significant difference in the percentage change of FEV_1, % MMEFR, and % FVC between the three conditions ($P < 0.01$). Scheffe's post-hoc comparison reveals that significant differences $P < 0.05$ occurred in all pulmonary variables between the control and the continuous warm-up conditions only. Post-hoc comparisons failed to show significant differences between the control and interval warm-up conditions or between the continuous warm-up and interval warm-up condition in any spirometry measurement.

The data related to respiratory heat and water loss are presented on table 3. There were no statistically significant changes in comparing the three experimental conditions. This study indicates that 15 minutes of continuous exercise, at an intensity equivalent to 60% of maximal oxygen consumption, followed by an exercise challenge test, results in significantly less post exercise bronchoconstriction than if no warm-up took place. All subjects demonstrated a statistically significant decrease in % FEV, % MMERF, and %FVC following the continuous warm-up intervention, in comparison with baseline testing (figure 1). Six of the 12 subjects decreased their FEV_1 less than 15% following the exercise challenge test after the continuous aerobic exercise and therefore did not satisfy the criteria for EIA. This suggests that, in some individuals with exercise – induced asthma, 15 minutes of a continuous, moderate intensity, warm-up prior to more strenuous exercise will significantly decrease or prevent post exercise bronchoconstriction. The interval warm-up period had less of an effect on post exercise bronchoconstriction following this form of intervention; two of the subjects demonstrated a greater than 15% decrease in FEV_1 from baseline values. There was a slight decrease in $\%FEV_1$, % MMEFR, and % FVC, between the interval and control condition (figure 1), but it is clear

that repeated, high-intensity exercise in the pattern previously described offers only a modest protection to the athlete with EIA. There are several anecdotal reports that suggest warm-up prior to exercise decreases post exercise bronchoconstriction. Unfortunately, the specificity of the warm-up activity has not been looked at in details. Morton, Fitch and Davis (1979) determine the effect of a warm-up, on a treadmill, limited to 3 minutes at an intensity equivalent to 60% VO_2max. No significant differences in post exercise bronchoconstriction were detected in the 18 subjects studied. However, it was suggested that the duration and intensity of the warm-up procedure should be increased prior to rejecting the hypothesis that warm-up can effect EIA. Reiff *et al* (1989) used this suggestion and studied seven patients with asthma following 30 minutes of sub-maximal exercise and reported that this form of exercise could induce refractoriness to EIA.

The intensity of exercise was approximately 64% of the maximal aerobic capacity (VO_2max ~ 50 ml.kg^{-1}.min^{-1}) and the mean heart rate during the warm-up was 88% of the predicted maximum. An exercise challenge test conducted 21 minutes after the warm-up run demonstrated a mean maximal fall in FEV_1 of 17% compared to the control challenge test which resulted in a 46% fall. PEFR was similarly affected (27% VS 51%). The results of the present study are in agreement with those of Reiff, Choudry, Pride and Ind (1989) and support the suggestion of Morton, Fitch and Davis (1979), it is apparent that the duration of continuous warm-up must be longer than 3 minutes in order to affect the degree of airway constriction. Schnall and Landau (1980) used interval training as a warm-up procedure and observed a statistically significant decrease in post exercise bronchoconstriction, as reflected in PEFR, FEV_1, and FEF 25% - 75%, following a series of 7 x 30 – second sprints (2.5 minutes between sprints) in six subjects. These results also agree with the present study, although our changes were more modest and did not show statistical significance.

Several authors have reported that repeated exercise will diminish the post exercise increase in airway resistance in patients with EIA (Bar-Yishay and Godfrey, 1984; Ben-Dov, Bar-Yishay, and Godfrey, 1982; James, Faciane and Sly, 1976). This refractory period is related to the time interval between exercise sessions. Edmunds, Tooley and Godfrey (1978) demonstrate a significant improvement in the PEFR in seven of eight patients when the interval between tests was 30 minutes. Schoefel, Anderson, Gillam and Lindsay (1980) report that 12 of 29 patients had significant protection from EIA on repeated challenge 40 minutes apart while James, Faciane and Sly (1976) observe protection in only 2 of 10 persons with asthma when the interval between tests was 60 minutes. When exercise is repeated after 2 hours there is no change from the initial response (Edmunds, Tooley and Godfrey, 1978). In this study, there were no significant differences in the values for RHL during the three trials. These data demonstrate that the reduction in %FEV_1, % MMERF, and % FVC seen after the continuous and interval warm-up is not due to

heat or water loss from the airways. These results support the data of Anderson and Schoeffel (1982), who studied 16 patients with asthma exposed to two exercise challenge tests 40-52 minutes apart. Fifty percent of the subjects had significant protection from EIA following the second challenge but there was no difference in the magnitude of heat or water loss from the airways during exercise. The author interpreted these findings as representative of the range of sensitivity to the same degree of heat and water loss in the population with asthma. Ben-Dov, Bar–Yishay and Godfrey (1982) have also reported a similar disassociation between RHL and the magnitude of the post exercise bronchoconstriction. These authors used inspired gases of different temperatures and humidity and thus manipulated the RHL under each condition. The refractory periods that occurred after exercise were, however, identical and therefore were not due to changes in RHL.

There are other factors that have been promoted as contributing to this refractory period. The time-dependent relationship between EIA and repeated exercise suggests that the mechanism responsible for the protection of the airways may be due to the depletion of mediators of bronchoconstriction that must be replaced before a second bout of equal reactivity can occur. Depletion of mast cell mediator stores is a popular theory to explain the refractory period that follows exercise (Edmunds, Tooley and Godfrey, 1978; Lee, Assoufi, and Kay 1983; Schoeffel, Anderson, Gillam and Lindsay, 1980). Godfrey (1975) has theorized that warm-up causes a gradual discharge of the mast cell mediators, and a time for replenishment is required. If exercise resumes immediately following warm-up, the depleted mediator stores will have a limited effect on the smooth muscle cells. This explanation fits with the data from the current study. With the relatively low intensity of exercise during the continuous warm-up, a gradual mediator release could occur (Godfrey, 1977). Fifteen minutes of slow mediator release may be sufficient to result in a substantial decrease in the mast cell mediator stores and this possibly led to a significant decrease in post exercise bronchoconstriction following the exercise challenge test. In these subjects, the higher intensity intermittent activity did not produce a significant protection.

If the mediator depletion theory is valid, then the duration of the warm-up period would appear to be the most critical variable in the exercise prescription and should be emphasized in patients with asthma who wish to exercise. The mechanisms responsible for the refractory period are not completely understood and the heterogeneity of the response to exercise may underline the different opinions reported in the literature (Margolskee, Bigby and Boushee, 1988; Morton, Fitch and Davis, 1979). There are opponents to the mediator depletion theory (Belcher, Murdock and Dalton, 1988; Broide *et al.*, 1990; Jarjour and Calhoun, 1992), and the most recent explanation of the refractory period centers on a change in the intra-airway thermal environment secondary to the release of catecholamines (Gilbert, Lennen and McFadden, 1988). The interval condition did not result in a

statistically significant change in any of the spirometry data. This may be due to the interval nature of the activity and the fact that this represents a total of only 4 minutes of activity. To well-trained athletes this is a mild training stimulus, and the periods of rest between sprints (1.5 minutes) may have been enough to allow near complete recovery between bouts of running. It is also possible that the exercise was of insufficient magnitude to significantly change catecholamine levels. It is speculated, however, that some intra-airway changes may have occurred that were responsible for the small observed decreases in % FEV_1, % FVC, and % MMEFR in each individual.

Table 1: Individual Subject Data

Subject No.	Age	Sex	Height (cm)	Weight (cm)	VO_2max ($ml.kg^{-1}$ - min^{-1})	PC_{20} (mg.ml-1)
1	24	F	159.8	53.0	54.4	0.50
2	22	F	170.0	68.0	50.3	0.26
3	24	M	181.2	65.8	52.5	0.70
4	25	F	158.0	55.5	50.1	0.50
5	21	F	160.8	50.7	56.1	0.26
6	20	M	165.5	75.3	45.6	0.20
7	42	M	165.5	75.3	45.6	0.26
8	42	F	170.6	62.5	56.7	0.10
9	25	F	159.7	57.5	69.2	0.50
10	23	F	165.5	56.6	51.6	4.00
11	23	F	165.5	56.6	51.6	0.70
12	28	F	171.5	66.3	45.0	4.00
Mean	26.5		169.2	62.3	52.7	1.00
+SD	7.8		9.5	9.0	4.6	1.40

VO_2max = Maximum Oxygen consumption express relative to body mass;
PC_{20} (mg.ml-1) = Provocation Concentration causing a 20% fall in FEV1
Source: Experimentation, 2013

Table 2: Baseline Values of FEV1, MMEFR, FVC (liters, means + SD)

Condition	FEV1	MMEFR	FVC
Control	3.42+1.05	3.22+1.41	4.21+1.15
Continuous exercise	3.30+0.91	3.03+1.29	4.08+1.02
Interval exercise	3.35+0.93	3.11+1.26	4.17+1.01

Source: Experimentation, 2013

Table 3: Mean values (+SD) for inspired (Ti) and expired (Te) air temperature, minute ventilation and calculated RHL during all three experimented conditions

Condition	Ti(oC)	Te(oC)	Ve(l.min-1)	RHL(kcal.min-1
Control	20+1.2	31.9+0.5	72.9+5.4	1.20+0.4
Continuous exercise	20.1+1.8	32.2+0.6	70.5+5.2	1.23+0.4
Interval exercise	20.7+16	32.5+0.7	68.7+4.2	1.17+0.3

Source: Experimentation, 2013

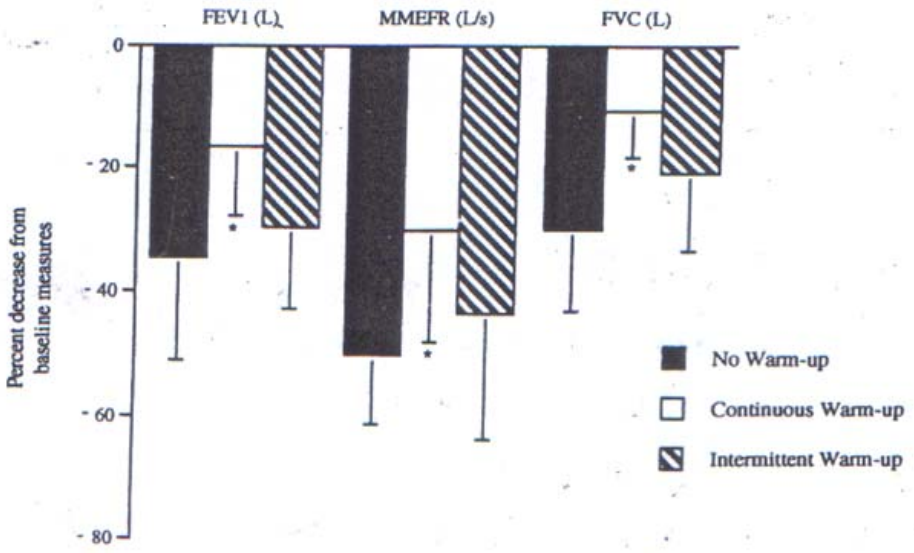

Figure 1: Percentage decrease in FEV1, MMEFR and FVC in comparison with baseline measures following each experimental condition.
* Continuous warm-up condition is significantly different than control

CONCLUSION

This study has demonstrated that a continuous period of moderately intense exercise can induce a significant protective effect in the athlete with EIA. The duration and intensity of exercise chosen for this study is comparable to that frequently chosen by athletes to achieve the cardiovascular, thermoregulatory, psychological, and injury-preventing benefits desired by this population. Such a program can be prescribed for the active persons with asthma that will enable increased activity with less risk of bronchoconstriction. An interval exercise program will also show positive changes in the degree of bronchoconstriction but these will be small and this form of warm-up will be much less effective than the program that utilizes continuous exercise.

REFERENCES

Anderson, S. D. and **Schoeffel, R. E.** (1982). Respiratory heat and water loss during exercise in patients with asthma. Effect of repeated exercise challenge. *European Journal of Respiratory Disease*, 63:472-480.

Anderson S. D., Schoeffel R. E., Follet R., Perry C. P., Daviskas E. and **Kendall M.** (1982). Sensitivity to heat and water loss at rest and during exercise in asthmatic patients. *European Journal of Respiratory Disease*, 63, 459-471.

Bar Yishay, E. and **Godfrey S.** (1984). Mechanisms of exercise-induced asthma. *Lung*, 164, 195-204.

Barnes P., Brown M. and **Silverman M. D.** (1981). Circulating catecholamines in exercise – and hyperventilation – induced asthma. *Thorax*, 36, 435-440.

Belcher, N. G., Murdock R. and **Dalton N.** (1988). Circulating concentrations of histamine, neutrophil chemotactic activity, and catecholamines during the refractory period in exercise induced asthma. *Journal of Allergy Clinical Immunology,* 81, 100-110.

Ben-Dov I., Bar–Yishay E. and **Godfrey S.** (1982). Refractory period following exercise – induced asthma unexplained by respiratory heat loss. *American Journal of Respiratory Disease,* 125, 530-534.

Broide D. H., Eisman S., Ramsdell J. W., Ferguson P., Schwartz L. B. and **Wasserman S. I.** (1990). Airway levels of mast cell-derived mediators in exercise – induced asthma. *American Journal of Respiratory Disease,* 141, 563-568.

Chen, W. Y. and **Horton, D. J.** (1977). Heat and water loss from the airways and exercise – induced asthma. *Respiration,* 34, 305-313.

Cockcroft, D. W., Murdock K. Y., Berscheid B. A. and **Gore B. P.** (1992). Sensitivity and specificity of histamine PC_{20} determination in a random selection of young college students. *Journal of Allergy Clinical Immunology,* 89, 23-30.

Deal, E. C., McFadden E. R., Ingram R. H. and **Jaeger J. J.** (1979). Hyperpnea and heat flux: initial reaction sequence in exercise – induced asthma. *Journal of Applied Physiology,* 46, 476-483.

Deal E. C. J., McFadden E. R. J., Ingram R. H. J., Strauss R. H. and **Jagger J. J.** (1979). Role of respiratory heat exchange in the production of exercise induced asthma. *Journal of Applied Physiology,* 46, 476-483.

Edmunds T., Jooley M. and **Godfrey S.** (1978). The refractory period after exercise – induced asthma: its duration and relation to severity of exercise. *American Journal of Respiratory Disease,* 117, 247-254.

Eggleston, P. A. (1986). Patho-physiology of exercise-induced asthma. *Medicine Science Sport Exercise,* 18:318-321.

Fitch, K. D. and **Godfrey, S.** (1976). Asthma and athletic performance. *Journal of American Medical Association,* 234, 152-157.

Gilbert I. A., Lenner K. A. and **McFadden E. R. J.** (1988). Sympatho-adrenal response to repetitive exercise in normal and asthmatic subjects. *Journal of Applied Physiology,* 64, 2667-2674.

Godfrey, S. (1975). Exercise – induced asthma – clinical, physiological and therapeutic implications. *Journal of Allergy Clinical Immunology,* 56, 1-17.

Godfrey, S. (1977). *Clinical variables of exercise – induced bronchospasm.* In J. A. Dempsey and C. E Reed (Eds). *Muscular Exercise and the Lung.* Madison: University of Wisconsin Press. Pp. 247-263.

James L., Faciane J. and **Sly R. M.** (1976). Effect of treadmill exercise on asthmatic children. *Journal of Allergy Clinical Immunology,* 57, 408-416.

Jarjour, N. N. and **Calhoun, W. J.** (1992). Exercise – induced asthma is not associated with mast cell activation or airway inflammation. *Journal of Allergy Clinical. Immunology,* 89:60-68.

Juniper, E. F., Cockcroft D. W. and **Hargreave F. E.** (1991). *Histamine and methacholine inhalation tests: tidal breathing method.* Sweden: Canadian Thoracic Society, Lund, Ab Dra Co Pp. 5-47.

Lee T. H., Assoufi B. K. and **Kay A. B.** (1983). The link between exercise, respiratory heat exchange, and the mast cell in bronchial asthma. *Lancet,* 1, 520-522.

Margolskee D. J., Bigby B. G. and **Boushey H. A.** (1988). Indomethacin blocks airway tolerance to repetitive exercise but not to eucaphic hyperpnea in asthmatic subjects. *American Journal of Respiratory Disease,* 137, 842-846.

McFadden, E. R. (1983). Respiratory heat and water exchange: physiological and clinical implications. *Journal of Applied Physiology,* 54, 331-336.

Morton A. R., Fitch K. D. and **Davis T.** (1979). The effect of "warm-up" on exercise-induced asthma. Annual. *Allergy,* 42:257-260.

Reiff D. B., Choudry N. B., Pride N. B. and **Ind P. W.** (1989). The effect of prolonged submaximal warm-up exercise on exercise-induced asthma. *American Journal of Respiratory Disease,* 139, 479-484.

Schnall, R. P., and **Landau L. I.** (1980). Protective effects of repeated short sprints in exercise – induced asthma. *Thorax,* 35, 825-832.

Schoeffel R. E., Anderson S. E., Gillam I. and **Lindsay D. A.** (1980). Multiple exercise and histamine challenges in asthmatic patients. *Thorax,* 35, 164-170.

Strauss R. H, Jagger J. J. and **Mc Fadden R. H. J.** (1986). Role of respiratory heat exchange in the production of exercise induced asthma. *Journal of Applied Physiology,* 46, 476-483