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ABSTRACT

In an effort to clarify the role of mast cell derived mediators (particularly histamine) in the pathogenesis of exercise induced asthma (EIA), twelve mild asthmatic subjects underwent exertional challenges following pretreatment with either aerosolized saline placebo, or the H_1 antagonist, chlorpheniramine maleate. Equivalent intrapulmonary thermal burdens were ensured by having each subject perform identical exercise tasks on a cyclergometer, while maintaining inspired air conditions at a constant temperature and low humidity with resulting equivalence of baseline, final minute and total minute ventilation throughout the study. All subjects exercised a total 5 to 7 minutes on each of the following three study days; a screeening day, during which no pretreatment was administered and each subject was determined to have EIA by demonstrating at least a 15% postexercise decline in the MEF40%(P), and the two randomly assigned protocol days, wherein each subject was administered in double blind fashion, the placebo or antihistamine.

Pulmonary function tests revealed parallel, signficant immediate post inhalation declines in FEV_1 (0.23 and 0.11 liter) and the MEF40%(P) (0.39 and 0.36 l/s) on both the antihistamine and placebo days respectively. By thirty minutes post inhalation, however, both the FEV_1 (2.94 ± 0.69 vs 2.65 ± 0.74 liter: mean ± S.D.) and the MEF40%(P) (2.32 ± 1.19 vs 1.80 ± 0.94 l/s, mean ± S.D.) had risen exclusively and significantly ($p<0.05$) on the antihistamine day. Although both the FEV_1 and the MEF40%(P) remained

significantly ($p < 0.01$) higher five minutes after exercise on the antihistamine day (i.e. 2.82 ± 0.70 vs 2.48 ± 0.83 liters, and 1.67 ± 0.79 vs 1.34 ± 0.73 l/s; mean ± S.D., respectively), analysis revealed statistically equivalent declines in both parameters, when the change from 30 minutes post inhalation to 5 minutes post exercise were compared. Finally, pulmonary function as determined by both the FEV_1 and the MEF40(P), were found to be greatly improved ($p < 0.01$) following post exercise administration of metaproterenol.

Based upon the observed effects of chlorpheniramine maleate, we conclude that a low grade release of mast cell derived histamine does in fact contribute to the increase in resting bronchomotor tone found in asthmatics. However, the failure of this potent antihistamine to prevent EIA, suggests that histamine is not an independent and central mediator of post exercise asthma.

I. Background and Literature Review

A. INTRODUCTION

"Asthma is a disorder characterized by an increased responsiveness of the trachea and bronchi to various stimuli in widespread narrowing of the airways, the severity of which changes either spontaneously or as a result of therapy".[1] The pathogenesis of this airway narrowing is known to include varying degrees of bronchial smooth muscle contraction, mucosal edema and inflammation, as well as an overproduction and inspissation of mucus[4]. This disease entity, manifested symptomatically by the triad of intermittent wheezing, dyspnea and coughing is estimated to affect 3-4 percent of the population of the U.S.[2,3]. Though much has been learned about asthma over the past few decades, it is readily apparent to the student of medicine, that such a common, often frightening and debilitating disease, necessitates continued research to further elucidate the pathogenetic mechanisms in the hope of defining more efficacious prophylactic and therapeutic interventions.

One of the most commonly used classifications divides asthma into two clinicopathologic entities: "Extrinsic" or "Allergic Asthma", and "Intrinsic" or "Nonallergic Asthma".[5] This nosology has enabled researchers and writers to distinguish groups of patients based on epidemiologic, etiologic and clinical factors. Thus, patients with extrinsic asthma are generally characterized by an atopic history and childhood onset, with more intermittent and acute exacerbations of an often milder form of airway narrowing, triggered by inhalation of dusts, pollens and dander etc..., as well as other antigenic stimuli. It is the binding of these allergens to mast cell bound IgE leading to a Type I hypersensitivity reaction and the release of mediators (see below) which results in airway narrowing.[9] In intrinsic asthma patients with "hyperactive airways"[6], respond in a more chronic and often severe nature to many

nonantigenic stimuli. These patients without allergic histories, commonly recognize the symptoms of wheezing, dyspnea and coughing following upper respiratory infections or exposure to various pollutants usually beginning after age 30. The pathophysiologic pathway(s) unlike that described for extrinsic asthma are less clearly defined. It is currently thought that intrinsic asthma involves neurogenic reflexes[6], certain immunologic mechanisms with mediator release[6] and adrenergic receptor imbalance[7], each acting alone or in combination, as well as other poorly elucidated mechanisms.

This categorization of asthma into subgroups of extrinsic and intrinsic forms has often been criticized[114], since most patients manifest clinical features common to both. One example of a stimulus evoking bronchoconstriction in almost all asthmatics[8,10], often attributed to the state of bronchial hyperirritability[6,114] present in all those with the disease, is exercise induced asthma (EIA). Interest surrounding this stimulant of reversible airway narrowing concerns not only its implications for the health and well being of those afflicted with it, but additionally, exercise has become recognized as a diagnostic aid and clinical tool for the evaluation of various therapeutic modalities used for asthma in general[23,24]. Moreover, exercise, a physiologic, reproducible and easily controlled variable in the research laboratory has enabled investigators utilizing it as a provocation of reversible bronchial obstruction to further their understanding of the pathogenetic process of asthma itself[115].

Although recent work on EIA has defined that heat flux and airway cooling as the initial link in the pathophysiologic chain of events leading to bronchoconstriction[11], controversy continues[12] as to how this thermal stimulus (cold) translates into bronchial narrowing. Some authorities believe

that it is the activation of mast cells[13] (see below) with release of chemical mediators such as histamine and SRS-A which then act directly on bronchial smooth muscle causing airway narrowing, that is the critical event following airway cooling in EIA.

The present study is intended to test the hypothesis that mast cell derived mediators, specifically histamine, is involved in the causation of EIA. By administering a potent aerosolized H_1 blocker, chlorepheneramine maleate, prior to exercise, and evaluating its effect on postexertional asthma, it is hoped that further insights will be gained regarding the nature of EIA in particular and asthma in general.

B. History of EIA[20]

The earliest historical record of the association of strenuous physical exertion and airway obstruction dates back to Aretaeus the Cappodocian[15] (roman era), centuries after Hippocrates[14] first described the asthmatic condition. Aretaeus succinctly noted:

"If from running, gymnastic exercises or any other work, the breathing becomes difficult, it is called asthma"[15,16].

It was not until the 17th century when Willis[17] (1679) eloquently redescribed this phenomenon:

"Whatsoever therefore makes the blood boyle or raises into effervescence as violent motion of the body or mind, excess of extern cold or heat ... both doth cause asthmatical assaults to such as predisposed".

Twenty years later, Sir John Floyer[18] (1698) not only realized the existence of a cause and effect relationship between exercise and airway obstruction by writing:

"All violent exercise makes the asthmatic to breath short",

he additionally, quite astutely recorded the graded symptomatic obstructive effects of differing forms of exercise and levels of ventilation. He noted:

"The most agreeabel exercise is riding, the greatest are sawing, bowling, swinging, dancing. Walking is more vehement than riding..., those exercises that move the arms, exercise the lungs most."

During the 19th century the notion (believed by many researchers until recently[10,16]) that exercise only caused obstructive symptoms in distinct group of asthmatics was promolgated by Salter[21] (1868), when he recorded that:

"Exertion was an exciting cause of symptoms"...

in 54 of 223 patients studied.

The modern era utilizing objective measures in the study of EIA was ushered in by Herxheimer[19] (1946). By recording postexercise changes in the vital capacity of asthmatic individuals, he demonstrated a crude though noble attempt to quantify the subjective phenomena that had been observed previously. Though his hypothesis that airway narrowing was caused by the hyperventilation associated with exercise was to be corroborated some 30 years later[22], his reasoning was erroneous, in that he attributed hyperventilation induced asthma to the development of hypocapnia. Nevertheless, it was Herxheimer's work that lit the fuse leading to an explosion of interest and information to follow on EIA.

C. Mechanism of EIA

1. Background

The pathogenetic pathway leading to EIA has been the subject of intensive investigation since Herxheimer published his findings in a paper entitled, "Hyperventilation asthma"[19]. Over the next 30 years many researchers followed his lead and focused on hypocapnea[29,30] as well as hyperventilation[26,28] as possible triggers of bronchospasm in asthmatic individuals. Hafez and Crompton[30] implicated hypocapnia as the cause of EIA by demonstrating significant decreases in the FEV_1 after hyperventilation not matched when hyperventilation was subsequently induced by CO_2 inhalation. Chan-Yeung et al.[25] however, provided evidence to support hyperventilation per se, with or without commensurate hypocapnia as the critical determinant of EIA. Specifically, they demonstrated a fall in the FEV_1 in only 3 of 7 patients following exercise, whereas all seven subjects were shown to have significant falls in their FEV_1 following voluntary hyperventilation inhaling both room air and air with 5.6% CO_2 content. In

another theory, proposed by Vassallo et al.[31], the release of lactic acid from exercising muscle and the subsequent development of acidemia was thought to act either directly or indirectly in the causation of bronchospasm. Additional hypotheses concerning reflex bronchoconstriction mediated by the vagus nerve were suggested by Schiffman et al.[32], who proposed that exercise induced metabolic alterations stimulated the carotid body, and Zeballos et al.[33], who posited stimulation of the pharyngeal receptors by cold, dry air as forming the afferent loop in the reflex arc. While others proposed adrenergic abnormalities[34], a strong body of literature developed in support of mast cell degradulation and mediator release in the pathogenesis of EIA (see below).[10,13]

Though no consensus has yet been reached as to the complete pathophysiologic series of events resulting in EIA, formulation of the initating stimulus, as well as clarification of many seeming inconsistencies in the literature has been accomplished by McFadden and Ingram et al.[16,22].

2. Heat Flux as the Initiating Stimulus in EIA

At first Strauss et al.[35] determined that production of bronchial obstruction necessitated an exercise workload that placed sufficient stress on either the arms or legs to cause hyperventilation, hypocapnia and lactic acid production. This determination indicated that no specific exercising muscle group was more asthmagenic than any others. Further experiments were performed by McFadden et al.[36] to isolate the effects of hyperpnea and hypocapnia. Their results demonstrated that neither adequately explained the development of EIA. They then eliminated lactate as a potential mediator responsible for bronchoconstriction when its intravenous injusion in levels equivalent to those generated during exercise failed to cause airway obstruction[37]. Furthermore, by exercising

subjects to exhaustion while concurrently infusing sodium bicarbonate to normalize pH, and then demonstrating undiminished attacks of EIA, Strauss et al.[37] eliminated the role of acidemia in the production of postexercise obstruction.

Though it was a well known clinical observation that asthmatic individuals complained of exacerbations of their disease when exposed to certain weather extremes[113], the importance of these subjective experiences were not put into an objective perspective until recently. Specifically, since it had always been believed that a dry climate was beneficial to asthmatics (consistent with the popularity of Arizona amongst asthmatic individuals), it came as quite a surprise when a study in Israel by Bar-Or et al[38], demonstrated that asthmatic children developed greater degrees of EIA when challenged in a dry climate as compared to more humid environments. Similar observations by Weinstein et al.[39], who recorded a 29.5% drop in the FEV_1 of children exercising in a dry environment as compared with only a 13.5% decline while inhaling nebulized saline supported the findings of Bar-Or[38]. Additionally, to ascertain the effects of breathing cold air, Strauss et al.[40], had subjects perform identical exercise tasks on a cyclergometer alternately breathing air at ambient and subfreezing temperatures. By simply reducing the air temperature, they demonstrated an increase in the postexercise decline in the FEV_1 from 21% to 40%.

Thus, it had become reasonably clear that breathing cold, dry air acted in a synergistic fashion to potentiate the bronchoconstrictive effects of exercise.

To evaluate the possibility of increased efferent vagal tone brought about by the thermal (cold) stimulus, Deal et al.[41] exercised

9 subjects who again breathed air at ambient and subfreezing temperatures, but with the added variable of concurrent atropine inhalation. They found that the cholinergic blockade in no way hindered the potentiating effect of cold air inhalation and postulated that EIA resulted from the local effects of incompletely conditioned air in the intrathoracic airways. They supported this theory by recording low intraesophageal temperatures during the performance of exercise in ambient air[40], which declined even further when the temperature and the water content of the inspirate were decreased[42]. Further evidence was provided by Strauss et al.[43], who demonstrated the elimination of EIA by having patients exercise while inspiring air at body temperature and 100% humidity.

When Deal et al.[44] reviewed the data collected in the preceding experiments, they found a striking correlation between respiratory heat loss and the magnitude of the postexercise obstruction. In a final experiment, Deal et al.[11], ironically recapitulating certain aspects of Herxheimer's theory of hyperventilation asthma[19], demonstrated that the operative mechanism in the production of EIA, was hyperventilation with subsequent airway cooling. This was accomplished by having subjects voluntarily breath, at minute ventilation equal to those attained while exercising, air conditioned to various temperatures and humidity. They found[11] that at equivalent minute ventilations, breathing subfreezing air, room air, and saturated room air, resulted in 39, 28, and 11% declines in the FEV_1 respectively. Significantly, hyperventilation of air heated to body temperature at 100% humidity resulted in no airway obstruction whatsoever.

As a result of these experiments, the heat flux hypothesis was formulated as a unifying concept, clarifying many previously confusing findings in the literature on EIA[16,22]. The following is a brief summary.

During physical exertion, ventilation increases to meet the metabolic demands imposed by working muscles. This necessitates inhalation of large volumes of air at ambient conditions. The body provides for initial conditioning of this air by transferring heat and humidity from the nasal mucosa. However, at such high minute ventilations, much of the inspirate reashes the interthoracic airways unchanged. Before gaseous exchange can take place at the alveoli, this air must be warmed to 37°C and saturated with water vapor. This is accomplished by heat transfer and water evaporation from the bronchial mucosa, which results in a mucosal temperature decline. The colder the inspired air the greater the heat transfer and consequently the larger temperature decline of the airways. Similarly,the drier the inspired air, the greater the evaporation of mucosal water, again resulting in larger temperature declines. Additionally, for any set of conditions of air temperature and humidity, the larger the minute ventilation, the greater the heat transfer. Why or how ventilation is increased is inconsequential. As shown[11] hyperventilation and exercise, produce equivalent degrees of airway obstruction as long as the same quantity of air, of equal temperature and humidity is inspired.

With the formulation and general acceptance[13] of the heat flux hypothesis, uncontrolled environmental conditions in various laboratories could now be implicated as the heretofore unknown confounding variables that led confusion and disagreement concerning the reproducibility as well as the prevalence of EIA[13,45].

Additionally, application of these tenets, reconcile the alleged differences in the asthmagenicity of such tasks as: walking, running, cycling and swimming[46,47]. As demonstrated by Strauss et al.[35], equivalent exercise stress, whether performed by arm or leg work, results in equal bronchoconstriction. Similarly, treadmill running and cycle ergometry, produced comparable levels of airway obstruction when performed in the same environment[47]. It is also theorized[13,22] that the inability of swimming to trigger EIA, is yet another manifestation of inspired air conditions and its effect on airway cooling. Although vigorous swimming generates larger minute ventilations, since the (usually) warm air directly above the pool is highly saturated with water vapor, its inspiration requires little respiratory conditioning, and therefore, minimal heat exchange.

With the initiating stimulus of EIA thus defined, i.e. heat flux with subsequent airway cooling, the logical next question to which this present study is addressed, is how does the airway cooling produce bronchoconstriction?

3. Events Following the Initiating Stimulus Responsible for EIA

Four separate theories have been proposed in an attempt to explain how respiratory cooling translates itself into bronchoconstriction.

a. Direct thermal effect on smooth muscle

Souhrade et al.[48], investigated the effect of temperature on the electrophysiologic and contractile properties of airway smooth muscle. After incubating guinea pig and bovine bronchial smooth muscle at various temperatures (40°, 37°, 29° and 21°C), for 60 minutes, they found significant progressive decreases in resting membrane potentials as the

temperature was lowered. They also noted a marked and progressive increase in sensitivity to histamine induced contraction as the temperature was decreased. They theorized, (based on Deal's[42] demonstration of reduced intrathoracic temperatures using esophageal temperature probes) that exercise and hyperventilation, by cooling the bronchial muscle, could lower their membrane potentials and lead to depolarization, contraction and bronchial obstruction. Thus, they postulated[48] that EIA was caused by cold induced smooth contraction alone.

Though elegant in its simplicity, Souhrada's theory cannot explain the time course of EIA. After exercise ceases, the intrathoracic airways reattain their resting temperature within 5 minutes[42]. Yet, bronchoconstriction progressively worsens several minutes postexercise, and lasts a total of 30 to 60 minutes[10]. This indicates, that even if in vivo temperatures were to reach low enough levels to cause spontaneous depolarization of the smooth muscle cells, other mechanims must be operating to sustain the contraction.

b. Adrenergic Receptor Imbalance

Drawing upon the conclusions of Jones[49], Patel et al.[50] theorized that EIA was a consequence of altered alpha and beta adrenergic receptor ratios in the asthmatic's airway. They postulated[50] that catecholamines released during strenuous physical exertion acted on the predominant (perhaps thermally regulated[16]) alpha receptor causing bronchoconstriction. They supported this theory by demonstrating the prophylactic efficacy of thymoxamine (an alpha blocker) pretreatment in EIA. These results corroborated those of Bianco et al.[51], who prevented postexercise obstruction using the alpha blocker indoramin. More recently, however,

Barnes et al[52], pointed to the multiple pharmacologic actions of both thymoxamine and indoramin in addition to their alpha antagonism as probably confounding earlier findings. They[52] then demonstrated significantly reduced postexercise obstruction, by administering aerosolized prazosin, a specific alpha blocker. However, prazosin's failure to prevent histamine induced bronchoconstriction led them to theorize that its action resulted from blockade of mast cell alpha receptors, inhibiting mediator release, and thus preventing EIA, and not, as a consequence of correcting an adrenergic receptor imbalance in airway smooth muscle as previously proposed[49-51]. The most potent evidence militating against the role of adrenergic imbalance in the pathogenesis of EIA is derived from another study by Barnes et al.[53], who demonstrated the failure of circulating catecholamines to rise altogether in hyperventilation induced asthma. They[53], also pointed out, that since intrapulmonary sympathetic innervation had yet to be demonstrated in man, prophylasix of EIA by alpha blockers could not possibly be attributed to direct inhibition of alpha mediated bronchoconstriction and, therefore, proposed that mast cell degranulation was the operative mechanism instead.

C. Role of Reflex Vagal Bronchoconstriction

The notion of a thermal stimulus activating irritant receptors in the airways, resulting in reflex bronchoconstriction, is consistent with studies[55] demonstrating that chemical or mechanical stimulation of these afferent nerves in the pharynx, trachea, and bronchi do indeed trigger vagal mediated airway narrowing. In fact, ten years prior to formulation of the heat flux hopothesis[11], Simonsson et al [54] suggested reflex mediation of cold induced airway obstruction . In a study comparing the prophylactic efficacies of ipatropium bromide (an anticholineergic agent) and cromolyn sodium in EIA, Thompson et al [56], subdivided his asthmatic subjects into two groups. In those patients in whom the main anatomic site of airflow limitation (as determined by changes in density dependence of MEF rates) was the lower airways, ipatropium bromide failed to prevent postexercise bronchoconstriction. However, significant inhibition of the postexercise fall in FEV_1 was demonstrated in those subjects with principally large airway narrowing. They concluded therefore, that upper airway-exercise induced constriction was mediated by vagal reflexes.

These findings were partially corrobroated by Menally et al.[57], who attempted to abolish afferent impulses originating in the irritant receptors by using oropharyngeal anesthesia during exercise. Since administration of 2% lidocaine did in fact prevent EIA in several of the subjects studied (though not all), they concluded that reflex bronchoconstriction was involved in the pathogenesis of EIA. However, in a similar study by Enright et al [58], it was noted that those individuals in whom upper airway anesthesia successfully prevented EIA had generated far smaller minute ventilations than subjects who

subsequently developed bronchospasm. Enright's conclusion that upper airway anesthesia abolished EIA was soon criticized[16], since he had merely effectively redemonstrated the critical stimulus of hyperventilation with subsequent airway cooling as the trigger of EIA.

Additional doubts as to the role played by reflex bronchoconstriction in EIA were raised by Breslin et al[59]. Although confirming the findings of Thompson et al[56], by demonstrating atropine's ability to prevent flow obstruction in the upper airways, they attributed this effect however, not to a cholinergic blockade, but rather to the drugs capacity to acutely transfer the site of obstruction to the lower airways, by interfering with the heat transfer of the upper bronchi. Similarly, despite using large doses of atropine, Deal et al[41] were unable to demonstrate any inhibitive effect on cold air potentiatin of EIA. Thus, although there is controversial evidence implicating some role for vagal mediated reflex bronchoconstriction in EIA, it is doubtful that this will be proven to be more than a limited one, necessitating finding other operating pathogenic mechanisms.

D. Role of the Mast Cell and Its Mediators In EIA

The central role of mast cell derived chemical mediators in the Type I immediate hypersensitivity reaction in man has been well documented[59]. The pathophysiologic events leading to bronchoconstriction in allergen induced asthma has similarly been determined to be dependent upon the immunologically mediated release of these mast cell substances[3]. Although it is not suggested that an IgE dependent mast cell degranulation occurs in EIA, many have focused on t he possibility of a nonimmunogenic release of these mediators and their

subsequent effects on the airway in their search for the ultimate mechanism of postexercise bronchoconstriction[10,12,13,22].

1) Background - The Mast Cell and its Mediators

(i.e. histamine, SRS-A, PGS)

Mast cells are present in the human lung, in the bronchial lumen and mucosa in concentrations averaging 1-7x 10^6 cells/gram of pulmonary tissue[60]. Each cell possesses hundreds of metachromatically staining granules containing an array of proteins, peptides, amines and complex polysaccharides, with chemotactic, vasoactive and bronchospastic properties[61]. Once activated, the mast cell releases these performed granulas elements (i.e. histamine, eosinophil chemotactic factor of anaphylaxis, neutrophil chemotactic factor) and subsequently generates and then secretes an array of newly formed mediators of inflammation (i.e. prostalgglandins and leukotrienes[62]. The surface of the mast cell is studded with 50-300,000 receptors for the Fc portion of IgE, as well as other receptors for: acetylcholine, prostaglandins, alpha and beta adrenergic compounds and histamine itself[3,63].

The classic immunologically dependent degranulation of mast cells occurs when pairs of adjacent cell bound pairs of IgE are bridged by divalent antigen. This induces a sequence of poorly defined membrane events which trigger the activation of adenyl cyclase and the subsequent formation of CAMP. This in turn leads to a series of intracellular protein phosphorylations eventuating in an energy dependent calcium ion influx into the cell culminating in exocytosis[59,63].

Of specific import to the role of mediators in EIA, it has been determined that mast cells may also be nonimmunogenically activated by

such stimuli as enzymes, inophores, polycationic amines, proteins, radiocontrast media and most notably cold[63,64].

The activation of the mast cell, however, is more complex than has been intimated above. Modifying the effects of various degranulatory stimuli, is an elegant intracellular regulatory mechanism. This regulation is predicated upon the existence of two funcitionally different classes of cell surface receptors (mentioned previously). One group of receptors, specific for PGE, histamine (H_2) and beta adrenergic compounds, when occupied, activates membrane adenyl cyclase, forming CAMP. The second class, consisting of cholinergic and alpha adrenergic receptors, mediate the activation of membrane guanyl cyclase and formation of CGMP[13,63]. In the preactivated (or resting) mast cell, elevations of intracellular CAMP inhibits subsequent excitation and degranulation of the cell with release of its mediators. Alternatively, reduction of CAMP by the enzyme phosphodiesterase, as well as elevation of intracellular CGMP levels, potentiates activating stimuli and degranulation[13,63]. Knowledge of these regulatory phenomena have allowed for a greater understanding of the antiallergic and antiasthmatic therapeutic efficacy of the adrenergic and methylxanthine compounds.

The two classes of mast cell deriverd mediators believed to play a central and direct role in the pathogenesis of asthma are: the products of arachidonic acid metabolism, and the biogenic amine, histamine.

2) The Role of Arachidonic Acid Metabolites in Asthma

In man, arachidonic acid (5,8,11,14-eicosatetraenoic acid) is the most abundant precursor from which the prostaglandins, thromboxanes and leukotrienes are derived[65]. After its mobilization from cellular phospholipid stores by the enzyme phospholipase A_2, arachidonic acid can be

converted either to the prostaglandins and thromboxanes via action of the enzyme cyclooxygenase, or alternatively, it can be metabolized by the lipoxygenases to the hydroxy acids (i.e. HETE) and the leukotrienes(formerly known as SRS-A)[59].

In terms of the effects of the prostaglandins on airway smooth muscle, those of the F series as well as the thrombaxanes are (in general) extremely potent bronchoconstrictors, whereas those of the E group (and possibly prostacyclin) are bronchodilators[66]. Thus, as might be expected, following lgE dependent activation of human lung tissue in vitro, a predominance of the bronchoconstricting PGF_2 is recovered, along with smaller quantities of the bronchodilatory PGE_2[66]. Similarly, when challenged, asthmatic patients demonstrate a particular sensitivity to PGF_2 and undergo severe bronchospasm, whereas aerosolized PGE_1, administered to the same subjects, has a bronchodilatory capacity exceeding that of isoproterenol[66]. Furthermore, the above actions of the prostaglandins are those independent of their capability to interact with mast cell receptors (i.e. PGE) in a modulatory capacity by affecting formation of intracellular cyclic nucleotides[13,63].

Although the prostaglandins are of obvious significance in the asthmatic diathesis, an even greater import has been ascribed to SRS-A (slow reacting substance of anaphylaxis), an acid, hydrophilic, sulfur containing lipid of m.w. 400, derived from arachidonic acid via the lipoxygenase pathway[68]. Unlike histamine which is stored in the metachromatic granules and released by exocytosis, SRS-A is a short lived newly generated chemical m ediators secreted by mast cells as well as other leukocytes (i.e. neutrophil)[59,67]. In addition to its (in vitro) demonstrated capacity to independently cause a slow sustained contraction of smooth muscle as

well as an increase in vascular permeability, SRS-A is also known to synergistically enhance the spasmogenic and vasodilatory capacity of histamine[68,69]. Other studies have demonstrated SRS-A's predilection for lower peripheral airway constriction with less effect on the central and larger airways[67].

Implicating SRS-A in the pathogenesis of asthma are the published effects of two drugs. Ketotifen, a newly developed antiallergic/antiasthmatic preparation with demonstrated therapeutic efficacy, has been shown to inhibit the release as well as the spasmogenic effects of SRS-A in asthmatic patients[116]. The other, diethylcarbamazine pamoate, a semispecific SRS-A antagonist, has been shown by Sly et al.[71] to inhibit EIA in fifteen children tested. Evidence for prostaglandin participation in EIA is currently lacking, as Anderson et al [72] as well as Field et al[73] failed to demonstrate significantly increased serum levels of either PGF_2 or PGE, in patients experiencing postexercise bronchoconstriction.

The importance of in vivo assessments such as these for the products of arachidonic acid as well as the need to develop specific inhibitors and antagonists has recently been emphasized by Goetzl[70]. He cautioned avoidance of early conclusions regarding the roles of arachidonic acid metabolites in inflammatory reactions, despite their demonstrated contractile and vasoactive properties, until the phenomena observed in vitro are confirmed by in vivo studies.

Thus although a role for the prostaglandins and SRS-A in the pathogenesis of asthma is certainly likely, its exact delineation must await further accumulation and integration of experimental information.

3) The Role of Histamine in Asthma

Histamine, or ß-aminoethylimidazole, formed by decarboxylation of the amino acid histamine, is the principal biogenic amine stored along with a heparin-protein complex in the secretory granules of mast cells and basophils[74,75]. Histamine was first isolated by Best, Dale, Dudley, and Thorpe from lung and liver extracts, but was soon shown to be present in numerous other tissues studied, and thus acquired its name from the Greek word for tissue -histos[74].

The very earliest observations regarding the pharmacologic properties of this agent, revealed its dual capacity to stimulate smooth muscle contraction as well as cause vasodilation[74]. The potential role of histamine as a mediator of inflammation was soon underscored by Lewis when he described the now classic "triple response" phenomenon, occurring following its intradermal injection, as well as identifying the release of this "H-substance" from skin following immunologic and injurious reactions[74,76].

More recently, Ash and Schild[77] in an attempt to organize and understand the myriad of actions of this amine, postulated the presence of two different histamine receptors - H_1 and H_2. This, they realized, would explain why certain histaminic responses, such as gastric secretion failed to be inhibited by the classic (H_1) antihistamines (i.e. pyrilamine). Black et al.[78] then identified selective H_1 and H_2 agonists, and of greater therapeutic significance demonstrated the effects of the selective H_2 receptor antagonist - burimamide.

Although many of histamines actions were determined to be mediated by either the H_1(i.e. smooth muscle contraction) or H_2 receptor (i.e. gastric secretion), it soon became apparent that a significant number of its effects

(i.e. vasodilation, lowering blood pressure) were consequences of the interaction of histamine with both of its receptors[79].

The first observations implicating histamine in the pathogenesis of asthma, were those of Weiss et al.[82], who noted that small amounts of the amine produced a "definite bronchial constrictor effect in patients with bronchial asthma." This was redemonstrated by Curry[80], who like Weiss[82] found asthmatics to be much more sensitive to the bronchospastic effects of histamine than normal subjects.

The exquisite sensitivity of asthmatics to even small doses of histamine[79] is in fact so characteristic of the asthmatic diathesis, that inhalation challenges using the amine have gained wide acceptance as a means of diagnosing it[81].

Not satisfied that histamine's acknowledged ability to constrict airway smooth muscle indicated a pathogenetic role for it in asthma, Bleecker et al.[83] set out to assess whether histamine inhalation induced other pulmonary changes found in spontaneous asthma attacks. They found that inhalation of the amine did in fact produce marked alterations in lung volumes (i.e. increased FRC and TLC, and decreased VC) and pulmonary mechanics as well as bronchoconstriction. They further demonstrated[83] that unlike animal studies in which histamaine induced bronchoconstriction was shown to be mediated by vagal reflex pathways, pretreatment with atropine failed to alter the asthmatic's responses to histamine, indicating a direct smooth muscle effect. They concluded, therefore,[83] that spontaneous asthma attacks can be accurately reproduced by the direct actions of inhaled histamine. However, in a challenge of asthmatics, intravenously infusing histamine, Brown et al.[84] only found significant bronchospastic effects on subjects whose prechallenge pulmonary function was already depressed.

Similarly, Kaliner et al.[85] demonstrated a significant fall in the PEFR in only one of six asthmatics undergoing histamine infusion. These studies[83,84,85] thus imply, that the asthmagenic potential of histamine, is to a large degree dependent on the route of its administration. Conceivably, local intrapulmonary concentrations of histamine sufficient to reproduce asthmatic attacks, can only be achieved by inhalation of the amine but not by systemic infusion. This is not to say, however, that locally elevated concentrations of histamine cannot also be detected systemically, as shown by Barnes et al.[86], who gave further credence to histamines putative role in asthma by demonstrating elevated plasma levels of the amine during episodes of nocturnal wheezing.

In attempting to identify the receptor mediating histamine induced bronchoconstriction, Casterline et al.[87] utilized the specific H_1 antagonist, diphenhydramine. By administering this drug prior to the histamine challenge, they were able to significantly block its bronchospastic effects. They concluded, therefore, that H_1 receptors in the human bronchial mucosa mediate histamine induced asthma. They additionally confirmed the findings of Bleecker et al.[83] by demonstrating atropine's inability to inhibit the induced bronchoconstriction as did the histamine antagonist.

Further clarification of the roles of histamine receptors in the human lung was provided by Nathan et al.[89]. They demonstrated that alternating pretreatment with an H_1 and then an H_2 antagonist yielded opposite effects on histamine induced bronchoconstriction. Specifically, administration of chlorpheniramine, a specific H_1 antagonist, significantly increased the threshold dose of histamine required to produce bronchospasm. Blockage of pulmonary H_2 receptors with cimetidine, however, significantly decreased the

threshold dose of inhaled histamine needed to produce an equivalent fall in the FEV_1. They concluded, therefore, that H_1 receptors in the airways of asthmatics mediate histamine induced bronchoconstriction whereas H_2 receptors when activated by the same amine induce bronchial relaxation. Schachter et al.[90] corroborated and then extended these findings in a study on histamine receptors in normal as well as asthmatic subjects. After determination of a threshold ("T") dose of histamine inducing a 20% fall in the MEF40%(P), the effects of oral pretreatment with antihistamines were studied. As expected, in both asthmatic and healthy subjects, chlorpheniramine, significantly reduced the bronchoconstrictive response to histamine at the "T" dose. By contrast, however, asthmatics pretreated with cimetidine, demonstrated significantly increased bronchoconstriction after administration of the "T" dose of histamine, whereas the response of healthy subjects to cimitidine was equivalent to changes seen after placebo pretreatment. Thus, they[90] concluded that although both asthmatic and healthy subjects possessed H_1 receptors mediating histamine induced bronchocostriction, it was only the asthmatics, who additionally demonstrated H_2 receptor activity mediating bronchodilation.

The complexity of the roles of histamine receptors in asthma is further underscored by the presence of H_2 receptors on the mast cells themselves[3,91]. It is postulated[3], that histamine, once released from mast cells (and basophils) can, by virtue of an integrated negative feedback control system, bind to the H_2 receptors of the mast cell activating adenyl cyclase, thereby raising the intracellular level of CAMP and consequently inhibiting any further mediator release. Clinically, however, histamine has been firmly established as bronchoconstrictive and asthmagenic[83]. Despite

these observations, controversy exists regarding histamine's role (as well a s the role of other mast cell mediators)in the pathogenesis of EIA.

4. Evidence for Role of the Mast Cell and Its Mediators in EIA

For many years, evidence implicating mast cell degranulation and mediator release in the pathogenesis of EIA was derived from two prominent features of this phenomenon. One line of evidence concerned the therapeutic efficacy of cromolyn sodium in the prevention of EIA (when administered prior to exercise), and the other was drawn from observations concerening the so called "refractory period"[92].

The notion of a refractory period in EIA (a fixed time interval following postexercise obstruction during which exercise induced bronchospasm could not be elicited)[10], was originally posited by MeNeil et al.[93]. During exercise trials, they noted the inability of successive challenges to elicit comparable airway obstruction. They suggested that this inability stemmed from the depletion of mediators or enzyme precursors, responsible for EIA. Definitive work on the "refractory period" was performed by Edmunds et al.[94], in a study designed to delineate the time course of recovery of the ability to bronchoconstrict postexercise in addition to defining the relationship between varying workloads in successive exercise trials. Each subject performed identical paired exercise tasks separated by varying lengths of time from ½ - 4 hrs. By comparing the percent fall in PEFR following each exercise period, they noted marked decreases in the bronchospasm produced by the second exercise test when it followed the first one by ½ to 2 hours. Full recovery of the ability to bronchoconstrict was found only when the interval between the first and second trial was 4 hours. In another protocol, again comparing the percent drop in PEFR following successive exercise challenges, they

varied the workload of the first exercise period, resulting in graded bronchoconstriction responses. They then had subjects perform the second exercise challenge at fixed workloads. They demonstrated that the response to the second fixed exercise trial was inversely porportional to the amount of EIA produced by the initial challenge (i.e. the greater the EIA in the first trial the less in the second and vice aversa). They concluded, therefore, that EIA resulted from mast cell derived mediators, depletion of which, following an exercise challenge, resulted in a refractoriness to further postexercise bronchoconstriction. Additionally, the release of mediators is not an all or nothing phenomenon, but rather, it is graded, in response to the varying levels of the exerecise stimulus. And finally, they noted that full recovery of a postexercise bronchospastic potential was predicted on mediator resynthesis and accumulation[10,94].

The second line of evidence implicating mast cell derived mediators in EIA is based upon the effects of the drug cromolyn sodium.

Cromolyn sodium (or disodium cromoglycate) was first introduced into clinical practice by Altounyan (1967)[95], who demonstrated its effectiveness in inhibiting the asthmatic response to inhaled antigen. Because the drug failed to prevent the spasmogenic effects of histamine, SRS-A, bradykinin, and acetylcholine on guinea pig ileum[96], and furthermore, demonstrated no capacity to inhibit either the binding of IgE to peritoneal mast cells or interaction between antigen and antibody[97], its efficacy in preventing allergen induced asthma was attributed to a mast cell stabilizing effect, resulting in an inhibition of mediator (i.e. histamine, SRS-A) release[96,98].

Attempts to refine this somewhat vague notion of mast cell stabilization has prompted some to theorize that the drug actually acts by

blocking calcium channels (and thereby interfering with stimulus secretion coupling), while others have tried to identify cromolyn sodium induced changes in cyclic nucleotides as well as protein phosphorylation[97]. Whatever its underlying mechanism of action, there is general agreement[98] that it is the drug's ability to prevent mast cell mediator release that is ultimately responsible for its prophylactic effects in asthma.

Soon after Altounyan's findings[95] concerning cromolyn sodium's prophylactic efficacy in antigen induced asthma, Davies[100] demonstrated an analogous effect in EIA. Later work[20] clearly delimited the drug's therapeutic usefulness as a prophylastic agent (i.e. administered before exercise) with little or no beneficial effects noted when given after the challenge.

In a recent study, Breslin et al.[99] were unable to attribute the drug's inhibition of EIA to an alteration of the respiratory heat exchange mechanism as they had previously demonstrated with the anticholinergic agent atropine[41]. Instead, they confirmed that cromolyn sodium not only blunted exercise induced bronchoconstriction, but additionally inhibited cold potentiation of EIA. Moreover, Godfrey[13] emphasized that since cromolyn sodium administration does not alter baseline lung function (i.e. does not cause resting bronchodilation) its inhibition of EIA only when administered prior to an exercise challenge verifies its capacity to interfere with the stimulus for bronchospasm i.e. mast cell degranulation. He[13] additionally corroborated the findings of Breslin et al.[99] in demonstrating that inhalation of the drug did not subsequently prevent the exercise associated esophageal temperature decline, and therefore,

was not inhibiting EIA by interfering with the initial trigger of postexercise bronchoconstriction. Godfrey[13], like others[20,96,98], concluded therefore, that the operating pathogenetic mechanism in EIA was essentially the same as that described in allergen induced asthma (AIA), if one makes allowances for differences in their respective "triggers". Thus antigen binding to mast cell IgE operating in AIA, and respiratory heat exchange leading to airway cooling occurring in EIA, both serve to activate the mast cell, resulting in degranulation, mediator release and subsequent bronchoconstriction.

Other, somewhat more recent evidence supporting the role of mast cell degranulation and mediator release in the pathogenesis of EIA has been derived from a study by Soter et al.[64], on cold urticaria. In their experiment, they found significantly elevated levels of histamine and eosinophil chemotactic factor of anaphylaxis in the arms of patients that had been induced to form urticarial lesions by immersion in cold water. They concluded, that degranulation of sensitized mast cells triggered by a thermal stimulus (cold), was the operative mechanism in cold urticaria. Appliction of this information to EIA, wherein heat flux and airway cooling has been shown to be the initiating stimulus[11], strongly implicates subsequent nonimmunologic degranulation of mast cells with release of its asthmagenic mediators as the critical pathogenetic event resulting in bronchoconstriction.

Similarly designed studies attempting to correlate changes in systemic (mast cell derived) mediator levels with EIA, have yielded mixed results[12,101-105]. The first report, by Graneurus et al.[101] measured urine levels of histamine and its metabolite, 1-methyl-4-imidazoleacetic acid, three hours before and after an exercise

challenge. Their failure to detect significant changes can in retrospect be attributed to their reliance upon the insensitive and now obsolete techniques of bioassay and chromatography. More recently, using the more sensitive radioenzyme assay for histamine, as well as a modified Boyden chamber assay for neutrophil chemotactic activity, Deal et al.[12], compared the changes in mediator levels in arterial blood following hyperventilation and antigen induced asthma. Although both challenges produced the expected and nearly identical alterations in lung function, neither was associated with a kinetic increase in systemic histamine levels. Since, however, the antigen, but not the hyperventilation induced asthma was accompanied by a sustained release of neutrophil chemotactic activity, they concluded that mast cell derived mediators were only involved in the pathogenesis of AIA. However, their inability to demonstrate elevated systemic histamine levels even after an antigen challenge, forced them to alternately suggest, that local intrapulmonary concentration may not be adequately reflected in the systemic circulation and therefore, mediator involvement does not have to be ruled out in EIA. This in fact, is somewhat analagous to the (see above) inability to demonstrate histamine induced bronchoconstriction by systemic infusion[85], but rather, only via inhalation[83], when high local concentrations of the amine are more certainly attained.

In another study, however, McFadden et al.[102], validated the utility of measuring systemic histamine levels. They found, that a distinct subgroup of asthmatics whose prechallenge arterial histamine levels were high (4 ng/ml as compared with 2 ng/ml), and had significantly greater impairment of their baseline lung function,

localized predominantly to the small airways, subsequently developed more severe EIA. However, since neither subgroup then demonstrated any significant exercise induced histamine elevations, McFadden et al.[102] seriously questioned the role of mast cell derived mediators in EIA.

Hartley et al.[103] in a similar study, compared the postexercise changes in systemic histamine levels in both normal and asthmatic subjects. Although they did find that during exercise, mean arterial histamine levels rose 48% in asthmatics and 42% in normals, neither rise was of statistical significance. It should be pointed out however, that neither Deal et al.[12] or McFadden et al.[102], were able to demonstrate any changes of this magnitude. Because they found insignificant mediator elevations for both asthmatics and normal subjects, Hartley et al.[103] concluded that mast cell derived mediators did not seem to play a role in EIA, and furthermore, attributed the observed elevations to an exercise induced leukocytosis and basophilia with a nonspecific histamine discharge. They[103] did caution however, that until intrapulmonary measurements could be performed to ensure that local concentrations of histamine were not dissimiliar to systemic levels, participation of this (and other) mediator(s) in postexercise bronchoconstriction could not definitely be ruled out.

Utilizing their own newly developed radioenzyme assay with purportedly improved sensitivity and precision for the detection of histamine, Barnes and Brown[104] compared postexercise and hyperventilation induced changes in venous plasma histamine levels in asthmatic and normal subjects. In contrast to the findings of Deal[12], McFadden[102] and Hartley[103], Barnes and Brown demonstrated a very significant postexercise elevation of plasma histamine

(from 6.2 nmol/ to 4 nmol/). They, therefore, rejected the role of an exercise induced leukocytosis and basophilia in the etiology of the histamine elevation found uniquely in the asthmatic group, and concluded that mast cell discharge was critical in the pathogenesis of EIA. In the second part of their protocol however, they found, that although hyperventilation resulted in nearly identical decreases in PEFR, no concomitant histamine elevations were demonstrated as is in EIA. On close examination of their protocol, however, it can be ascertained that the maximum interval between exercise and hyperventilation challenges was less than 2 hours. Thus, by rechallenging their asthmatics when they were conceivably partially refractory to further EIA[94], Barnes and Brown[104] may have inadvertently elicited a diminished histamine release, allowing for a systemically nondetectable local elevation, sufficient to cause bronchoconstriction. Alternatively, their demonstration of systemic postexercise histamine elevations may in fact be a manifestation of exercise induced leukocytosis, detectable only in asthmatics whose higher and hence more accurately measurable baselines allow for an ehhanced capability to determine concentration changes.

In a more recent study, Lee et al.[105], by measuring postexercise serum concentrations of neutrophil chemotactic factor (NCF), successfully demonstrated systemic elevations of a mast cell derived mediator. Serial challenges of atopic asthmatics with both treadmill exercise and antigen inhalation, resulted in nearly identical kinetic elevations of NCF, coninciding with parallel falls in the PEFR and FEV_1 expected in EIA and AIA. Furthermore, they found that pretreatment with cromolyn sodium prevented the postexercise NCF elevation as well

as bronchoconstriction. Additionally, they challenged three atopic (but nonasthmatic) individuals, and four normal subjects, using the same exercise protocol, and found no elevations of NCF. They thus dismissed as very unlikely the possibility that the observed NCF elevations occurring in asthmatics only (and not in other atopic individuals) were secondary to an exercise induced leukocytosis and basophilia. Based upon these observations (i.e. an exercise induced kinetic elevation of NCF mirroring the rise produced by antigen inhalation, as well as its inhibition by pretreatment with cromolyn sodium), Lee et al.[105] concluded that mast cell degranulation and mediator release was responsible for the pathogenesis of EIA.

In summary, whereas several studies[104,105] focusing on postexercise changes in systemic mediator concentrations demonstrate that exertion as a stimulus for asthma does indeed result in mast cell degranulation and mediator release, strongly implicating it in the pathogenesis of EIA, others[12,102,103], finding no such relationship, using both exercise and hyperventilation challenges, seriously question mast cell participation in postexercise asthma. Furthermore, since none of the investigators were able to demonstrate mediator release with hyperventilation[12,104], one is forced to question whether this challenge is indeed equivalent to exercise as claimed[8,11,12,16], or alternatively, whether exercise associated histamine and NCF elevations[104,105] were merely misleading findings.

Recently, Stearns et al.[106], did indeed demonstrate the non identity of hyperventilation and exercise challenges in the production of EIA. By re-examining the refractory period, they corroborated the findings of others[93,94], that repeated exercise challenges separated by

short intervals results in progressively decreased postexercise bronchoconstrictive responses. However, successive trials of eucapnic hyperventilation, produced no refractoriness, and resulted instead in continuous, consistent posthyperventilation asthma. Stearns[106], concluded therefore, that mediator depletion was not operative in the causation of refractoriness to EIA as had been thought[10,13,94], but rather secondary sympathoadrenal consequences of repeated exercise acted to temporarily prevent recurrent bronchoconstriction.

Supporting the postulate of Stearns et al.[106] is the findings of Barnes et al.[53], who demonstrated that hyperventilation is not associated with the catecholamaine elevations found during vigorous physical exertion. Thus it is conceivable that other as yet unidentified processes might account for elevations in systemic mediator concentrations following exercise but not hyperventilation. Alternatively, however, one can similarly reason that hyperventilation and exercise induced asthma are not mediated by identical pathophysiolog ic mechanisms[106], and the inability to identify mast cell derived mediator elevations in post hyperventilation asthma, has no bearing on the findings unique to EIA.

Using yet another approach to determine the role of mast cell derived mediators in EIA, Weiler-Ravell et al.[92], compared the asthma inducing mechanisms of antigen and exercise challenges. In designing their protocol, they reasoned that since antigen induced asthma (AIA) was mediated by a Type I immediate hypersensitivity reaction with resultant mast cell degranulation, serially exercising asthmatics over short intervals, rendering them refractory to further EIA, should by virtue of mediator depletion, similarly block AIA if challenged with

antigen during this refractory period. Their results demonstrated the existence of two subgroups, blocked and nonblocked. In 6 of the 12 asthmatics studied, refractoriness to EIA resulted in an inability to cause subsequent AlA, despite a known susceptability as demonstrated in baseline studies. However, the other half of the group (who interestingly manifested lower baseline levels of lung function), did indeed respond to antigen challenge with a full blown attack of brochoconstriction, despite being rendered refractory to EIA. Weiler-Ravell[92] concluded therefore, that mast cell degranulation and mediator release operates to cause postexercise bronchospasm in one subgroup of asthmatics whereas, other as yet to be defined mechanisms mediate EIA in the other asthmatics.

In testing the therapeutic efficacy of a new class of drugs, the calcium channel blockers, many investigators[108-112] have attempted to clarify the pathogenetic mechanism mediating EIA. A priori, one would indeed expect these agents to interfere with postexercise constriction at several loci in the pathophysiologic chain of events, already determined be calcium dependent processes. Those best identified include: activation of mast cells and liberation of its mediators[107,109], as well as excitation contraction coupling and discharge of propogated action potentials in smooth muscle cells[112].

Although administration of sublingual nifedipine by Cerrina et al.[110] failed to alter baseline bronchial tone, it did, however, prevent the exercise induced decreases in PEFR and Vmax50% found after placebo ingestion. Their conclusion[110] that calcium blockers prevent EIA was corroborated by Patel[108], who administered aerosolized verapamil to compare its prophylactic capacity with that of cromolyn

sodium. Patel interpreted verapamil's success in reducing the postexercise fall in FEV_1 even more than cromolyn sodium, without affecting baseline airway functioning, as indicating the drugs ability to block calcium dependent mediator release in EIA.

In a complex study designed to answer several questions, Barnes et al.[111], found that sublingual nifedipine only partially (though significantly) inhibited EIA. They also noted however, that a significant postexercise rise in venous plasma histamine levels that occurred with placebo, was blocked completely by nifedipine. Finally they reported that the dose of inhaled histamine required to provoke a 20% fall in PEFR was nearly doubled when patients were pretreated with nifedipine as compared to placebo. They concluded therefore, that although the drug seemed to inhibit both mast cell mediator release and bronchial smooth muscle contraction, it was not of the therapeutic utility suggested by Patel[108] and Cerrina[110]. Patel[109] then found (as had Barnes et al.[111]), that sublingual nifedipine offered partial but significant protection from EIA in nine patients. Additionally, however, he also noted complete prevention in four and no protection in two subjects challenged. Despite these mixed results, he concluded that calcium ions play a central role in EIA, which is inhibited therefore, by nifedipine pretreatment. Finally, in an attempt to localize the site of action of the calcium blockers, Patel[112] then examined the effect of verapamil on histamine and methacholine induced bronchoconstriction. In contrast to the findings of Barnes et al[111], Patel discovered that verapamil inhalation failed to alter the provocative concentrations of either spasmogen needed to induce a 20% fall in FEV_1, and its pretreatment thus offered no more protection from this challenge than did saline placebo. Combining this data with that determined by him

previously[108,109], he concluded that the efficacy of the calcium channel blockers in inhibiting EIA, was predicated upon its action on mast cells, preventing the release of its mediators.

In summary then, the mast cell and its mediators have certainly been implicated in the pathogenesis of exercise induced asthma, however, further work must be done, to clarify the many outstanding controversies and inconsistencies in the literature to date.

II. Introduction

The pathophysiologic mechanism(s) mediating the phenomenon of EIA, wherein the thermal stimulus of airway cooling brought about by the hyperventilation of exercise,[11] triggers a bronchospastic attack in almost all asthmatic patients challenged,[10,16] continues to elude the grasp of researchers trying to delineate it. Conflicting and often confusing findings concerning the roles of adrenergic receptor imbalance,[49-53] vagal reflexes,[54-58] and temperature dependent smooth muscle depolarization[48] in postexercise bronchoconstriction, have led many investigators[10,13,71,94] to implicate the mast cell and its chemical mediators in the pathogenesis of this event. However, analysis of the accumulated data from the many experimental protocols and designs, including the study of: cromolyn sodium,[95-100] postexercise systemic mediator concentrations,[101-105] calcium antagonists,[108-112] and successive exercise and antigen challenges,[92] does not allow for an unequivocal conclusion as to the proposed central role of mast cell derived mediators in EIA. One such mediator, histamine, has long been known to induce bronchoconstriction,[80-83] and in fact was recently shown to produce pulmonary changes following its inhalation indistinguishable from those occurring in spontaneous asthma.[83]

Thus, some researchers have begun reassessing the role of antihistamines in asthma, in an ironic though obviously refined recapitulation of the work of Herxheimer.[117,118]

It was 35 years ago, soon after he ushered in the modern era in the study of EIA,[19] that Herxheimer[117] compared the therapeutic effects of a synthetic catecholamine, aleudrine, with the antihistamine pyranisamine

maleate ("anthisan"), in bronchial asthma. He reported that anthisan did indeed significantly increase the vital capacity (though not as much as aleudrine) of asthmatics when administered either orally or by inhalation. However, its sedative actions as well as its irritating effects when inhaled (1-3 min. coughing and numbness) led him to suggest that its use be limited to oral ingestion at bedtime. In a follow up study Herxheimer[118] delimited the utility of phenergan (a phenothiazine with antihistaminic actions) and anthisan specifically for mild to moderate asthmatic episodes since he found they were not efficacious in severe attacks. Herxheimer's advocacy of including antihistamines in the therapeutic regimen for mild asthma fell into disfavor in the 1950's, when it had been clearly demonstrated that the antihistamines were themselves bronchospastic agents.[119] This spasmogenic capacity was demonstrated in man (high oral or 1-3% inhalant concentrations) as well as animals.[119] Thus, although most authorities agreed that the antihistamines were of no pharmacologic usefulness in the treatment of asthma,[120] the controversy quietly smoldered on until the mid 1970's, when Popa,[120] in a well controlled study, demonstrated the bronchodilating capacity of chlorpheniramine in 10 asthmatic subjects. Popa attributed previous negative findings in the literature to poorly designed studies wherein the antihistamines were orally administered in insufficient doses. He therefore proposed and indeed demonstrated that intravenous administration of a specific, potent H_1 blocker with relatively little sedative and anticholinergic effects- chlorpheniramine, at higher than recommended doses (10 mg) dilates the bronchi of asthmatic patients. Although of smaller magnitude, he found that 8 mg of orally administered chlorpheniramine was also effective in airway dilatation. He[120] prudently

concluded that chlorpheniramine was of definite value in the investigation of the pathophysiology of asthma, particularly as pertaining to the possible role of histamine in the resting tonus of bronchial muscle, but not necessarily as a clinically useful therapeutic agent, since many subjects experienced drowsiness following its administration.

Although Popa[120] successfully demonstrated the bronchodilatory capacity of this alkylamine competitive H_1 receptor antagonist, chlorpheniramine, in patients with allergic asthma, the mechanism mediating this event remained to be clarified. The "classic" (H_1) antihistamines (of which chlorpheniramine is considered among the most potent[121]) not only possess the potential to block histamine receptors, but additionally are known to mimic the atropine like drugs in their ability to block the muscarinic cholinergic receptors. Thus, one could argue that chlorpheniramine induced bronchodilation was mediated by an atropine like effect were it not for a study by Woenne et al.[122] By alternately pretreating asthmatic children with either aerosolized chlorpheniramine or ipatropium bromide (an acetylcholine antagonist), and then challenging them with histamine or methacholine, they[122] determined that chlorpheniramine specifically and unequivocably inhibited histamine but not methacholine induced bronchoconstriction, thus supporting Popa's contentions.[120]

Despite the proven efficacy of orally or intravenously administered chlorpheniramine (8-10 mg) as a bronchodilating agent,[120] many researchers[116,123-129] interested in the effects of antihistamines in asthma have turned towards other, less sedating and possibly more potent H_1 antagonists. One agent, as yet not available in the U.S., clemastine, is a member of the benzhydrylether group of antihistamines with purported

greater H_1 blocking abilities than chlorpheniramine as well as reduced CNS depressive actions.[123] Theorizing that inhalation of this drug with resultant high intrapulmonary concentrations would circumvent the need to administer high systemic (i.e. oral or intravenous) and possibly sedating doses, Nogrady et al.[123] administered aerosolized clemastine to 12 asthmatic patients. They found that the mean maximum increases in the FEV_1 and PEFR (21.1% and 31.2% respectively) were not significantly different than that produced by administration of salbutamol. They concluded therefore, that inhaled clemastine was an effective bronchodilator. In a follow up study Nogrady et al.,[124] demonstrated the drug's specific competitive antagonism to inhaled histamine, without finding any protective effect when administered prior to methacholine challenges, thus identifying its antihistamic character as that responsible for its bronchodilating effects. They further postulated,[124] concurring with Popa,[120] that low grade mast cell derived histamine release not detectable in systemic measurements, caused a mild baseline bronchoconstriction, which when prevented by administration of an H_1 antagonist resulted in the demonstrated bronchodilation. Additionally, they proposed utilization of the antihistamine as a therapeutic agent in the management of asthma, since its inhalation was not accompanied by any irritation or sedation.[123,124]

Their conclusions were strongly contested, however, by Partridge et al.,[125] who administered equal and even double doses (as compared to Nogrady et al.[123,124]) of aerosolized clemastine yet failed to show similar consistent and significant bronchodilation, raising serious questions as to the pathogenic role of histamine as well as the H_1 antagonist's utility in asthma.

Other researchers[116,126-129] have focused their attention on a new tricyclic benzocycloheptathiophene derivative--ketotifen, another drug not yet available in the U.S. with purported antihistaminic and anti-anaphylactic properties, to determine its potential pharmacologic utility in asthma.

In a multifaceted trial, Craps et al.,[126] demonstrated ketotifen's protective efficacy against bronchospasm induced by allergans, histamine and even exercise as well as illustrating its superior long term antiasthmatic potential as compared with clemastine and cromolyn sodium. Similarly, Beumer[127] found ketotifen to be an effective long term prophylactic agent in the treatment of asthma, while corroborating its inhibitory capacity on histamine induced bronchospasm.

Enthusiasm concerning the addition of ketotifen to the anti-asthmatic therapeutic arsenal has been recently tempered, however, by Groggins et al.[129] who failed to demonstrate its prophylactic superiority to placebo administration in 23 asthmatic children. Additionally, Sarsfield,[128] in a recent review, cautioned against premature acceptance of ketotifen, while conflicting evidence derived from several therapeutic trials remain unresolved.

Superseding the present controversy regarding the use of ketotifen, however, are the fairly well documented pharmacologic characteristics of this drug, i.e. a mast cell stabilizer, SRS-A antagonist and a calcium channel blocker as well as an antihistamine.[116] Thus, even if future studies do indeed find this antiasthmatic compound therapeutically beneficial, its multiplicity of actions precludes advancement and refinement of our understanding of the specific pathophysiologic events, particularly mast cell derived histamine release in the pathogenesis of asthma.

In summary then, many authorities[117,118,120,123,126,127] have garnered evidence supporting the pathogenetic role of mast cell derived histamine in asthma by demonstrating the therapeutic efficacy of various compounds with antihistaminic activity. However, conflicting and contradictory findings of other researchers[125,128,129] using similar protocols prohibit conclusive and unequivocable ascription of a major pathophysiologic function for histamine in this disease.

Few studies[130,131] have addressed themselves, however, to the efficacy of (H_1) antihistamine administration in the prevention of exercise induced asthma. Although Zielinski et al.,[130] found that 50 mg of thiazinamium given intramuscularly prior to exercise did indeed significantly reduce EIA, it remained unclear whether the drug's apparent success was attributable to prevention of post exercise histamine induced bronchoconstriction, or alternatively a pre exercise inhibition of baseline histamine bronchial muscle tonus with resultant prechallenge bronchodilation. In a more carefully designed protocol, Hartley and Nogrady,[131] studied the effects of inhaled clemastine prior to and post exercise in 10 adult asthmatics. Based upon their finding significantly diminished post exertional decreases in the FEV_1 and PEFR as compared to placebo (12.2% and 12.6% vs. 22.0% and 25.4%, respectively) without noting prechallenge bronchodilation, they concluded that histamine was necessarily involved in the pathogenesis of EIA.

The present study was undertaken in an effort to define the role (if any) of low grade mast cell degranulation and histamine release maintaining increased resting bronchomotor tone in asthmatic subjects, as well as to determine whether, in fact, airway cooling triggers a large scale mast cell mediator release (specifically histamine) which is then

responsible for the pathophysiologic manifestations and consequences of exercise induced asthma. Additionally, it is hoped that a conclusive determination be achieved as to the purported therapeutic utility of the "classic" antihistamines in bronchial asthma.

The H_1 antagonist, chlorpheniramine maleate, was chosen for this study since it has been unquestionably shown[120] to elicit bronchodilation in asthmatic subjects, by specifically and unequivocably inhibiting histamine induced bronchoconstriction.[122]

Furthermore, by offering the drug as an inhalant in aerosolized form, it is hoped that the required high intrapulmonary concentrations[120] will be achieved while concurrently avoiding the sedating sequelae of systemic administration.

III. Methods

A. Subjects

Twelve mild asthmatic subjects (9 female, 3 male) were recruited as paid volunteers. Criteria for inclusion in the study included a history of asthma as defined by the American Thoracic Society,[1] as well as demonstrated EIA during the screening procedure (see below). All subjects gave informed consent as approved by the Yale University Human Investigations Committee. Additionally each subject completed a detailed questionnaire concerning the presence of allergies, chronic bronchitis, EIA and use of medications. The collected anthropometric data appears in Table 1. Although one of the 12 subjects claimed not to suffer from EIA, pulmonary function tests performed five minutes post exercise on the screening day (see Table 5) revealed the presence of exercise induced asthma in all the subjects (i.e. a minimum of 15% decline in the $MEF_{40\%}(P)$).[134] Similarly, baseline pulmonary function parameters revealed moderate obstruction commensurate with mild asthma (Table 2).

B. Pulmonary Function Testing

Subjects performed forced vital capacity maneuvers using a pneumotachograph-integrator system;[133] they inhaled to approximately 50-70 percent of their vital capacity, and then exhaled as fast as possible to residual volume, thereby generating a partial expiratory flow-volume (PEFV) curve.[132] The subjects then immediately inhaled to total lung capacity and subsequently exhaled as fast as possible to residual volume thus generating the maximal expiratory flow-volume (MEFV) curve.[132] All generated curves were recorded on a Brush 500 X-Y recorder (Gould, 3054, Cleveland Ohio). A programmable marker, set to trigger at one second

permitted identification of the forced expiratory volume at one second (FEV_1). Analysis of the resultant curves enabled measurement of the forced vital capacity (FVC), peak expiratory flow rate (PEFR), and maximum expiratory flow rates at 60 percent of the vital capacity, below total lung capacity on the MEFV curve ($MEF_{40\%}$) and PEFV curve ($MEF_{40\%}(P)$).[134] To facilitate comparisons of the subjects' baseline to expected normal values (see Table 2), the maximum expiratory flow rate at 50% of the vital capacity on the MEFV curve (Vmax50% or $MEF_{50\%}$) was determined for the Screening Day only. In order to minimize instantaneous variability, all pulmonary function tests were performed in triplicate over three minutes, the results of which were subsequently averaged.

C. Exercise Challenge

Exercise studies were performed only if the subject refrained from taking his/her usual asthmatic medications (see Table 1) for at least 12 hours prior to the study. All subjects performed identical exercise challenges on a cycloergometer (Monark).

The subjects were instructed to pedal at a constant speed (20 kilometers per hour) throughout the challenge, while exclusively inspiring (through a mouthpiece) air dried by having passed through a column of calcium sulfate (Drierite, W.A. Hammond Drierite Co., Xenia, Ohio).

Random measurements of this column of air revealed an average humidity ($\pm$S.D.) of 3.20$\pm$0.69, 3.10$\pm$0.19, and 3.24$\pm$0.49 mmHg on the Screening, Antihistamine and Placebo days, respectively (none of the differences statistically significant as measured by student's t-test). Additionally, the temperature of the lab itself was controlled resulting in average temperatures ($\pm$S.D.) of 74.75$\pm$4.92, 74.35$\pm$3.30, and 75.50$\pm$3.51 degrees

Farenheit, with no significant differences detected between the three study days. At the outset of each challenge, the workload against which the subjects pedaled was set at 0.0 kiloponds. After completion of each minute of exercise, the subjects' heart rate and minute ventilation were recorded (using an electrocardiograph (Hewlett-Packard) and a volume meter (American Meter Co., Boston, Ma.), respectively) and the workload subsequently increased by 1/2 kilopond for the following minute. This procedure was continued until the subjects fatigued, or their heart rate exceeded 150 beats/min. (average of 5-7 minutes of exercise). The amount of exercise performed by each subject on the screening day was matched on the subsequent protocol days, thus ensuring identical challenges throughout the study.

D. Drug Administration

Chlorpheniramine maleate (Schering, Kenilworth, N.J.) supplied as a clear liquid solution in 1 ml vials at a concentration of 10 mg/ml was prepared by dilution with normal saline to a concentration of 1 mg/ml. Five milliliters of this solution were then placed into an "Acorn" nebulizer chamber (Devilbiss, Jamestown, Calif.) for immediate use or stored no more than 24 hours in a sealed flask in a dark refrigerator. The antihistamine was administered by having subjects inhale (by tidal breathing) through a mouthpiece (while wearing noseclips) for a total of 5 minutes. The driving force for aerosolization was provided by attachment of the Acorn nebulizer to a tank of compressed air, flowing at a fixed pressure of 20 pounds per square inch.

The placebo preparation consisted of 5 ml of sterile normal saline, delivered in identical fashion in a double blind random order. Subjects

were informed prior to each inhalation that the inhaled solutions were capable of causing throat and airway irritation and were instructed to continue the drug inhalation even if coughing ensued. Of note, none of the subjects were forced to discontinue the drug inspiration because of coughing, irritation or other side effects. A total of 10 subjects did experience mild transient throat and airway irritation as well as 1/2-2 minutes coughing while inhaling the chloropheniramine maleate, whereas no similar responses were observed with placebo.

E. Study Design (Figure 1)

The study consisted of exercise challenges on three separate days; an initial Screening Day, and the subsequent two Protocol Days.

1. Screening Day (Day 1)

To determine baseline lung function, each subject underwent pre-exercise pulmonary function testing in triplicate as described above (see Table 2). Following this, the subjects were instructed as to the use of the cycloergometer, breating apparatus and electrocardiograph. They then performed 5-7 minutes of exercise (as described above), after which they quickly underwent another series of 3 pulmonary function tests (i.e. Immediate Postexercise or PEO'). After a waiting period of 5 minutes, pulmonary function testing was repeated (i.e. 5 minutes post-exercise or PE5'). Two metered doses (0.65 mg each) of metaproterenol sulfate (Alupent^{R}) inhaler were then administered, which was followed after another 10 minute waiting period, by a final set of pulmonary function tests ((Post Bronchodilator or PBd), Tables 3-5).

2. Protocol Days (Day 2 and 3)

After performance of an initial set of prechallenge baseline pulmonary function tests, the subjects were administered, on alternate randomly assigned days (in a double blind fashion) the aerosolized solution consisting of either normal saline or chlorpheniramine maleate for 5 minutes as described. Over the ensuing 30 minutes following the drug inhalation, each subject performed 3 sets of pulmonary function tests (see Figure 1); the first, immediately postinhalation (PAH0'), the second, 10 minutes postinhalation (PAH10') and the third at 30 minutes postinhalation (PAH30').

After completion of the postinhalational testing, the subjects were challenged with the identical exercise task performed on the Screening Day. Pulmonary Function testing as well as bronchodilator administration were similarly carried out as in the Screening Day (Tables 6-15).

F. Analysis of Results

For each of the 12 subjects, the mean values derived from every triple set of pulmonary function tests were tabulated into columns according to the time locus within the study at which they were performed (i.e. Baseline, PAH0', PAH10', etc.). In addition to calculating the mean and standard deviation for each column, comparisons were performed between each time locus and the baseline of that day (% Baseline). To assess statistical significance, each time locus for a particular day was compared to Baseline using a two tailed paired student's t-test. Additional t-tests were performed comparing equivalent loci on the Antihistamine and Placebo Days, Antihistamine and Screening days as well as Screening and Placebo Days.

IV. Results

A. Screening Day

1. Baseline and Post Exercise Pulmonary Function Tests

Observations recorded in Table 2, reveal moderate (though insignificant) reductions in the FEV_1 and PEFR, as well as a large decrease in the Vmax50% ($P < 0.001$) in preexercise pulmonary function tests as compared to expected normal values, which are commensurate with mild asthma.

As evident in Tables 3-5, comparisons of all pulmonary function parameters to their respective baseline values (% Baseline) demonstrated a slight trend towards immediate post exercise bronchodilation, whereas 5 minutes post exercise reductions in: The FVC from 4.14 to 3.98 (L) ($P < 0.05$), the FEV_1 from 3.00 to 2.77 (L) ($P < 0.001$), the PEFR from 5.78 to 5.20 (L/S) ($P < 0.01$) and finally the $MEF_{40\%}(P)$ from 2.11 to 1.51 (L/S) ($P < 0.001$) all demonstrate the presence of EIA in this group of subjects. Additionally, after administration of the bronchodilator, all pulmonary function measures either returned to baseline (FVC) or significantly surpassed it (i.e. FEV_1, PEFR and $MEF_{40\%}(P)$). Figure 2 displays the entire sequence of the above pulmonary function changes (as measured by the FEV_1 and $MEF_{40\%}(P)$) for all subjects on the screening day.

B. Protocol Days

1. Antihistamine Day

Significant reductions in all pulmonary function tests occurred immediately following inhalation of the chlorpheniramine maleate (Tables

6, 8, 10, 14), demonstrating drug induced bronchoconstriction. By 10 minutes postinhalation, however, all parameters returned towards baseline. Measurements of pulmonary function 30 minutes after inhalation demonstrated moderate though insignificant increases in the FEV_1 and PEFR (Tables 8 and 10) as well as a significant increase in the sensitive $MEF_{40\%}(P)$ ($P < 0.05$) as compared to baseline (Table 14). Immediately after exercise, although the FVC remained unchanged (Table 6), the FEV_1 rose (insignificantly) from 2.85 to 3.01 (L) (Table 8), and the PEFR and $MEF_{40\%}(P)$ both increased significantly from 5.42 to 5.91 (L/S) and 1.88 to 2.37 (L/S) respectively (Tables 10 and 14). Five minutes after the exercise challenge, all parameters demonstrated slight and insignificant decreases as compared to baseline except for the FVC which dropped by 0.14 (L) ($P < 0.05$). Finally, postbronchodilation, all measures of lung function significantly increased again except for the FVC which remained unchanged.

2. Placebo Day

Immediately following inhalation of saline, all pulmonary function parameters (Tables 7, 9, 11 and 15) were significantly decreased as compared to the baseline of that day ($P < 0.05$). Ten minutes later, however, all measures returned towards the prechallenge values and remained at those levels at 30 minutes postinhalation as well. Although all the determinants of lung function increased slightly immediately after exercise, no value reached statistical significance. Measurements five minutes post exercise revealed a strong, though again insignificant trend towards reduced lung function with $MEF_{40\%}(P)$ falling over 16% from 1.67 to 1.34 (L/S) (Table 14). Finally, all parameters showed marked

increases after administration of the bronchodilator ($P < 0.01$) except for the elevation in the FVC which did not reach statistical significance.

C. Comparison of Antihistamine, Placebo and Screening Days

1. Antihistamine and Placebo Days

Results of the t-tests comparing the FVC, FEV_1, PEFR and $MEF_{40\%}(P)$ of equivalent time loci on the two protocol days, appear under their respective columns in Tables 6, 8, 10 and 14 (i.e. AH → Pl t-test). Additionally, Figures 5-10 illustrate comparisons of the changes in pulmonary function for each time locus (as measured by the FEV_1 and $MEF_{40\%}(P)$) on the Antihistamine and Placebo days. Finally, composite illustrations, demonstrating the entire sequence of changes in, as well as the differences between, the FEV_1 and $MEF_{40\%}(P)$ during each of the protocol days appears in Figures 3 and 4.

Except for the FVC, no significant differences were noted between the baseline pulmonary function tests. Although slightly (but not significantly) more pronounced on the Antihistamine day, all parameters showed similar declines immediately post inhalation on both days (Figure 5). Figures 3, 4 and 6 demonstrate the parallel return of pulmonary function toward baseline which occurred 10 minutes postinhalation of both chlorpheniramine and saline, with no significant differences detected in the other parameters as well (Tables 6 and 10). These parallel trends cease, however, by 30 minutes postinhalation, as the FEV_1 (Figures 3 and 7) and $MEF_{40\%}(P)$ (Figures 4 and 7) both rise exclusively on the Antihistamine day ($P < 0.05$), demonstrating chlorpheniramine (but not saline) induced bronchodilation. Similarly, statistically significant differences between the FEV_1 and $MEF_{40\%}(P)$ observed on the two

protocol days were detected immediately post exercise, once again illustrating the greater bronchodilation which occurred on the antihistamine day (see Figures 3, 4 and 8, and Tables 8 and 14). Although the pulmonary function parameters, FVC and PEFR show similar, parallel discrepancies between the protocol days (i.e. greater bronchodilation occurring with the antihistamine 30 minutes post inhalation as well as immediately post exercise) these did not reach statistical significance (see Tables 6 and 10, 7 and 11).

Of particular note, are the incongruities between the decline in the FEV_1 and $MEF_{40\%}(P)$ 5 minutes post exercise on the two days. Whereas the FEV_1 fell less than 1% and $MEF_{40\%}(P)$ less than 7% relative to baseline on the antihistamine day, greater declines of 5.25% and 16% in the FEV_1 and $MEF_{40\%}(P)$ were noted on the Placebo day. Comparisons of the absolute values of these pulmonary function tests on the two days clearly demonstrated statistical significance ($P < 0.01$) (see Figure 9). Similarly, significant differences between the FVC and PEFR ($P < 0.05$) on the two protocol days measured five minutes after exercise were detected as well (Tables 6 and 10).

In an effort to distinguish between the occurrence of preexercise bronchodilation with subsequent bronchoconstriction back to baseline, and the actual prevention of postexercise bronchoconstriction (i.e. EIA) a separate "delta" calculation was performed. The ΔFEV_1 and $\Delta MEF_{40\%}(P)$ representing the mean differences between these pulmonary function values recorded 30 minutes post inhalation and 5 minutes postexercise of each individual day were found to be 0.12 (L) and 0.57 (L/S) respectively on the antihistamine day, and 0.17 (L) and 0.46 (L/S) on the placebo day. These values were not significantly different, nor were

there any such differences between the two protocol days noted for the ΔFVC and ΔPEFR. Examination of Figures 3 and 4 similarly reveal that although the 5 minutes postexercise values of the FEV_1 and $MEF_{40\%}(P)$ merely return to baseline on the Antihistamine day, their drop from their PAH30' values were essentially the same as those occurring on the Placebo day.

Finally, pulmonary function tests performed postbronchodilation, on the Antihistamine day, revealed significantly greater airflow as measured by the FEV_1 ($P < 0.01$, see Figures 3 and 10) as well as increased (but not statistically significant) values for the FVC, PEFR and $MEF_{40\%}(P)$ compared to the Placebo day. A similar "delta" calculation performed by subtracting the pulmonary function values obtained 5 minutes postexercise from those obtained postbronchodilation on each separate day again failed to reveal a significant difference between the two protocol days.

2. Antihistamine and Screening Days

Although the FEV_1 on the Screening day dropped over 8% below baseline 5 minutes after exercise, whereas a less than 1% fall from baseline occurred on the Antihistamine day, comparison of the absolute pulmonary function values revealed no significant differences between the two days (see Tables 3 and 8). Similarly, the greater percent fall in the $MEF_{40\%}(P)$ from baseline on the Screening day, 5 minutes postexercise (28.52%) as compared to the Antihistamine day (6.23%) did not reach statistical significance when the absolute values were compared.

3. Placebo and Screening Days

Although comparison of all baseline pulmonary function values reveals significantly greater prechallenge bronchoconstriction on the Placebo day

(Tables 7, 9, 11 and 15), examination of the percent falls in the FEV_1 and $MEF_{40\%}(P)$ on the two days demonstrates the parallel and statistically equivalent changes occurring between baseline and 5 minutes postexercise. Thus the 8.37% drop, and a similar 5.21% fall in the FEV_1 on the Screening and Placebo days respectively (Tables 3 and 9), as well as a 28.52% Screening day decrease and 16.02% Placebo day decline in the $MEF_{40\%}(P)$ all serve to demonstrate the slight (but statistically insignificant) reduction in EIA on the Placebo day.

D. Minute Ventilation

Summation of the total minute ventilation generated by the 12 subjects performing identical exercise tasks on the Screening, Antihistamine and Placebo days resulted in mean values of ($\pm$S.D.) 158$\pm$14, 144$\pm$16 and 148$\pm$16 (L) respectively. Comparison by way of a two-tailed, paired student's t-test revealed no significant differences in ventilation between any pair of days during the study. Similarly, no significant differences were found when both the baseline and final minute ventilation were compared for the three study days. The mean baseline values ($\pm$S.D.) were calculated to be: 9.59$\pm$3.92, 10.50$\pm$4.23 and 11.25$\pm$3.49 liters, whereas the mean final minute ventilation ($\pm$S.D.) were determined to be: 41.59$\pm$11.75, 37.42$\pm$10.60, and 39.50$\pm$13.72 liters for the Screening, Antihistamine and Placebo days, respectively.

V. DISCUSSION

A. The Exercise Challenge

Results of pulmonary function testing on the screening day (Figure 2) serve to redemonstrate the classic and expected sequelae[10,134] of an exercise challenge in asthmatics. Following an initial transient mild improvement in airway function all asthmatic subjects responded, 5 minutes after exertion, with significant reversible bronchoconstriction. In an effort to ensure consistency and reproducibility, each subject identically reproduced the exercise challenges on each of the 3 study days. Similarly, to guarantee equivalent thermal burdens[8,22], laboratory temperature, inspired air humidity as well as total ventilation were matched and remained statistically constant throughout the study. Finally, subjects were requested to undergo the 3 exercise challenges at approximately the same time each day to avoid potential diurnal variation.

B. Effect of Inhaled Chlorpheniramine

1. Initial Bronchoconstriction

Inhalation of chlorpheniramine maleate clearly caused mild, transient bronchoconstriction (Figures 3-5), an effect not unexpected in view of similar findings with other antihistamines by Herxheimer[117,118] and Hawkins[119]. A parallel, significant, immediate post saline-placebo inhalation bronchospasm also occurred. (Figures 3-5). Whether psychogenic or physiologic in origin (i.e. loosening of viscous secretions or stimulation of irritant receptors), the mechanism of this bronchoconstriction may similarly underlie, to an indeterminate extent, the post antihistamine airway narrowing as well. Nevertheless, the exclusive occurrence of coughing and airway irritation as well as the development of greater (though not significantly) airway obstruction after chlorpheniramine

inhalation, necessitates at least partial attribution of the cause of post inhalation bronchoconstriction to a direct and unique irritant effect of the antihistamine itself.

2. Recovery and Bronchodilation

Despite the initial reduction of airflow, by 30 minutes post inhalation, the effect of chlorpheniramine was clearly and unequivocably bronchodilatory in nature (Table 14, Figure 4 and 7), consistent with the findings of Popa[120]. However, by aerosolizing a solution of the drug, and administering it via inhalation, thereby (apparently) achieving sufficiently high local intrapulmonary concentrations to effect histamine blockade without resorting to the usage of high systemic doses, we circumvented the troublesome sedating activity reported by others[117,118,120].

3. The Exercise Challenge

By recording pulmonary function at various intervals following the antihistamine inhalation, prior to the exercise challenge, we have demonstrated the H_1 blocker's ability to improve airway function in asthmatics, by raising their flow rates to a new higher baseline level. This was clearly shown by demonstrating significant differences between the PAH 30' pulmonary function tests on the antihistamine and placebo days (Figures 3, 4 and 7). However, although comparisons between the absolute values of the FEV_1 (measuring predomonantely large airway function[134]) and the MEF40%(P) (measuring predominately small airway function[134]) at 5 minutes after exercise on the protocol days revealed significantly decreased lung function on the placebo day (Figures 3, 4 and 9), we are forced to conclude that the antihistamine did not prevent or inhibit the development of EIA. Analysis of Figures 3 and 4 (particularly Figure 4) reveals a sharp decline in lung function between the 30 minutes post antihishistamine

inhalation - preexercise challenge and the 5 minutes post exercise recording of airway functioning. Similarly, the absolute decline in the MEF40%(P) from the PAH30' value to the PE5' value (i.e., the MEF40%(P)) of 0.57 (L/s) on the antihistamine day, actually surpassed the MEF40%(P) value on the placebo day of 0.46(L/s). Thus, although comparisons of the PE5' to baseline pulmonary function values on the antihistamine day reveal no significant bronchoconstriction, this merely reflects a prechallenge elevation to a new baseline level (i.e. PAH30') from which a large fall in pulmonary function did in fact occur following exercise.

It should be noted, however, that the fall in the FEV_1 from PAH30' to PE5' (i.e. FEV_1) on the antihistamine day of 0.12 (L) as compared to a 0.17(L) decline on the placebo day, did demonstrate an insignificant yet observable trend of decreased large airway post exercise bronchoconstriction with chlorpheniramine inhalation (see Figure 3).

4. Use of a Bronchodilator

Although chlorpheniramine maleate inhalation induced significant bronchodilation (Table 14) not matched by placebo control (Figure 7), this effect was quite modest in comparison to the marked improvement in airway function following administration of the ß agonist, metaproterenol (Figures 3,4 and 10). This demonstrated delimited efficacy of histamine antagonism in asthma (i.e. in reversing histamine induced brochoconstriction), though consistent with the findings of Herxheimer[117,118] and Nogrady et al.[123,124], strongly implicate the action of other non inhibited chemical mediators (i.e. SRS-A) as well as perhaps other pathogenic mechanisms in this disease.

5. Comparison to Other Antihistamines

Our findings support those of Herxheimer[117,118], Nogrady[123,124], Craps[116,126] and Beumer[127], that antihistamine administration reverses the

bronchoconstriction found in asthmatic patients. However, the failure of chlorpheniramine to more than mildly bronchodilate the small airways of the subjects tested, forces us to agree with those[119,125,129,130] who find this class of drugs therapeutically inferior to other agents currently utilized. That ketotifen has been demonstrated by some researchers[116,126,127] to have excellent antiasthmatic activity, may in fact be attributed to its other pharmacologic properties (i.e. SRS-A antagonism, mast cell stabilization, calcium channel blockade).

The results of the present study do, however, sharply conflict with those of Zielinski, et al.[130] who found the antihistamine thiazinamium, efficacious in the prevention of EIA. However, as pointed out by Hartley[131], it remained unclear from the data generated by Zielinski et al.[130], whether actual inhibition of post exercise bronchoconstriction occurred, or alternatively they merely observed the prechallenge brochodilatory capacity of the antihistamines as demonstrated in the present study. Administering aerosolized clemastine, however, Hartley and Nogrady[131] reported antihistaminic inhibition of EIA without elevating the prechallenge baseline. Thus results of the present study conflict with those of Hartley and Nogrady[131] on two major points. First, we do in fact find that antihistamines (H_1) cause mild prechallenge bronchodilation, and second they fail to prevent EIA. These differences can be reconciled by several lines of reasoning. Nogrady et al.[123,124] and Hartley et al.[131] claim that clemastine is more potent an H_1 antagonist than chlorpheniramaine, which if true, reimplicates histamine in the pathogenesis of EIA and indicates that our inability to prevent EIA was a consequence of insufficient H_1 antagonism. This seems very unlikely, since we (as have others[117,118,120]) demonstrated antihistamine induced bronchodilation

elevating baseline lung function, whereas clemastine failed to do so in Hartley's study[131]. Thus, it may be possible that clemastine's efficacy in inhibiting EIA was secondary to an as yet unknown pharmacologic action of this drug.

C. Resting Bronchomotor Tone

Based upon the demonstrated significant (though mild) bronchodilation occurring 30 minutes after chlorpheniramine inhalation, we conclude (as intimated by Popa[120]) that low grade mast cell derived histamine release contributes to the increase in resting bronchomotor tone found in asthmatics. Because administration of metaproterenol resulted in a far greater degree of airway dilitation (Figures 3 and 4), we further propose that other mechanisms are at play in maintaining increased airway resistance in asthmatic patients. Whether this non histamine induced bronchoconstriction is mediated by other mast cell derivatives (i.e. the leukotrienes-SRS-A) or other mechanisms entirely (i.e. increased resting vagal efferent tone[135]) remains to be clarified.

D. Histamine and EIA

As a result of the potent H_1 antagonist - chlorpheniramine maleate's inability to inhibit EIA, despite achieving sufficient local intrapulmonary concentrations to cause prechallenge bronchodilation after its inhalation as an aerosolized solution, we conclude that mast cell derived histamaine does not play a major role in the pathogenesis of postexercise asthma. Furthermore, because this mode of delivery of the antihistimine resulted in significant prechallenge bronchodilation of the smaller airways (i.e. significant increase in the MEF40%(P)[134]) we cannot attribute its inability to prevent EIA to a failure in drug delivery to the more peripheral sections of the lung.

An unlikely alternate explanation for the full development of EIA, is the possibility that the large minute ventilations generated during exercise simply washed out the unbound antihistamine solution from the airways leading to an overwhelming displacement by histamine, once large scale mast cell degranulation occurred.

E. Mast Cell Derived Mediators in EIA

In an effort to reconcile the findings of the present study to those that have implicated the mast cell and its mediators in the pathogenesis of EIA; i.e.: the efficacy of calcium channel blockers[108-112] and cromolyn sodium[13,99,100] in preventing EIA, the demonstration of cold induced mast cell degranulation[64], as well as the finding of kinetic elevations in postexercise plasma histamine[104] and NCF concentrations[105] in asthmatics, two pathophysiologic scenarios can be proposed. Conceivably, exercise induced asthma is in fact the consequence of thermally (cold) induced mast cell activation with liberation of its chemical mediators. However, the synergistic combination of the leukotrienes (SRS-A) with histamine[68,69] and perhaps certain prostaglandins constitutes a far too powerful bronchoconstrictive and inflammatory environment to allow for significant inhibition of its sequelae by isolated histamine antagonism.

Alternatively, it is also possible, that although the mast cell and its mediators participate in the pathogenesis of EIA, other as yet to be defined mechanisms concurrently operative following respiratory heat exchange and airway cooling, contribute to this condition.

Future studies may do well therefore, to attempt to control and eliminate the presumed pertinent mast cell effects, by administering in various combinations specific antagonists of SRS-A, prostaglandins as well as histamaine, prior to an exercise challenge in order to determine whether

EIA is the pathophysiologic consequence of mast cell activation or alternatively, whether other processes previously overlooked are responsible for postexertional asthma.

In summary, the failure of chlorpheniramine maleate to inhibit the development of EIA, eliminates histamine as a independent, central and critical mediator of EIA. However, the H_1 blocker's capacity to mildly bronchodilate asthmatic subjects prior to an exercise challenge suggests that low grade mast cell degranulation and histamine release partially contributes to the increased resting bronchomotor tone found in asthma.

Table 1

Anthropometric Data

Subject	Age (yrs)	Ht (cm)	Wt (kg)	Sex	Allergies	Smoking History	Chronic Bronchitis	EIB	Medications	Dyspnea[1] Scale
1	31	165	67	F	+	-	-	+	Alupent prn	2
2	26	168	51	F	+	-	-	+	Theodur/Alupent prn	2
3	30	160	58	F	+	-	-	+	Primatene prn	1
4	26	185	83	M	+	+[a]	±	+	None	3
5	43	173	72	F	-	-	-	+	Alupent prn	2
6	26	165	58	F	+	-	±	+	Vanceril	1
7	25	163	52	F	+	-	-	+	Intal, Theodur	1
8	39	165	60	F	+	-	-	-	Theodur, Metaprel	3
9	20	179	66	M	-	-	-	+	Ventolin prn	3
10	32	178	76	F	+	-	-	+	None	2
11	29	168	56	M	-	+[a]	-	+	None	1
12	21	160	54	F	+	-	-	+	Primatene prn	2
Mean	29.00	169.09	62.75	9F 3M	9(+) 3(-)	2(+) 10(-)	2(±) 10(-)	11(+) 1(-)	9(+) 3(-)	1.92
S.D.	±6.73	±7.98	±10.13							±0.79

[a]Past history only.

[1]Patient's subjective assessment of the amount of Dyspnea experienced during a typical asthmatic attack, i.e. 0 = nominal, 5 = extreme

Table 2

Comparison of Observed and Expected[1] Baseline Pulmonary Function Tests on the Screening Day

Subject	FVC Observed (L)	FVC Expected (L)	% Expected	FEV_1 Observed (L)	FEV_1 Expected (L)	% Expected	PEFR Observed (L/S)	PEFR Expected (L/S)	% Expected	$V_{max}50\%$ Observed (L/S)	$V_{max}50\%$ Expected (L/S)	% Expected	$MEF_{40\%}$ Observed (L/S)	$MEF_{40\%}$ (P) Observed (L/S)
1	4.07	3.65	111.51	3.25	2.99	108.70	7.57	5.90	128.31	3.79	3 99	94.99	2.75	3.12
2	3.58	3.55	100.85	2.58	3.06	84.31	5.73	5.59	102.50	2.28	4.07	56.02	1.74	1.66
3	3.48	3.39	102.65	3.14	2.82	111.35	6.12	5.56	110.07	4.22	3.88	108.76	3.46	3.45
4	6.60	5.55	118.92	4.71	4.47	105.37	9.43	8.79	107.28	4.36	5.37	81.19	3.42	3.32
5	2.51	3.77	66.58	1.47	2.96	49.66	3.52	5.98	58.86	1.04	3.73	27.88	0.83	0.95
6	3.42	3.58	95.53	2.41	3.03	79.54	4.62	5.73	80.63	2.38	4.06	58.62	1.73	1.24
7	4.24	3.42	123.98	3.22	2.94	109.52	5.38	5.49	98.00	2.71	4.03	67.25	2.10	1.98
8	3.68	3.46	106.36	2.39	2.80	85.36	4.13	5.58	74.01	1.57	3.76	41.76	1.16	0.64
9	5.29	4.77	110.90	3.35	4.04	82.92	5.42	7.81	69.40	2.08	5.30	39.25	1.65	1.79
10	3.93	4.30	91.40	3.11	3.38	92.01	4.92	6.54	75.23	2.78	3.99	69.67	2.15	2.77
11	5.08	4.26	119.25	3.65	3.49	104.58	7.74	7.21	107.35	2.77	4.42	62.67	2.30	2.43
12	3.77	3.31	113.90	2.77	2.89	95.85	4.77	5.44	87.68	2.30	4.03	57.07	1.81	1.99
Mean	4.14	3.92	105.15%	3.00	3.24	92.43%	5.78	6.30	91.61%	2.69	4.22	63.76%	2.09	2.11
S.D.	±1.07	±0.68	±15.63%	±0.79	±0.52	±17.69%	±1.70	±1.08	±20.49%	±1.01	±0.55	±23.07%	±0.80	±0.93
t-Test[2]		1.21			-1.50			-1.39			5.43***			

[1]Expected values: Schoenberg, J.B., et al: Growth and Decay of Pulmonary Function in Healthy Blacks and Whites. Respir. Physio, 33:367, 1978.

[2]Comparison of observed and expected values using paired two tailed student's t-test.

*** P <0.001

Table 3

Baseline and Post Exercise Pulmonary Function Tests on The Screening Day: FVC and FEV_1 (L)

Subject	FVC Baseline	FVC PEO'	% Baseline	FVC PE5'	% Baseline	FVC PBd	% Baseline	FEV_1 Baseline	FEV_1 PEO'	% Baseline	FEV_1 PE5'	% Baseline	FEV_1 PBd	% Baseline
1	4.07	3.88	95.33	3.68	90.42	4.01	98.53	3.25	3.07	94.46	2.80	86.15	3.41	104.92
2	3.58	3.54	98.88	3.31	92.46	3.65	101.96	2.58	2.71	105.04	2.38	92.25	3.02	117.05
3	3.48	3.51	100.86	3.35	96.26	3.28	94.25	3.14	3.14	100.00	3.05	97.13	3.05	97.13
4	6.60	6.85	103.79	6.81	103.18	7.11	107.73	4.71	4.92	104.46	4.85	102.97	5.37	114.01
5	2.51	3.21	127.89	2.31	92.03	3.09	123.11	1.47	1.94	131.97	1.29	87.76	1.87	127.21
6	3.42	3.59	104.97	3.14	91.81	3.55	103.80	2.41	2.61	108.30	2.07	85.89	2.81	116.60
7	4.24	4.27	100.71	4.23	99.76	4.32	101.89	3.22	3.32	103.11	3.12	96.89	3.36	104.35
8	3.68	3.85	104.62	3.63	98.64	3.90	105.98	2.39	2.64	110.46	2.20	92.05	2.71	113.39
9	5.29	5.18	97.92	5.07	95.84	5.17	97.73	3.35	3.31	98.81	3.11	92.84	3.46	103.28
10	3.93	3.61	91.86	3.41	86.77	3.96	100.76	3.11	2.67	85.85	2.70	86.82	3.12	100.32
11	5.08	5.04	99.21	5.00	98.43	5.08	100.00	3.65	3.43	93.97	3.18	87.12	3.78	103.56
12	3.77	3.78	100.27	3.76	99.73	3.88	102.92	2.77	2.66	96.03	2.54	91.70	3.04	109.75
Mean	4.14	4.19	102.19%	3.98	95.44%	4.25	103.22%	3.00	3.04	102.71%	2.77	91.63%	3.25	109.84%
S.D.	±1.07	±1.03	±8.92%	±1.18	±4.78%	±1.10	±7.24%	±0.79	±0.73	±11.49%	±0.85	±5.31%	±0.82	±8.81%
t-Test[1]		-0.74		2.90*		-1.68			-0.43		4.61***		-4.07**	

PEO' - Immediate Post Exercise
PE5' - 5 Minutes Post Exercise
PBd - Post Bronchodilator

[1]Comparison of all points to baseline using two tailed paired student's t-test.

* P < .05
** P < .01
*** P < .001

Table 4

Baseline and Post Exercise Pulmonary Function Tests on The Screening Day: PEFR and $MEF_{40\%}$ (L/S)

Subject	PEFR Baseline	PEFR PEO'	% Baseline	PEFR PE5'	% Baseline	PEFR PBd	% Baseline	$MEF_{40\%}$ Baseline	$MEF_{40\%}$ PEO'	% Baseline	$MEF_{40\%}$ PE5'	% Baseline	$MEF_{40\%}$ PBd	% Baseline
1	7.57	6.72	88.77	5.77	76.22	7.90	104.36	2.75	2.23	81.09	1.82	66.18	3.50	127.27
2	5.73	6.36	110.99	5.32	92.84	7.51	131.06	1.74	2.01	115.51	1.53	87.93	2.72	156.32
3	6.12	5.65	92.32	5.45	89.05	6.01	98.20	3.46	3.31	95.66	3.17	91.62	3.53	102.02
4	9.43	10.10	107.10	9.43	100.00	10.08	106.89	3.42	3.78	110.53	3.50	102.34	4.66	136.26
5	3.52	4.44	126.14	3.12	88.64	4.16	118.18	0.83	1.54	185.54	0.67	80.72	1.42	171.08
6	4.62	5.24	113.42	4.16	90.04	5.52	119.48	1.73	2.15	124.28	1.05	60.69	2.68	154.91
7	5.38	6.06	112.64	5.48	101.86	6.46	120.07	2.10	2.24	106.67	2.01	95.71	2.83	134.76
8	4.13	4.64	112.35	3.65	88.38	4.78	115.74	1.16	1.49	128.44	0.93	80.17	1.58	136.21
9	5.42	5.53	102.03	4.78	88.19	5.98	110.33	1.65	1.62	98.18	1.36	82.42	1.73	104.85
10	4.92	4.24	86.18	4.14	84.15	4.96	100.81	2.15	1.68	78.14	1.53	71.16	2.13	99.07
11	7.74	7.69	99.35	6.93	89.53	7.82	101.03	2.30	2.39	103.91	2.07	90.00	2.40	104.35
12	4.77	4.64	97.27	4.13	86.58	5.07	106.29	1.81	1.65	91.16	1.40	77.35	2.21	122.10
Mean	5.78	5.94	104.05%	5.20	89.62%	6.35	111.04%	2.09	2.17	109.93%	1.75	82.19%	2.62	129.10%
S.D.	±1.70	±1.66	±11.83%	±1.70	±6.69%	±1.70	±9.91%	±0.80	±0.72	±28.41%	±0.85	±12.22%	±0.93	±23.72%
t-Test[1]		-0.95		4.25**		-3.84**								

[1]Comparison of all points to baseline using two tailed paired student's t-test.

** $P < 0.01$

Table 5

Baseline and Post Exercise Pulmonary Function Tests on The Screening Day: $MEF_{40\%}(P)$ (L/S)

Subject	$MEF_{40\%}(P)$ Baseline	$MEF_{40\%}(P)$ PEO	% Baseline	$MEF_{40\%}(P)$ PE5	% Baseline	$MEF_{40\%}(P)$ PBd	% Baseline
1	3.12	2.20	70.51	1.95	62.50	4.80	153.85
2	1.66	2.36	142.17	1.42	85.54	3.51	211.45
3	3.45	2.93	84.93	2.72	78.84	2.77	80.29
4	3.32	2.93	88.25	2.38	71.69	5.36	161.45
5	0.95	1.93	203.16	0.58	61.05	2.18	229.47
6	1.24	1.74	140.32	0.83	66.94	3.30	266.13
7	1.98	2.23	112.63	1.63	82.32	3.06	154.55
8	0.64	1.12	175.00	0.50	78.13	1.09	170.31
9	1.79	1.65	92.18	1.25	69.83	1.80	100.56
10	2.77	2.16	77.98	1.88	67.87	3.40	122.74
11	2.43	2.60	107.00	1.84	75.72	2.85	117.28
12	1.99	1.27	63.82	1.14	57.29	2.40	120.60
Mean	2.11	2.09	113.16%	1.51	71.48%	3.04	157.39%
S.D.	±0.93	±0.58	±43.58%	±0.69	±8.84%	±1.19	±55.17%
t-Test[1]		0.10		6.59***		-3.71**	

[1]Comparison of all points to baseline using two tailed paired student's t-test.

** P < 0.01
*** P < 0.001

Baseline Post Inhalation and Post Exercise Pulmonary Function Tests on the Antihistamine Day: FVC (L)

Subject	Baseline	PAH0'	% Baseline	PAH10'	% Baseline	PAH30'	% Baseline	PE0'	% Baseline	PE5'	% Baseline	PBd	% Baseline
1	3.64	3.59	98.63	3.77	103.57	3.85	105.77	3.80	104.40	3.69	101.37	3.94	108.24
2	3.21	2.55	79.44	2.76	85.98	3.20	99.69	3.48	108.41	3.24	100.93	3.42	106.54
3	3.58	3.17	88.55	3.55	99.16	3.17	88.55	3.19	89.11	3.28	91.62	3.20	89.39
4	5.81	5.42	93.29	5.74	98.80	5.96	102.58	6.15	105.85	5.75	98.97	5.99	103.10
5	2.70	2.71	100.37	2.87	106.30	2.94	108.89	3.33	123.33	2.52	93.33	3.26	120.74
6	3.48	3.51	100.86	3.44	98.85	3.60	103.45	3.70	106.32	3.32	95.40	3.70	106.32
7	4.16	3.88	93.27	4.11	98.80	4.08	98.08	4.02	96.63	3.99	95.91	4.19	100.72
8	3.66	3.12	85.25	3.26	89.07	3.55	96.99	3.49	95.36	3.26	89.07	3.20	87.43
9	4.99	4.16	83.37	4.54	90.98	4.86	97.39	4.80	96.19	5.08	101.80	5.12	102.61
10	4.19	3.48	83.05	4.02	95.94	3.57	85.20	3.67	87.59	3.80	90.69	4.24	101.19
11	4.84	4.77	98.55	4.62	95.45	4.76	98.35	4.78	98.76	4.76	98.35	4.81	99.38
12	3.86	3.93	101.81	4.19	108.55	3.85	99.74	3.78	97.93	3.74	96.89	3.75	97.15
Mean	4.01	3.69	92.20%	3.91	97.62%	3.95	98.72%	4.02	100.82%	3.87	96.19%	4.07	101.90%
S.D.	±0.86	±0.82	±8.00%	±0.83	±6.72%	±0.86	±6.63%	±0.84	±9.66%	±0.91	±4.31%	±0.86	±8.71%
t-Test[1] Baseline		3.48**		1.45		0.84		-0.06		3.02*		-0.72	
All → Pl t-Test[2]	-2.36*	-0.33	1.54	-1.74	0.60	-1.98	0.47	-2.12	0.24	-2.37*	-0.05	-1.06	1.28
Sc → All t-Test[3]	1.44							2.49*		1.00		1.62	

PAH0' - Immediate Post Inhalation
PAH10' - 10 Minutes Post Inhalation
PAH30' - 30 Minutes Post Inhalation

PE0' - Immediate Post Exercise
PE5' - 5 Minutes Post Exercise
PBd - Post Bronchodilator

[1]Comparison of all points to baseline using two tailed paired student's t-test.
[2]Comparison of equivalent points on antihistamine and placebo days using two tailed paired student's t-test.
[3]Comparison of equivalent points on antihistamine and screening days using two tailed paired student's t-test.

* $P < 0.05$
** $P < 0.01$

Table 7

Baseline, Post Inhalation and Post Exercise Pulmonary Function Tests on the Placebo Day: FVC (L)

Subject	Baseline	PAH0'	% Baseline	PAH10'	% Baseline	PAH30'	% Baseline	PE0'	% Baseline	PE5'	% Baseline	PBd	% Baseline
1	3.47	3.49	100.58	3.62	104.32	3.69	106.34	3.49	100.58	3.26	93.95	3.87	111.53
2	3.31	3.09	93.35	3.19	96.37	3.04	91.84	3.24	97.89	2.56	77.34	3.27	98.79
3	3.37	3.15	93.47	3.53	104.75	3.39	100.59	3.18	94.36	3.47	102.97	3.29	97.63
4	5.88	5.39	91.67	5.28	89.90	5.18	88.10	5.78	98.30	5.26	89.46	5.58	94.90
5	2.82	2.42	85.82	2.57	91.13	2.72	96.45	2.90	102.84	2.61	92.55	3.21	113.83
6	2.98	3.11	104.36	3.34	112.08	3.54	118.79	3.42	114.77	3.06	102.68	3.64	122.15
7	4.06	4.07	100.25	3.98	98.03	4.07	100.25	4.09	100.74	4.02	99.01	4.06	100.00
8	2.68	2.32	86.57	2.55	95.15	2.74	102.23	2.73	101.87	2.53	94.40	3.47	129.48
9	4.42	4.27	96.61	4.52	102.26	4.46	100.90	4.98	112.67	4.59	103.85	4.94	111.76
10	4.02	4.07	101.24	4.13	102.74	3.78	94.03	3.94	98.01	3.93	97.76	3.86	96.02
11	4.65	4.73	101.72	4.65	100.00	4.78	102.80	4.65	100.00	4.71	101.29	4.84	104.09
12	3.83	3.74	97.65	3.63	94.78	3.73	97.39	3.69	96.34	3.73	97.39	4.01	104.70
Mean	3.79	3.65	96.11%	3.75	99.29%	3.76	99.98%	3.84	101.53%	3.64	96.05%	4.00	107.07%
S.D.	±0.90	±0.91	±6.01%	±0.82	±6.34%	±0.77	±7.81%	±0.91	±6.18%	±0.90	±7.43%	±0.75	±10.91%
t-Test[1] Baseline		2.32*		0.58		0.35		-0.76		1.81		-2.15	
Sc→ Pl t-Test[2]	2.97*							3.07*		1.96		1.92	

[1]Comparison of all points to baseline using two tailed paired student's t-test.
[2]Comparison of equivalent points on placebo and screening days using two tailed paired student's t-test.

* $P < 0.05$

Table 8

Baseline, Post Inhalation and Post Exercise Pulmonary Function Tests on Antihistamine Day: FEV_1 (L)

Subject	Baseline	PAH0'	% Baseline	PAH10'	% Baseline	PAH30'	% Baseline	PE0'	% Baseline	PE5'	% Baseline	PBd	% Baseline
1	2.85	2.85	100.00	3.05	107.02	3.17	111.23	3.07	107.72	3.00	105.26	3.35	117.54
2	2.27	1.68	74.01	1.80	79.30	2.32	102.20	2.76	121.59	2.34	103.08	2.60	114.54
3	3.17	2.84	89.59	3.00	94.64	2.89	91.17	2.97	93.67	3.07	96.85	3.00	94.64
4	4.24	3.98	93.87	4.30	101.42	4.48	105.66	4.39	103.54	4.13	97.41	4.70	110.85
5	1.54	1.63	105.84	1.68	109.09	1.74	112.99	2.04	132.47	1.45	94.16	2.08	135.06
6	2.69	2.71	100.74	2.75	102.23	3.04	113.01	3.03	112.64	2.26	84.01	3.00	111.52
7	3.08	2.89	93.83	3.04	98.70	3.16	102.60	3.10	100.65	3.04	98.70	3.34	108.44
8	2.29	2.06	89.96	1.98	86.46	2.38	103.93	2.52	110.04	2.20	96.07	2.38	103.93
9	2.66	1.97	74.06	2.38	89.47	2.77	104.14	2.92	109.77	3.03	113.91	3.44	129.32
10	3.50	2.58	73.71	3.02	86.29	2.76	78.86	2.72	77.71	2.80	80.00	3.32	94.86
11	3.26	3.40	104.29	3.34	102.45	3.72	114.11	3.73	114.42	3.63	111.35	3.78	115.95
12	2.64	2.76	104.55	2.91	110.23	2.89	109.47	2.84	107.58	2.93	110.98	3.36	127.27
Mean	2.85	2.62	92.04%	2.77	97.28%	2.94	104.11%	3.01	107.65%	2.82	99.32%	3.20	113.66%
S.D.	±0.68	±0.69	±12.20%	±0.73	±10.01%	±0.69	±10.23%	±0.59	±13.65%	±0.70	±10.44%	±0.68	±12.65%
t-Test[1] Baseline		2.38*		1.05		-1.01		-1.53		0.28		-3.89**	
All → P1 t-Test[2]	-1.88	-0.89	0.77	-1.46	0.79	-2.67*	-0.26	-2.47*	0.02	-3.30**	-0.99	-4.15**	0.96
Sc → All t-Test[3]	1.70							0.35		-0.57		0.65	

[1]Comparison of all points to baseline using two tailed paired student's t-test.
[2]Comparison of equivalent points on antihistamine and placebo days using two tailed paired student's t-test.
[3]Comparison of equivalent points on antihistamine and screening days using two tailed paired student's t-test.

* $P < 0.05$
** $P < 0.01$

Baseline, Post Inhalation and Post Exercise Pulmonary Function Tests on the Placebo Day: FEV_1 (L)

Subject	Baseline	PAH0'	% Baseline	PAH10'	% Baseline	PAH30'	% Baseline	PE0'	% Baseline	PE5'	% Baseline	PBd	% Baseline
1	2.68	2.70	100.75	2.88	107.46	2.88	107.46	2.60	97.01	2.40	89.55	3.15	117.54
2	2.44	2.23	91.39	2.36	96.72	2.20	90.16	2.49	102.05	1.74	71.31	2.58	105.74
3	2.90	2.85	98.28	3.09	106.55	2.94	101.38	2.96	102.07	3.03	104.48	2.97	102.41
4	4.23	3.75	88.65	3.70	87.47	3.74	88.42	4.14	97.87	3.65	86.29	4.29	101.42
5	1.64	1.46	89.02	1.54	93.90	1.57	95.73	1.67	101.83	1.30	79.27	1.99	121.34
6	1.85	1.98	107.03	2.27	122.70	2.63	142.16	2.49	134.59	2.01	108.65	2.85	154.05
7	3.04	3.00	98.68	3.02	99.34	3.12	102.63	3.07	100.99	3.02	99.34	3.26	107.24
8	1.11	0.98	88.29	1.03	92.79	1.12	100.90	1.37	123.42	1.04	93.69	1.98	178.38
9	2.21	2.14	96.83	2.43	109.95	2.45	110.86	2.97	134.39	2.45	110.86	3.37	152.49
10	3.01	3.03	100.66	3.08	102.36	2.88	95.68	2.98	99.00	2.97	98.67	3.02	100.33
11	3.49	3.27	93.70	3.34	95.70	3.44	98.57	3.48	99.71	3.53	101.15	3.72	106.59
12	2.76	2.57	93.12	2.53	91.67	2.82	102.17	2.77	100.36	2.60	94.20	2.95	106.88
Mean	2.61	2.50	95.53%	2.61	100.55%	2.65	103.01%	2.75	107.77%	2.48	94.79%	3.01	121.20%
S.D.	±0.84	±0.78	±5.83%	±0.76	±9.82%	±0.74	±13.90%	±0.73	±14.24%	±0.83	±11.73%	±0.65	±25.89%
t-Test[1]		2.57*		0.10		-0.41		-1.69		1.60		-3.49**	
Baseline Sc → Pl t-Test[2]	3.06*							2.37*		1.98		2.38*	

[1]Comparison of all points to baseline using two tailed paired student's t-test.
[2]Comparison of equivalent points on placebo and screening days using two tailed paired student's t-test.

* $P < 0.05$
** $P < 0.01$

Table 10

Baseline, Post Inhalation and Post Exercise Pulmonary Function Tests on the Antihistamine Day: PEFR (L/S)

Subject	Baseline	PAH0'	% Baseline	PAH10'	% Baseline	PAH30'	% Baseline	PE0'	% Baseline	PE5'	% Baseline	PBd	% Baseline
1	6.77	6.55	96.75	6.77	100.00	7.39	109.16	7.27	107.39	6.68	98.67	8.33	123.04
2	5.50	3.68	66.91	3.95	71.82	5.04	91.64	6.35	115.45	4.77	86.73	5.68	103.27
3	5.46	4.96	90.84	5.24	95.97	5.10	93.41	5.32	97.44	5.52	101.10	5.95	108.97
4	8.97	8.53	95.09	8.83	98.44	8.82	93.33	9.96	111.04	8.46	94.31	9.33	104.01
5	3.78	3.78	100.00	3.88	102.65	4.19	110.85	4.67	123.54	3.28	86.77	4.76	125.93
6	5.19	5.11	98.46	5.25	101.16	5.91	113.87	6.08	117.15	4.73	91.14	5.86	112.91
7	5.78	5.42	93.77	5.64	97.58	6.20	107.27	5.89	101.90	5.78	100.00	6.50	112.46
8	4.42	3.71	83.94	3.48	78.73	4.38	99.10	4.80	108.60	3.91	88.46	4.60	104.07
9	4.15	3.17	76.39	3.75	90.36	4.53	109.16	4.79	115.42	5.03	121.20	6.08	146.51
10	4.63	3.91	84.45	4.68	101.08	4.06	87.69	4.44	95.90	4.31	93.09	5.38	116.20
11	6.29	6.49	103.18	6.75	107.31	7.28	115.74	7.13	113.35	6.71	106.68	7.23	114.94
12	4.08	3.84	94.12	3.89	95.34	3.96	97.06	4.25	104.17	4.60	112.75	5.16	126.47
Mean	5.42	4.93	90.33%	5.18	95.04%	5.57	102.36%	5.91	109.28%	5.32	98.41%	6.24	116.57%
S.D.	±1.45	±1.60	±10.59%	±1.61	±10.24%	±1.57	±9.68%	±1.63	±8.34%	±1.42	±10.75%	±1.42	±12.45%
t-Test[1] Baseline		3.17**		1.58		-1.05		-4.05**		0.72		-5.38***	
All → Pl t-Test[2]	-1.00	-0.30	1.58	-0.54	1.25	-1.22	0.51	-1.98	-0.09	-2.53*	-1.00	-1.82	0.94
Sc → All t-Test[3]	1.91							0.23		-0.82	-2.29*	0.60	

[1]Comparison of all points to baseline using two tailed paired student's t-test.
[2]Comparison of equivalent points on antihistamine and placebo days using two tailed paired student's t-test.
[3]Comparison of equivalent points on antihistamine and screening day using two tailed paired student's t-test.

* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$

Baseline, Post Inhalation and Post Exercise Pulmonary Function Tests on the Placebo Day: PEFR (L/S)

Subject	Baseline	PAH0'	% Baseline	PAH10'	% Baseline	PAH30'	% Baseline	PE0'	% Baseline	PE5'	% Baseline	PBd	% Baseline
1	5.95	5.79	97.31	6.27	105.38	6.37	107.06	5.76	96.81	5.23	87.90	7.41	124.54
2	6.51	5.19	79.72	5.91	90.78	5.63	86.48	6.44	98.92	4.21	64.67	6.52	100.15
3	4.98	5.11	102.61	5.22	104.82	5.59	112.25	5.38	108.03	5.38	108.03	5.46	109.64
4	9.40	8.50	90.43	8.13	86.49	8.49	90.32	9.23	98.19	7.78	82.77	9.22	98.09
5	3.88	3.53	90.98	3.71	95.62	3.87	99.74	4.03	103.87	3.03	78.09	4.66	120.10
6	3.76	3.86	102.66	4.54	120.74	5.20	138.30	5.05	134.31	4.24	112.77	5.66	150.53
7	5.78	5.70	98.62	5.78	100.00	6.17	106.75	5.96	103.11	5.81	100.52	6.38	110.38
8	1.90	1.65	86.84	1.73	91.05	1.81	95.26	2.26	118.95	1.78	93.68	3.39	178.42
9	3.38	3.30	97.63	3.84	113.61	3.91	115.68	5.02	148.52	3.79	112.13	5.84	172.78
10	4.79	4.82	100.62	5.00	104.38	4.72	98.54	4.72	98.54	4.78	99.79	5.00	104.38
11	6.65	6.56	98.65	6.34	95.34	6.61	99.40	6.73	101.20	6.94	104.36	7.18	107.97
12	4.64	4.16	89.66	4.01	86.42	4.60	99.14	4.45	95.91	4.29	92.46	4.99	107.54
Mean	5.14	4.85	94.64%	5.04	99.55%	5.25	104.08%	5.42	108.86%	4.77	94.76%	5.98	123.71%
S.D.	±1.93	±1.83	±7.08%	±1.64	±10.69%	±1.68	±13.69%	±1.69	±16.71%	±1.63	±14.56%	±1.51	±27.97%
t-Test[1] Baseline		2.31*		0.59		-0.61		-1.66		1.44		-3.60**	
Sc → Pl t-Test[2]	2.24*							2.50*		1.83	-1.08	2.43*	-1.56

[1]Comparison of all points to baseline using two tailed paired student's t-test.
[2]Comparison of equivalent points on placebo and screening days using two tailed paired student's t-test.

* $P < 0.05$
** $P < 0.01$

Baseline, Post Inhalation and Post Exercise Pulmonary Function Tests on the Antihistamine Day: $MEF_{40\%}$ (L/S)

Subject	Baseline	PAH0'	% Baseline	PAH10'	% Baseline	PAH30'	% Baseline	PE0'	% Baseline	PE5'	% Baseline	PBd	% Baseline
1	2.57	2.49	96.89	2.93	114.01	3.54	137.74	3.20	124.51	2.76	107.39	4.22	164.20
2	1.63	0.84	51.53	0.90	55.21	1.72	105.52	2.54	155.83	1.67	102.45	2.11	121.45
3	3.14	2.29	72.93	3.06	97.45	2.67	85.03	2.64	84.08	2.98	94.90	3.39	107.96
4	3.30	2.59	78.48	3.37	102.12	3.87	117.27	4.48	135.76	2.73	82.73	4.22	127.88
5	0.98	1.04	106.12	1.15	117.35	1.21	123.47	1.69	172.45	0.78	79.59	1.68	171.43
6	2.40	2.36	98.33	2.53	105.42	3.35	139.58	3.34	139.17	1.41	58.75	3.32	138.33
7	2.09	1.65	78.95	2.06	98.56	2.15	102.87	2.10	100.48	2.00	95.69	2.60	124.40
8	0.99	0.72	72.73	0.56	56.57	1.13	114.14	1.33	134.34	0.82	82.83	0.96	96.97
9	1.03	0.46	44.66	0.74	71.84	1.10	106.80	1.29	125.24	1.46	141.75	1.86	180.58
10	2.03	0.99	48.77	1.73	85.22	1.60	78.82	1.17	57.64	1.42	69.95	2.29	112.81
11	1.94	1.91	98.45	2.09	107.73	2.45	126.29	2.50	128.87	2.17	111.86	2.49	128.35
12	1.53	1.90	124.18	2.05	133.99	1.94	126.80	1.93	126.14	1.92	125.49	2.75	179.74
Mean	1.97	1.60	81.00%	1.93	95.46%	2.23	113.69%	2.35	123.71%	1.84	96.12%	2.66	137.84%
S.D.	±0.79	±0.76	±24.73%	±0.94	±24.14%	±0.96	±18.97%	±0.98	±30.77%	±0.72	±23.49%	±0.99	±28.97%

Table 13

Baseline, Post Inhalation and Post Exercise Pulmonary Function Tests on the Placebo Day: $MEF_{40\%}$ (L/S)

Subject	Baseline	PAH0'	% Baseline	PAH10'	% Baseline	PAH30'	% Baseline	PE0'	% Baseline	PE5'	% Baseline	PBd	% Baseline
1	2.27	2.28	100.44	2.79	122.91	2.87	126.43	1.96	86.34	1.65	72.69	3.57	157.27
2	1.80	1.30	72.22	1.69	93.89	0.96	53.33	1.99	110.56	0.72	40.00	1.94	107.78
3	2.63	2.51	95.44	3.21	122.05	2.96	112.55	2.92	111.03	3.05	115.97	3.12	118.63
4	3.10	2.10	67.74	1.97	63.55	2.03	65.48	3.03	97.74	2.03	65.48	3.20	103.23
5	1.00	0.78	78.00	0.84	84.00	0.96	96.00	1.03	103.00	0.48	48.00	1.59	159.00
6	1.03	1.24	120.39	1.87	181.55	2.85	276.70	2.59	251.46	1.28	124.27	3.54	343.69
7	2.07	1.98	95.65	2.02	97.58	2.25	108.70	2.19	105.80	2.05	99.03	2.52	121.74
8	0.38	0.22	57.89	0.25	65.79	0.36	94.74	0.48	126.32	0.28	73.68	1.16	305.26
9	0.79	0.68	86.08	0.97	122.78	1.04	131.65	1.66	210.13	1.04	131.65	2.14	270.89
10	1.82	1.95	107.14	2.06	113.19	1.64	90.11	1.83	100.55	1.76	96.70	1.81	99.45
11	2.16	2.05	94.91	1.94	89.81	2.20	101.85	2.15	99.54	2.14	99.07	2.56	118.52
12	1.88	1.37	72.87	1.41	75.00	1.95	103.72	1.55	82.45	1.58	84.04	2.76	146.81
Mean	1.74	1.54	87.40%	1.75	102.68%	1.84	113.44%	1.95	123.74%	1.51	87.55%	2.49	171.02%
S.D.	±0.80	±0.72	±18.16%	±0.81	±32.75%	±0.86	±56.02%	±0.73	±52.02%	±0.79	±28.90%	±0.78	±85.48%

Baseline, Post Inhalation and Post Exercise Pulmonary Function Tests on the Antihistamine Day: $MEF_{40\%}$(P) (L/S)

Subject	Baseline	PAH0'	% Baseline	PAH10'	% Baseline	PAH30'	% Baseline	PE0'	% Baseline	PE5'	% Baseline	PBd	% Baseline
1	2.65	2.90	109.43	3.60	135.85	4.36	164.52	3.53	133.21	2.68	101.13	5.33	201.13
2	1.75	0.83	47.43	0.90	51.43	1.74	99.43	3.07	175.43	1.55	88.57	2.23	127.43
3	2.95	1.60	54.24	2.70	91.53	2.74	92.88	2.10	71.19	2.58	87.46	3.22	109.15
4	3.11	2.55	81.99	3.34	107.40	4.03	129.58	4.37	140.51	2.30	73.95	4.99	160.45
5	1.23	1.20	97.56	1.43	116.26	1.73	140.65	2.14	173.98	0.81	65.85	2.30	186.99
6	2.52	2.04	80.95	2.87	113.89	3.85	152.78	3.60	142.86	1.08	42.86	3.84	152.38
7	1.22	0.96	78.69	1.15	94.26	1.49	122.13	1.48	121.31	1.20	98.36	2.15	176.23
8	0.87	0.55	63.22	0.33	37.93	0.95	109.20	1.16	133.33	0.67	77.01	0.79	90.80
9	0.96	0.36	37.50	0.60	62.50	1.07	111.46	1.23	128.13	1.34	139.58	1.98	206.25
10	2.25	1.24	55.11	2.09	92.89	1.43	63.56	1.31	58.22	1.70	75.56	2.50	111.11
11	1.93	2.03	105.18	2.28	118.13	2.59	134.20	2.65	137.31	2.42	125.39	2.83	146.63
12	1.13	1.59	140.71	1.67	147.79	1.85	163.72	1.78	157.52	1.69	149.56	2.91	257.52
Mean	1.88	1.49	79.33%	1.91	97.49%	2.32	123.68%	2.37	131.08%	1.67	93.77%	2.92	160.51%
S.D.	±0.80	±0.78	±30.04%	±1.08	±33.18%	±1.19	±30.25%	±1.07	±35.40%	±0.69	±31.23%	±1.28	±48.05%
t-Test[1] Baseline		2.53*		-0.22		-2.20*		-2.28*		1.29		-4.58**	
P1 → All t-Test[2]	-1.09	-0.49	0.32	-1.23	0.57	-3.02*	-0.06	-2.95*	0.06	-3.21**	-0.80	-2.02	1.03
Sc → All t-Test[3]	1.30							-1.03	-1.53	-1.61	-2.30*	0.66	-0.14

[1]Comparison of all points to baseline using two tailed paired student's t-test.
[2]Comparison of equivalent points on antihistamine and placebo days using two tailed paired student's t-test.
[3]Comparison of equivalent points on antihistamine and screening days using two tailed paired student's t-test.

* P < 0.05
** P < 0.01
*** P < 0.001

Table 15

Baseline, Post Inhalation and Post Exercise Pulmonary Function Tests on the Placebo Day: $MEF_{40\%}$ (P) (L/S)

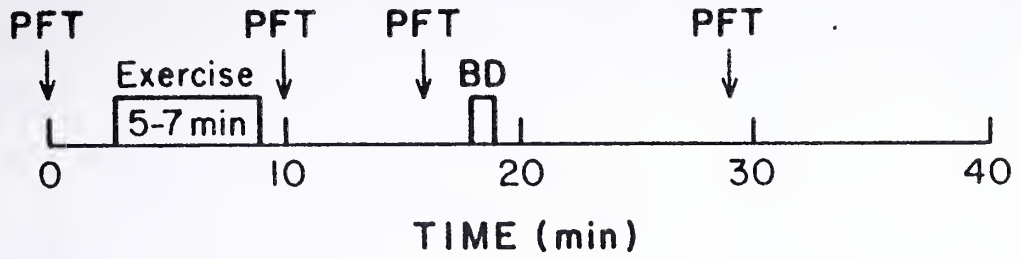
Subject	Baseline	PAH0'	% Baseline	PAH10'	% Baseline	PAH30'	% Baseline	PE0'	% Baseline	PE5'	% Baseline	PBd	% Baseline
1	2.68	2.82	105.22	3.35	125.00	3.45	128.73	2.03	75.75	1.73	64.55	4.53	169.03
2	1.91	1.30	68.06	1.63	85.34	1.00	52.36	2.00	104.71	0.63	32.98	2.19	114.66
3	1.98	1.34	67.63	2.52	127.27	2.44	123.23	2.07	104.55	2.38	120.20	2.63	132.83
4	2.83	1.93	68.20	1.92	67.84	2.06	72.79	2.98	105.30	1.88	66.43	3.58	126.50
5	1.07	0.81	75.70	1.01	94.39	1.18	110.28	1.40	130.84	0.52	48.60	2.06	192.52
6	0.80	0.98	122.50	1.83	228.75	3.07	383.75	2.72	340.00	1.07	133.75	4.32	540.00
7	1.37	1.13	82.48	1.34	97.81	1.65	120.44	1.46	106.57	1.20	87.59	2.03	148.18
8	0.18	0.10	55.56	0.11	61.11	0.16	88.89	0.28	155.56	0.13	72.22	0.86	477.78
9	0.75	0.60	80.00	0.87	116.00	0.95	126.67	1.62	216.00	0.92	122.67	2.02	269.33
10	2.21	2.40	108.60	2.46	111.31	1.62	73.30	1.53	69.23	1.82	82.35	2.00	90.50
11	2.38	2.27	95.38	2.18	91.60	2.43	102.10	2.40	100.84	2.43	102.10	2.95	123.95
12	1.91	1.18	61.78	1.21	63.35	1.63	85.34	1.52	79.58	1.42	74.35	2.39	125.13
Mean	1.67	1.41	82.59%	1.70	105.81%	1.80	122.32%	1.83	132.41%	1.34	83.98%	2.63	209.20%
S.D.	±0.83	±0.80	±20.90%	±0.87	±44.86%	±0.94	±85.92%	±0.71	±76.61%	±0.73	±30.75%	±1.06	±147.96%
t-Test[1]		2.49*		-0.19		-0.54		-0.80		2.13		-3.48**	
Baseline Sc → Pl t-Test[2]	3.17**							1.68	-0.91	1.49	-1.35	1.78	-1.40

[1]Comparison of all points to baseline using two tailed paired student's t-test.
[2]Comparison of equivalent points on placebo and screening days using paired two tailed student's t-test.

* P <0.05
** P <0.01

SCHEMATIC REPRESENTATION OF EXPERIMENTAL PROTOCOL

SCREENING DAY



PFT = Pulmonary Function Tests
BD = Bronchodilator

PROTOCOL DAYS

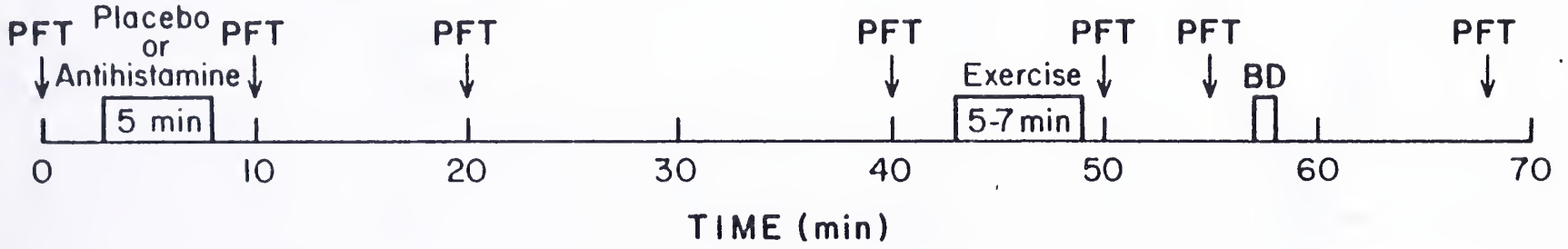


FIGURE 1

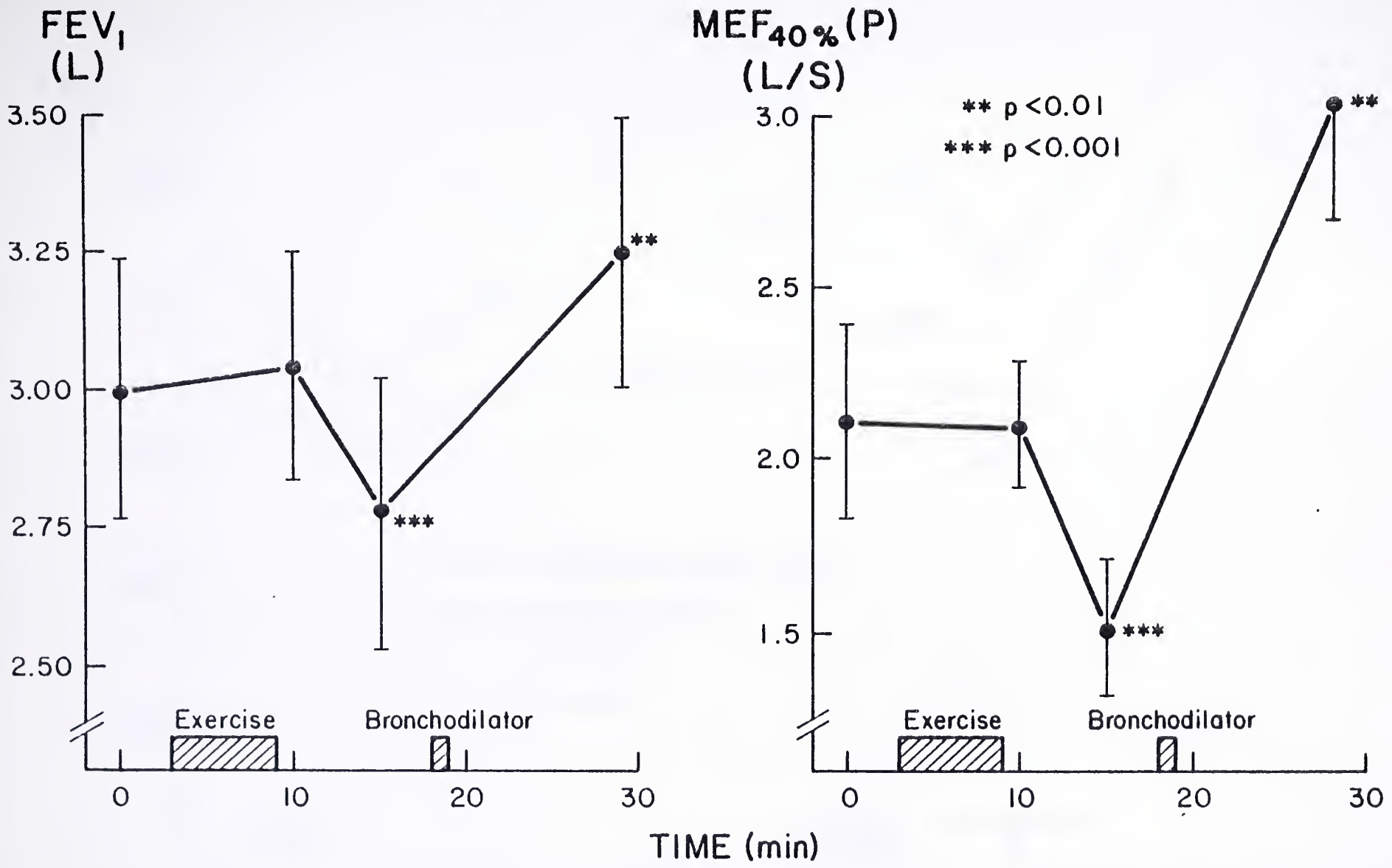
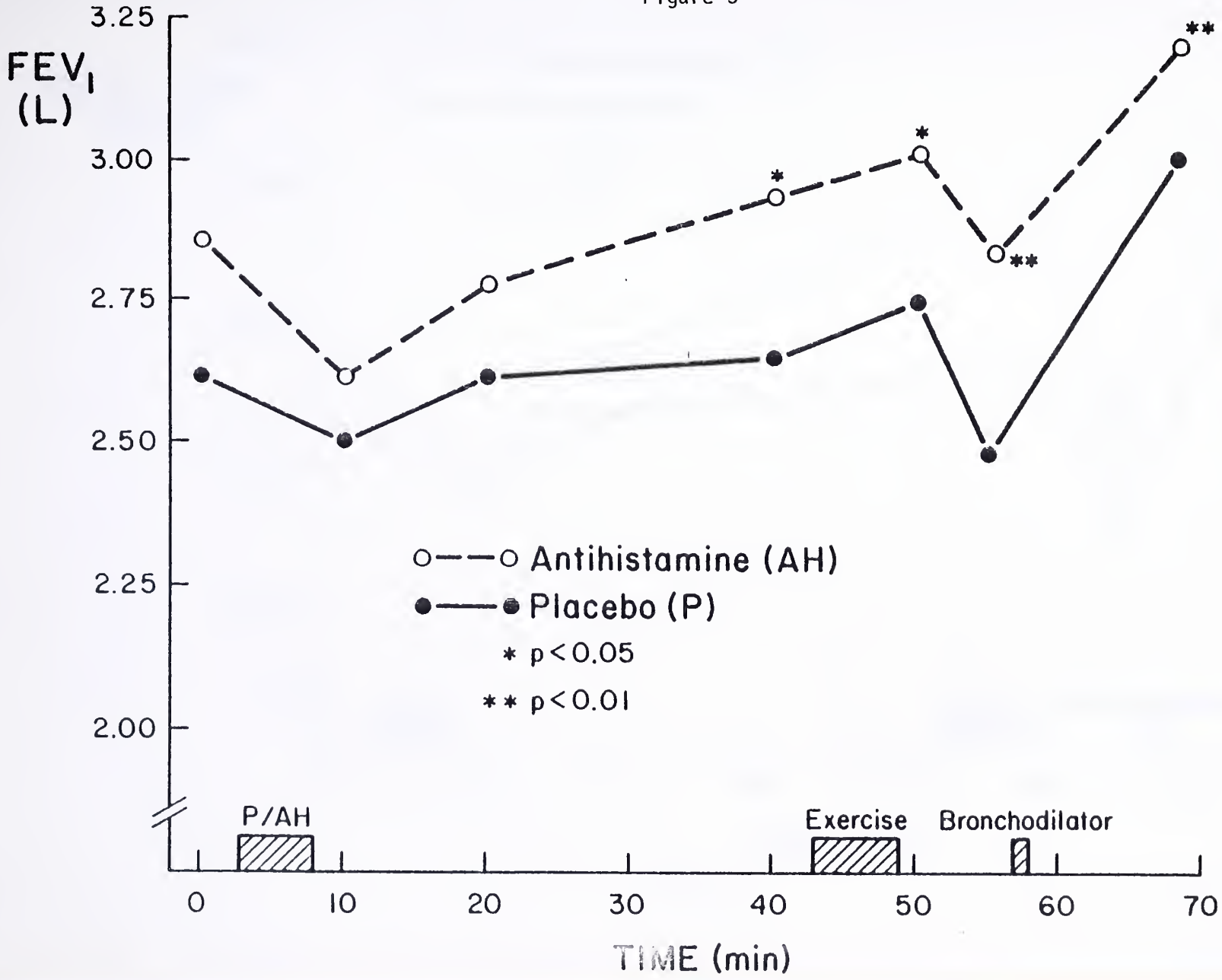

CHANGES IN FEV1 AND MEF40%(P) FOLLOWING EXERCISE ON THE SCREENING DAY (mean±S.E.)
FEV1 (L)
3.50
3.25
3.00
2.75
2.50
**
***
Exercise
Bronchodilator
0
10
20
30
MEF40%(P) (L/S)
** p <0.01
*** p <0.001
3.0
2.5
2.0
1.5
**
***
Exercise
Bronchodilator
0
10
20
30
TIME (min)

Figure 2

AND DRUG INHALATION ON PROTOCOL DAYS

Figure 3



CHANGES IN $MEF_{40\%}(P)$ FOLLOWING EXERCISE AND DRUG INHALATION ON PROTOCOL DAYS

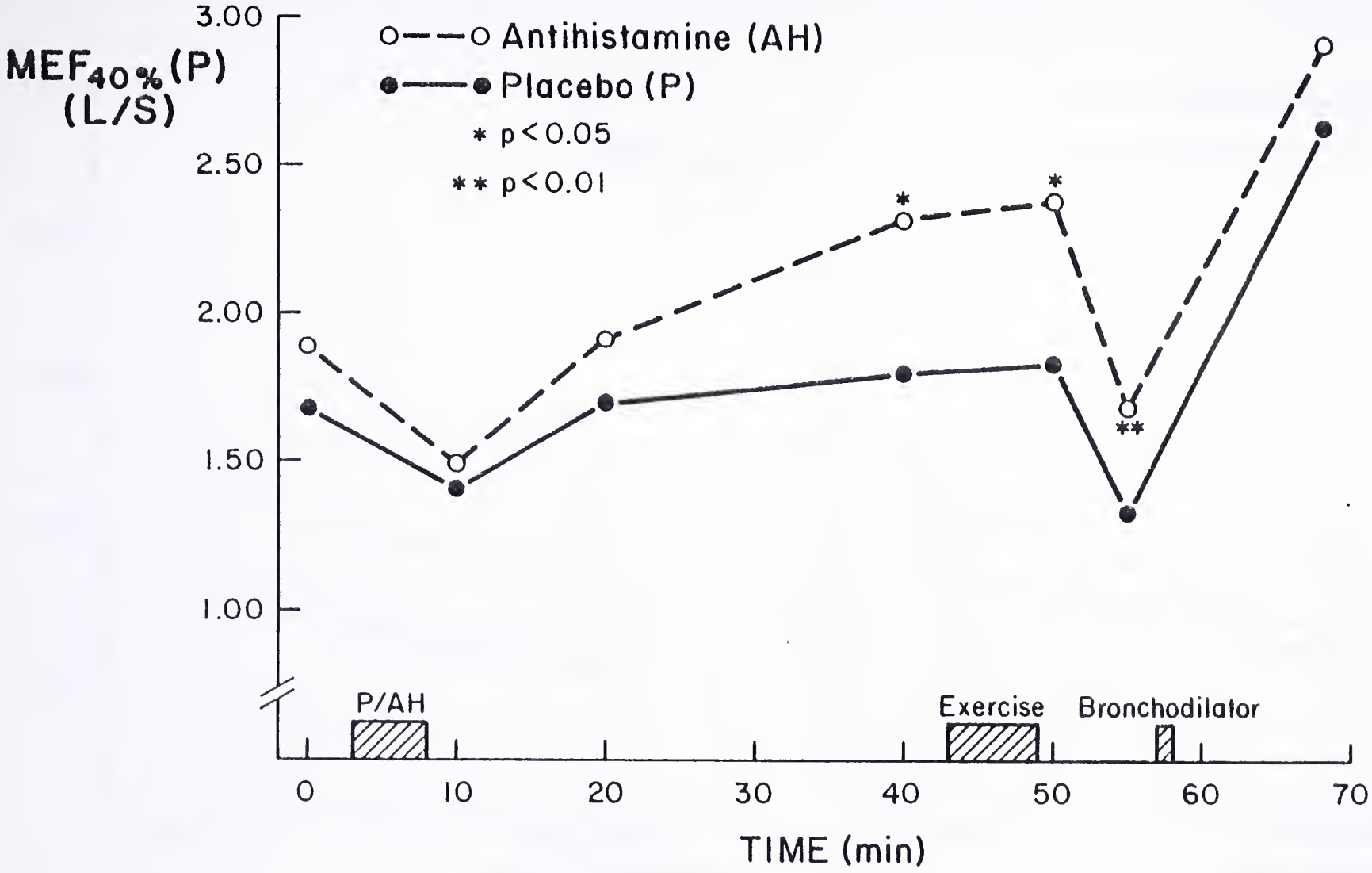
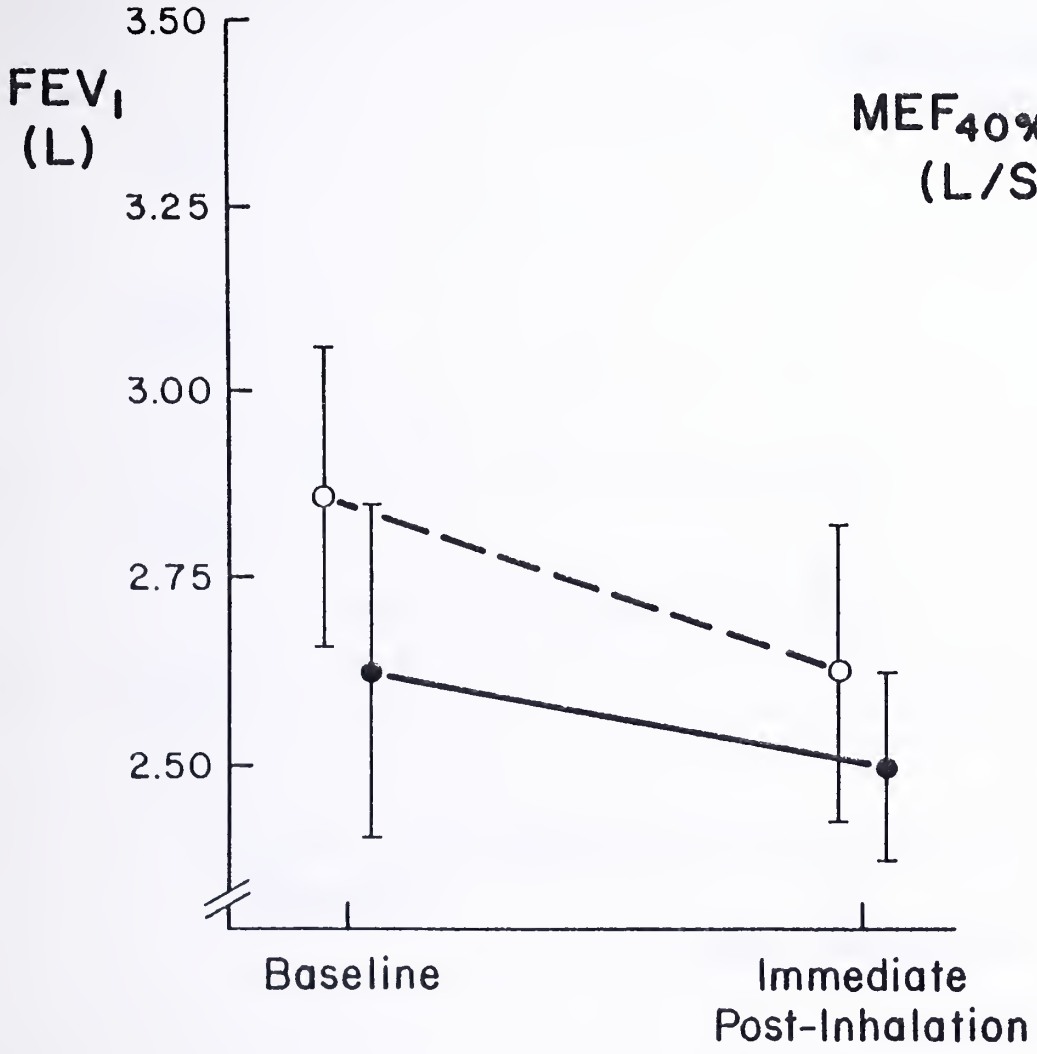
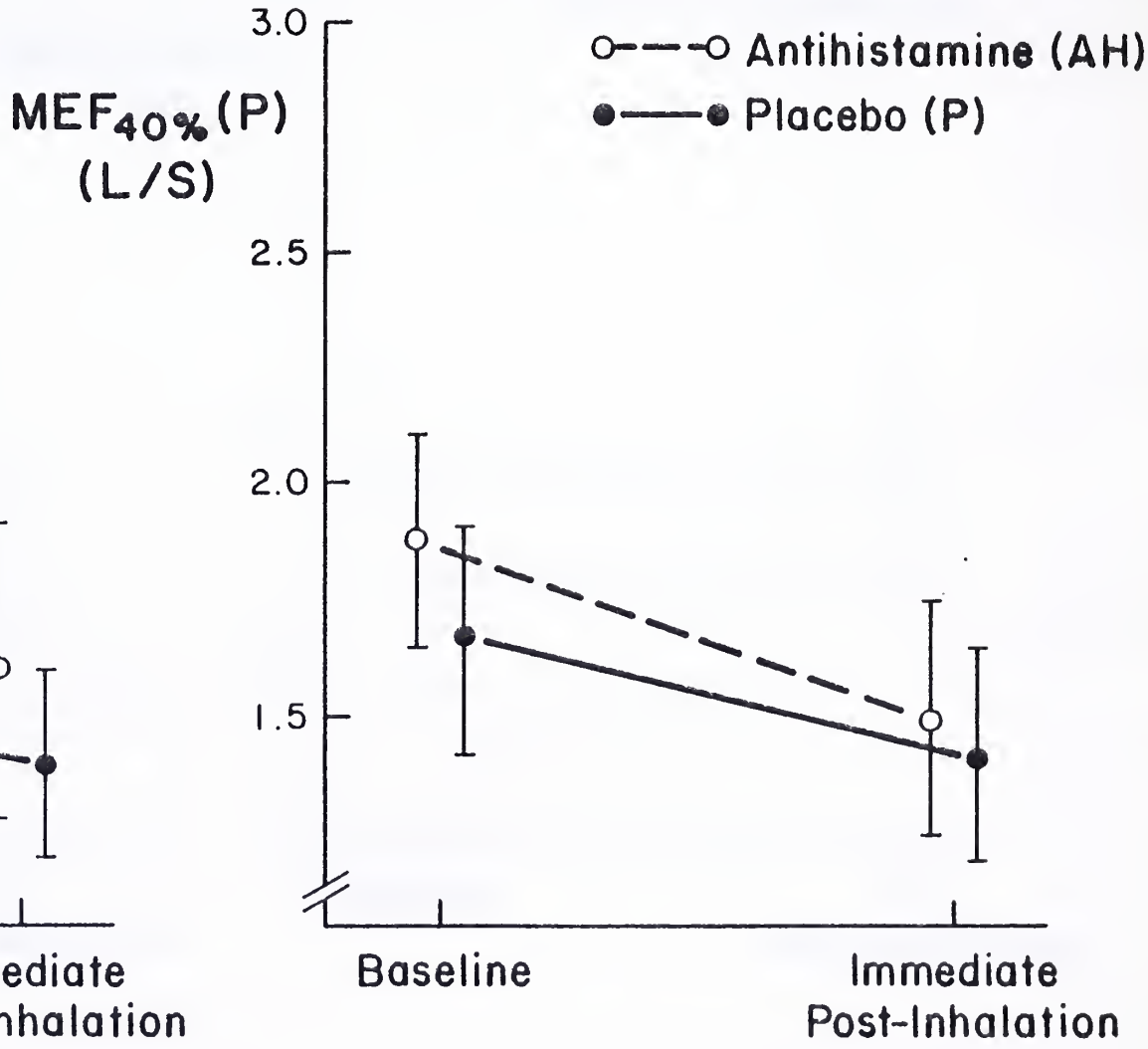


Figure 4

CHANGES IN FEV_1 AND $MEF_{40\%}(P)$ IMMEDIATELY POST-INHALATION OF DRUGS ON PROTOCOL DAYS (mean ± S.E.)





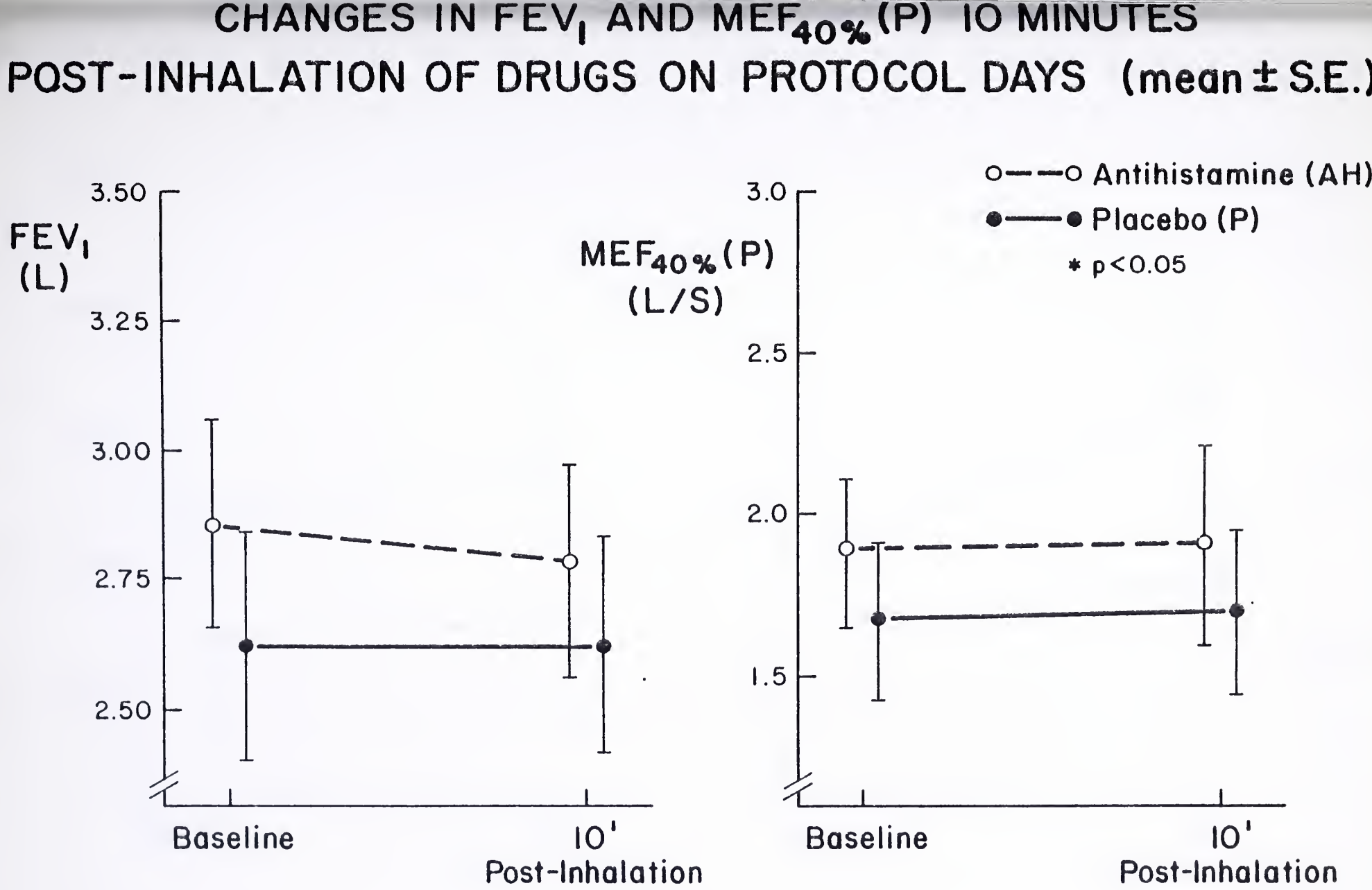

CHANGES IN FEV1 AND MEF40%(P) 10 MINUTES
POST-INHALATION OF DRUGS ON PROTOCOL DAYS (mean ± S.E.)
FEV1 (L)
3.50
3.25
3.00
2.75
2.50
Baseline
10' Post-Inhalation
MEF40%(P) (L/S)
3.0
2.5
2.0
1.5
Baseline
10' Post-Inhalation
Antihistamine (AH)
Placebo (P)
* p<0.05

Figure 6

CHANGES IN FEV_1 AND $MEF_{40\%}$(P) 30 MINUTES POST-INHALATION OF DRUGS ON PROTOCOL DAYS (mean ± S.E.)

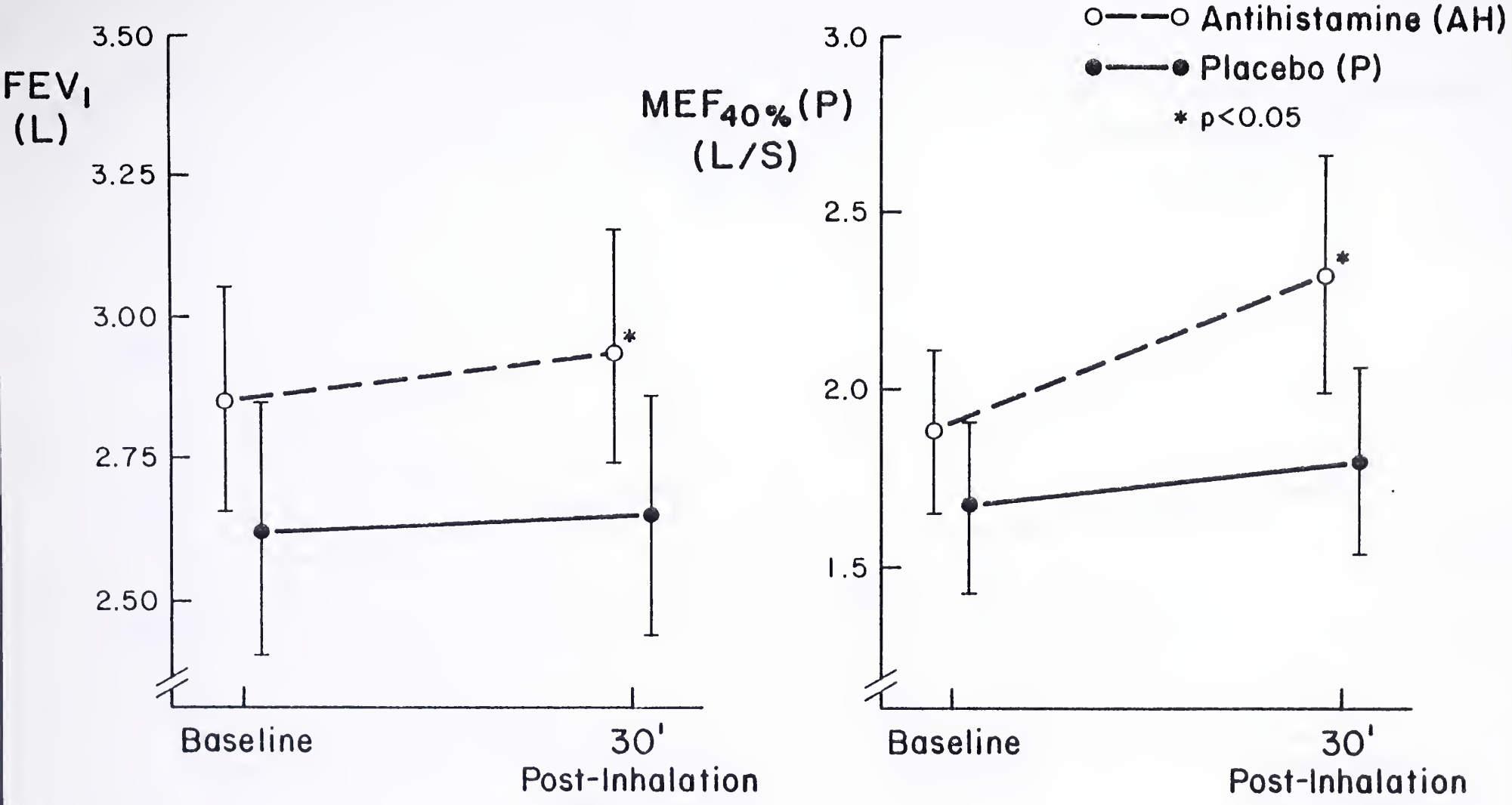


Figure 7

CHANGES IN FEV_1 AND $MEF_{40\%}(P)$ IMMEDIATELY POST-EXERCISE ON PROTOCOL DAYS (mean ± S.E.)

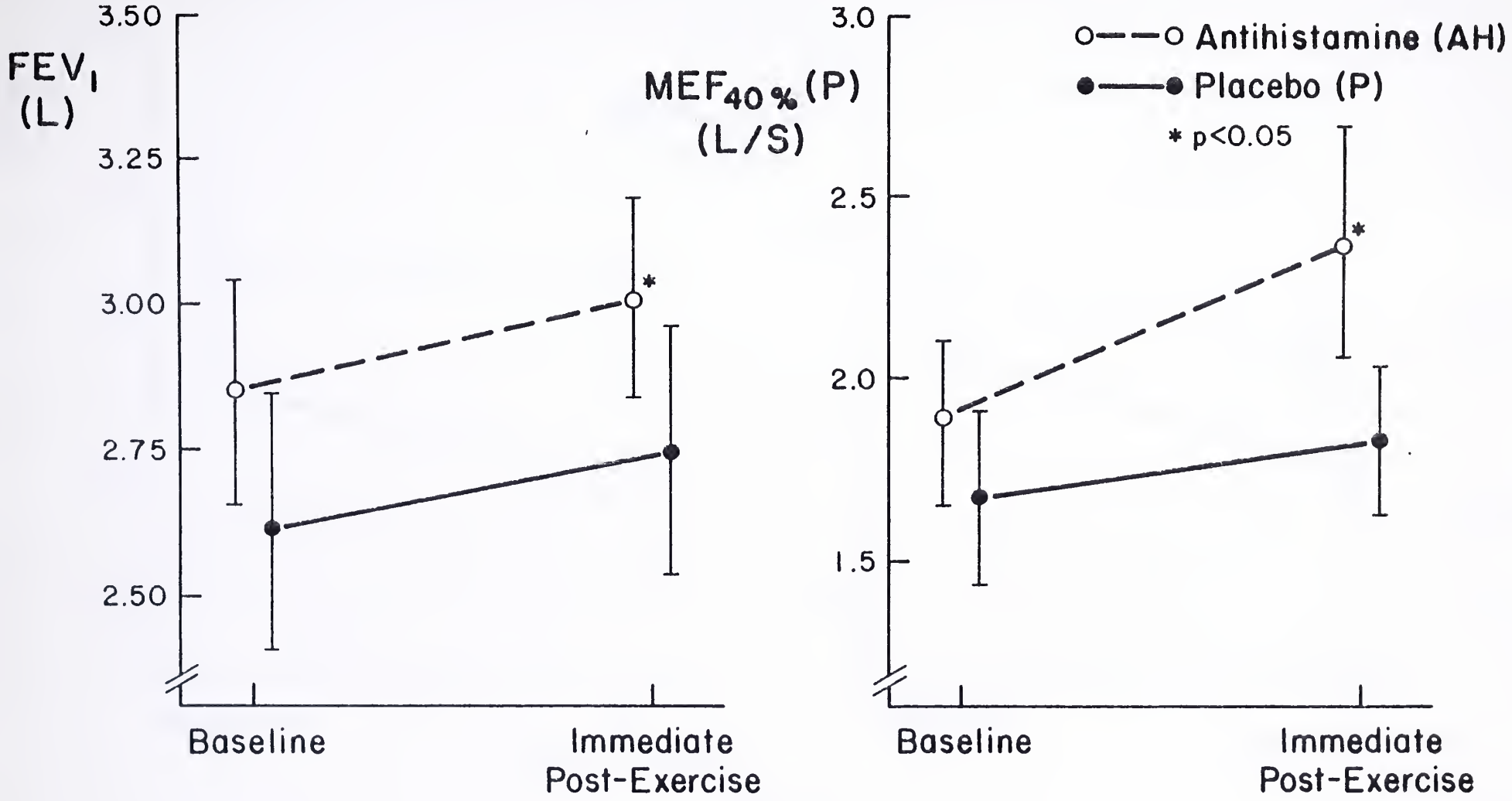


Figure 8

CHANGES IN FEV_1 AND $MEF_{40\%}$(P) 5 MINUTES POST-EXERCISE ON PROTOCOL DAYS (mean ±S.E.)

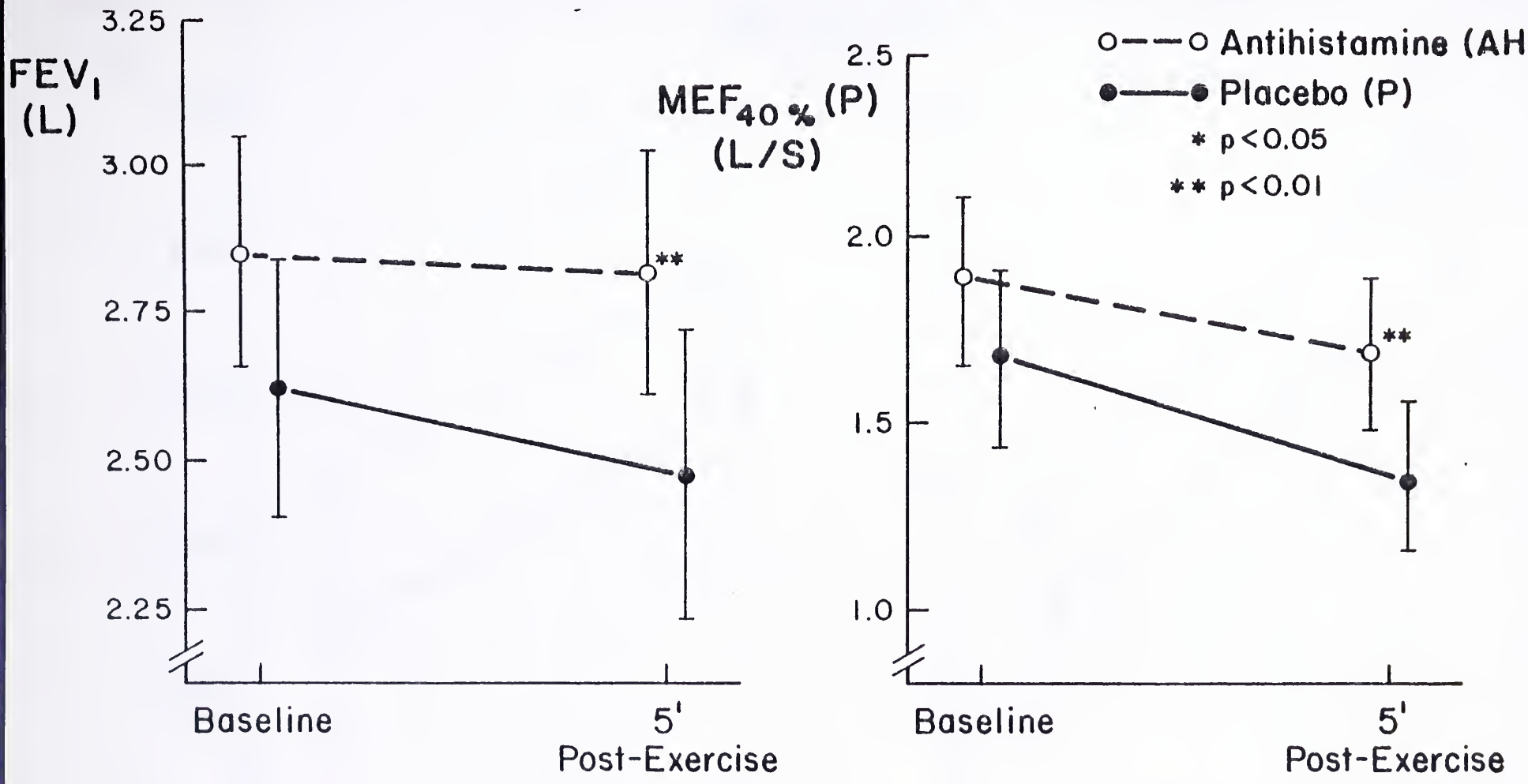


Figure 9

CHANGES IN FEV_1 AND $MEF_{40\%}$ (P)

POST BRONCHODILATION ON PROTOCOL DAYS (mean ± S.E.)

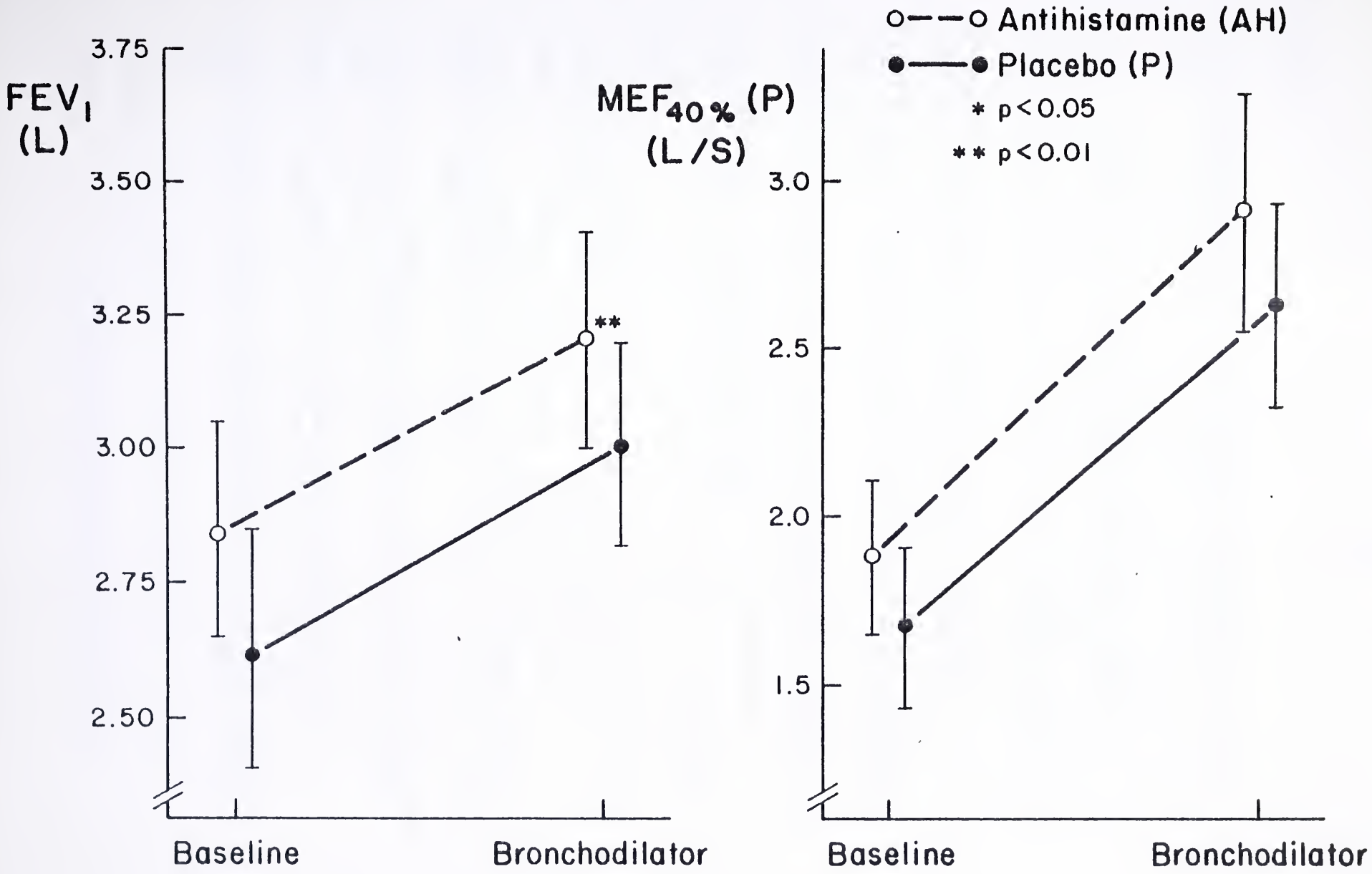


Figure 10

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