Relationship Between Bronchial Asthma And Gastroesophageal Reflux Disease

Thesis submitted for partial fulfilment of master degree in internal medicine
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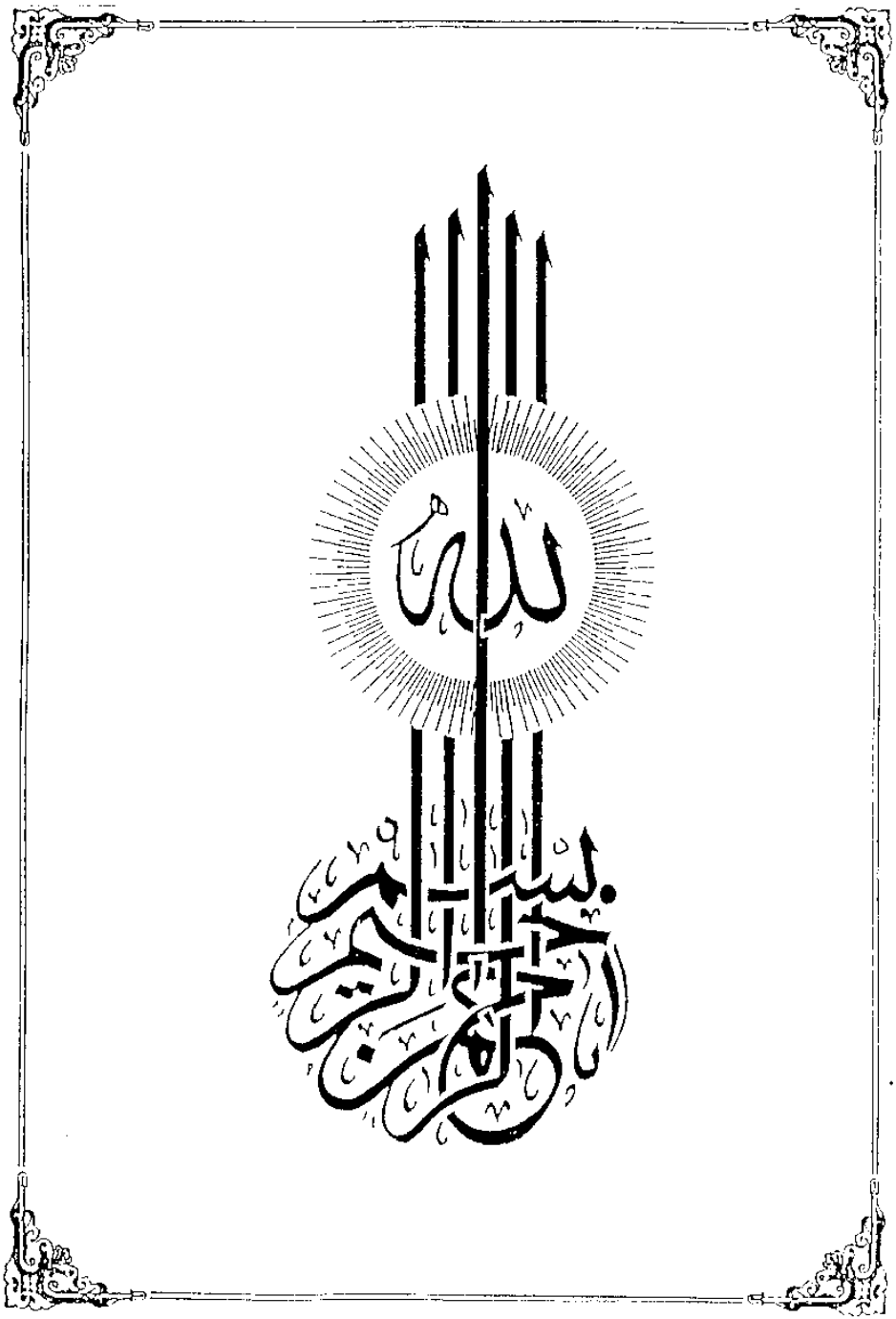

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INTRODUCTION

It is well known that patients with established reflux may suffer from secondry pulmonary complications and that the dominant symptoms may be related to the respiratory rather than the gastrointestinal tract.

It also has been reported that the pulmonary fibrosis of obescure orgin may be secondry to repeated small pulmonary aspirations associated with gastroesophageal incompetence.

In addition to gastro-pulmonary aspiration, pulmonary infection or respiratory disease of obscure aetiology were found to be related with gastroesophageal reflux.

A possible relationship between bronchial asthma and reflux is less well defined . However a high frequency hiatus hernia with or without reflux in adults with bronchial asthma has been noted.

More attention has been drown to an association between reflux and exacerbations of bronchial asthma. There also have been several studies suggesting subjective improvement in such patients after surgical correction of hiatus hernia.

Aim of Work

In this study we will try to demonstrate the relationship between bronchial asthma and gastroesophageal reflux and also to demonstrate the measurable improvement in symptoms and respiratory functions in a group of asthmatic patients by controlling their reflux symptoms with cimetidine.

Innervation Of Bronchopulmonary System

Human lung has afferent and efferent neural pathways ,the afferent neural pathways arise as sensory nerve endings from epithelium and smooth muscle ,the efferent neural pathways are three ,the cholinergic,the adrenergic and the non cholinergic non-adrenergic [NCNA] neural pathways. (Richardson,1983).

*Afferent pathway:-

The main afferent pathway from airway smooth muscle is via reflexes from the bronchopulmonary stretch receptors which were thought to be important in the Hering Breur reflex , other known afferent receptor types;irritant and pulmonary J.receptors are thought to be situated on bronchial epithelium and in alveolar wall.

They may have an effect on airway smooth muscle through reflex action causing bronchoconstriction,cough and hyperpnea.(Laitinen and Laitinen,1987)

*Efferent pathways:-

There are three efferent neural pathways and they are divided into excitatory and inhibitory pathways . These efferent neural pathways not only supply the airway secretory tissue, pulmonary and vascular bed which may also have indirect effects on airway smooth muscle.The mediators released from efferent nerves may act on isolated migratory cells such as leukocytes and mast cells as well as on the amine containing cells of the epithelium which may influence the airway smooth muscle (Laitinen and Laitinen,1987).

The Parasympathetic Nervous System.

The parasympathetic nervous system is the dominant neural bronchoconstrictor mechanism in all animal including humans and plays an important role in the regulation of airway-smooth muscle tone.(Bares,1987)

*Cholinergic innervation:-

Preganglionic parasympathetic fibers travel to the airway by the way of the vagus nerves and terminate in the ganglia scattered within the airway walls .Short postganglionic fibers proceed from the ganglia to airway smooth muscle cell,where they release the excitatory neurotransmitter,acetyl choline,from their an axon varicosities (Laitinen and Laitinen,12987).Cholinergic nerve fibers are f**ound in smooth muscle of human airways from trachea to terminal bronchioles,but the density of innervation markedly decreases in smaller airways (Barnes,1987).

Stimulation of parasympathetic cholinergic fibers causes constrictions from trachea to terminal bronchioles which is less pronounced in bronchioles than bronchi (Barnes,1987).The bronchoconstriction is most pronounced is airways with resting diameters of 1 to 5 mm and is less significant in airways smaller than 0.5 mm in diameter. Alveolar ducts are not affected by vagal stimulation.(Laitinen and Laitinen,1987).

*Cholinergic receptors:-

Acetyl choline released from preganglionic cholinergic fibres in airway ganglia activates nicotinic receptors on ganglionic neurons. These receptors are stimulated by nicotinic agonists,such as dimethyl phenyl piperazinium causing contraction of airway smooth muscle and this contraction is blocked by the nicotinic antagonists,hexamethonium.(Barnes,1987).

Acetyl choline released from postganglionic nerves activates muscarinic receptors on smooth muscle cells which are blocked by atropine and related drugs such as ipratropium bromide, activation of muscarinic receptors in airway smooth muscle causes contraction by stimulating the breakdown of membrane phosphoinositides, which results in the release of calcium iones from intracellular stores.(Barnes,1987).

Activation of muscarinic receptors also inhibit adenylate cyclase;leading to a reduction in cyclic AMP concentration. (Madison,1985).

*Cholinergic mechanisms in airway disease:-

Because parasympathetic nerves are the dominant bronchoconstrictor system in human airways,it was logical to suggest that overactivity of cholinergic mechanisms might contribute to airway obstruction and to bronchial hyperresponsiveness in airway diseases.This view was supported by the observation that many of the stimuli that produce bronchospasm in asthma as dust,sulfur dioxide, prostaglandins and histamine, also stimulate vagal afferent receptors in the airways leading to an increase in vagal reflex activity.Exaggeration of vagal reflex mechanisms seemed an alternative explanation for the bronchoconstrictor response occurring in asthma.(Barnes,1987).There are several possible mechanisms by which cholinergic mechanisms may be increased in asthma:

1-There could be an increase in airway afferent irritant receptor discharge as a result of inflammatory mediators and exposure of afferent nerve endings by the airway epithelial damage found in asthma.

2-Inflammatory mediators such as thromboxane may facilitate the neurotransmission through cholinergic ganglia and facilitate the release of acetyl choline from nerve terminals, and may also inhibit sympathetic inhibition of cholinergic nerves.

3-Enzymes released from inflammatory cells may inactivate a vasoactive intestinal peptide , which is a neuropeptide found in lung ,normally counteract cholinergic bronchoconstriction.

4-Inflammatory mediators such as prostaglandins may inhance cholinergic responsiveness of airway smooth muscle either by an increase in muscarinic receptor number or affinity.(Barnes,1987).

The Sympathetic Nervous System.

Catecholamine containing nerve fibres have been found in airway smooth muscle in humans, but they are fewer in number than cholinergic fibers representing only a small percentage of the total innervation of smooth muscles in human. This is in contrast to rich adrenergic nerve supply to bronchial and pulmonary blood vessels (Laitinen and Laitinen,1987).

Human airway smooth muscles appear completely devoid of noradrenergic nerves, though a few fibers were found to be present from secondary bronchi to the terminal bronchiols and it is now clear that the inhibitory nerves of human airway smooth muscle are entirely nonadrenergic (Zaogsma et al,1987).

In agreement with the absence of noradrenergic innervation , it was found that relaxation of smooth muscle of human airways by catecholamines,including norepinephrine is only mediated by B2-adrenoceptors which are found in airway smooth muscles. (Zaogsma, et.al.,1987).

B2-adrenoceptors are also found in mast cells and alveolar walls. B2 adrenoceptor agonists cause bronchodilatation and prevent release of mediators from mast cells and from other cells in alveolar walls.

Although there is no doubt about the occurrence of adrenoceptors in animal and human lung,the functional significance of this receptors is questionable (Zaogsma et al.,1987)

Diffusion of neurotransmitters from adrenergic nerves innervating the bronchial and pulmonary vessels may represent a mechanism whereby sympathetic nerve stimulation causes bronchodilation (Laitinen and Laitinen, 1987).

The Nonadrenergic, Noncholinergic Innervation

The main inhibitory neural pathway in human airway is nonadrenergic, noncholinergic pathway. (Laitinen and Laitinen,1987).

Stimulation of intrinsic nerves of smooth muscle by electric field, in the presence of cholinergic and adrenergic blockade produces relaxation of airway smooth muscle and the neural nature of this response is confirmed by the fact that it can be tetrodotoxin (Palmer et al., 1987)

*Noncholinergic nonadrenergic neurotransmitters :-

The neurotransmitters in the nonadrenergic noncholinergic pathway were described intially in gastrointestinal tract (Palmer et al., 1987).

Evidence is now accumulating that vasoactive intestinal peptides (VIP) and peptide histidine methionine (PHM) are the neurotransmitters in this inhibitory pathway .

The VIP and PHM neurones receptors are present in smooth muscle of bronchioles. VIP and PHM are potent bronchodilators. VIP coexists with acetyl choline in cholinergic nerves. and it counteracts the constrictor effect of acetyl choline, acting as a braking mechauissmo on cholinergic bronchoconstriction (Palmer et al., 1987)(Barnes, 1987).