

Hypertensive Effect of Bronchial Asthma

M. F. Lutfi and M. Y. Sukkar

Abstract

Background: Both bronchial asthma and hypertension are spastic disorders of smooth muscle, salt sensitive and sometimes associated with higher renin-angiotensin system activity, suggesting similarities between their aetiologies. This study was intended to assess the blood pressure status in asthmatic patients.

Patients and Methods: The study involved two groups: a control group of 56 healthy subjects matched for gender and age with the study group of 100 patients with a medical history of asthma but no other respiratory disease. Asthma history was recorded to assess asthma activity at the time of examination together with medications. The non-invasive auscultatory method was used for measuring the systolic (SBP) and diastolic (DBP) blood pressures. Mean arterial blood pressure (MABP) was determined by the formula: $MABP = DBP + [(SBP - DBP)/3]$.

Results: DBP was significantly higher in asthmatics (mean±SD = 80±10 mmHg) compared with non-asthmatics (mean±SD = 75±10 mmHg) ($P = 0.002$). DBP of off-treatment asthmatics was significantly higher compared with that of non-asthmatics ($P = 0.015$). Diastolic blood pressure of asymptomatic patients was not significantly higher compared with that of symptomatic patients ($P = 0.774$). Systolic and mean arterial blood pressures were not significantly different in asthmatics and control groups ($P = 0.267$ and 0.116 respectively).

Conclusions: In contrast to systolic and mean arterial blood pressures, diastolic blood pressure was significantly elevated in asthmatics (even in off-treatment patients) compared with non-asthmatics indicating mechanisms that predominantly increases peripheral vascular resistance.

Keywords: osmolarity, renin-angiotensin, catecholamines, endocrinometabolic.

Both bronchial asthma and hypertension are spastic disorders of smooth muscle. Asthmatics and hypertensives are salt sensitive^{1,2}. Possible mechanisms that may lead to airway reactivity include direct effect of salt on bronchial smooth muscle contractility³ as well as potential enhancement of the release of mast cell-derived inflammatory mediators, possibly through airway osmolarity changes⁴⁻⁶. Interestingly, the renin-angiotensin system was found to be activated in patients with asthma during severe acute attacks⁷. Previous studies indicate that endogenous angiotensin II promotes antigen-induced airway hyperresponsiveness and eosinophil accumulation by acting at type-1 receptors⁸. Angiotensin II is a potent vasoconstrictor which may increase blood pressure in asthmatics. Therefore, these similarities between the pathophysiology of asthma and

hypertension may predispose the patients with one disease to the other⁹. Stress hormones like cortisol and catecholamines may increase in stressful conditions like asthma and expected to induce hypertension¹⁰⁻¹². Some anti-asthma medications can induce hypotension e.g. beta-blockers, while others are known hypertensive agents e.g. steroids. However, most medications are administered through the inhalation route and are less likely to cause systemic endocrinometabolic effects¹³. Based on the above observations, patients with asthma should have a regular blood pressure check during follow-up visits. This study aims to investigate the relationship between bronchial asthma and blood pressure in a case control study.

Patients and Methods

Patients were selected from chest clinics of teaching hospitals in Khartoum State. The study involved two groups: a control group of 56 healthy subjects matched for gender and

1. Department of Physiology, AlNeelain University.

2. Department of Physiology, Nile College.

age with the study group of 100 patients with a medical history of asthma (at least for two years) but no other respiratory or heart diseases. The control groups were recruited mainly from among university students and employees.

Following verbal consent, asthma history and drug therapy were recorded to assess asthma activity at the time of examination. The non-invasive auscultatory method was used for measuring the blood pressure (Mercury in glass Sphygmomanometer – GOH Industries Limited - Japan). The systolic blood pressure (SBP) was determined by appearance of heart sounds (Korotkoff sound I) while diastolic blood pressure (DBP) was determined by disappearance of the sounds (Korotkoff sound V). Mean arterial blood pressure (MABP) was determined by the formula: $MABP = DBP + [(SBP - DBP)/3]$. Patients were

grouped according to the presence of symptoms and according to anti-asthma medication taken during the time of examination. Screening studied variables for significant differences in the means between the groups was performed using analysis of variance. When significant differences were identified, individual groups were compared using the Student two-tailed, unpaired T-test. In all of these statistical tests, only $P < 0.05$ was considered significant.

Results

Diastolic blood pressure was significantly higher in asthmatics (mean±SD = 80 ± 10 mmHg) compared with non-asthmatics (mean±SD = 75 ± 10 mmHg) ($P = 0.002$). This was true for both symptomatic ($P = 0.014$) and symptoms-free asthmatics ($P = 0.006$) (table 1).

Table-1: (A) means (M) and standard deviations (SD) of blood pressures for non-asthmatics, asthmatics with and without symptoms (B) the significance of mean difference.

A	Non Asthmatics (N = 56)		Asthmatics (N = 100)		Asthmatics without Symptoms (N = 53)		Asthmatics with Symptoms (N = 47)	
	M	SD	M	SD	M	SD	M	SD
SBP	118.32	13.69	115.80	13.25	116.70	13.66	114.79	12.85
DBP	75.04	9.98	80.20	10.02	80.47	10.39	79.89	9.70
MABP	89.46	9.61	92.07	10.00	92.55	10.30	91.52	9.73
B	Non Asthmatics Vs Asthmatics		Non Asthmatics Vs Asthmatics without Symptoms		Non Asthmatics Vs Asthmatics with Symptoms		Asthmatics without Symptoms Vs Asthmatics with Symptoms	
SBP		0.267		0.537		0.180		0.473
DBP		0.002*		0.006*		0.014*		0.774
MABP		0.116		0.110		0.284		0.611

* Significant mean difference

Diastolic blood pressures of asymptomatic patients were not significantly different compared with that of symptomatic patients ($P = 0.774$).

Systolic and mean arterial blood pressures

were not significantly different in asthmatics and control groups ($P = 0.267$ and 0.116 respectively). Diastolic blood pressure of off-treatment asthmatics was significantly higher compared with that of non-asthmatics ($P = 0.015$) (table 2).

Table-2: (A) means (M) and standard deviations (SD) of blood pressures for non-asthmatics, asthmatics classified according to drug taken (B) the significance of the difference between means

A	Non Asthmatics (N = 56)		Asthmatics (N = 100)		Asthmatic Not Taking Beta Agonist or Steroid (N = 26)		Asthmatic Taking Beta Agonist only (N = 27)		Asthmatic Taking Steroid only (N = 7)		Asthmatic Taking both Beta Agonist and Steroid (N = 40)	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
SBP	118.32	13.69	115.80	13.25	115.69	13.07	115.85	13.42	115.69	13.07	117.75	14.41
DBP	75.04	9.98	80.20	10.02	80.00	9.64	80.28	10.24	80.00	9.64	83.38	10.65
MABP	89.46	9.61	92.07	10.00	91.90	10.27	92.14	9.96	91.90	10.27	94.83	10.70

B	Non Asthmatics Vs Asthmatics Not Taking Beta Agonists or Steroids	Non Asthmatics Vs Asthmatics Taking Beta Agonists Only	Non Asthmatics Vs Asthmatics Taking Steroids Only	Non Asthmatics Vs Asthmatics Taking Both Beta Agonists or Steroids	Asthmatics Not Taking Beta Agonists or Steroids Vs Asthmatics Taking Beta Agonists Only	Asthmatics Not Taking Beta Agonists or Steroids Vs Asthmatics Taking Steroids Only	Asthmatics Not Taking Beta Agonists or Steroids Vs Asthmatics Taking Both Beta Agonists or Steroids
SBP	0.963	0.032*	0.383	0.845	0.460	0.301	0.924
DBP	0.015*	0.495	0.570	0.000*	0.048*	0.319	0.273
MABP	0.066	0.577	0.834	0.013*	0.103	0.206	0.531

* Significant mean difference

Discussion

The finding that off-treatment asthmatics have higher diastolic blood pressure compared with non-asthmatics indicates that high diastolic blood pressure in asthmatics is not attributable to hypertensive anti-asthma drug therapy. Furthermore, symptomatic patients, which were expected to be on β -2 agonist treatment (hypotensive agent), were found to have higher diastolic blood pressures compared with the control group ($P = 0.014$). Stress hormones like cortisol and catecholamines, which may be increased in stressful conditions like asthma, are expected to increase both systolic and diastolic blood pressures alike¹⁰⁻¹². Therefore, a mechanism that predominantly increases peripheral vascular resistance and consequently diastolic blood pressure may exist to explain these findings.

Previous studies of vessels in asthmatics have focused on the pulmonary arteries¹⁴ and the bronchial capacitance vessels in the bronchial mucosa¹⁵. There is an old report on the larger bronchial arteries¹⁶ and almost no studies on systemic arteries of asthmatic patients. However, recent studies on abnormalities of the bronchial arteries in asthmatics focused on systemic arteries and peripheral vascular resistance^{17,18}. Green et al described intimal thickening of bronchial arteries in cases of both fatal and non-fatal asthma¹⁸. The lesion described was distinct from atherosclerosis and was not related to changes associated with cor pulmonale, which involves smooth muscle proliferation in both intima and media.

Although these findings could be part of remodeling of airways compartments and not

necessarily systemic process of all systemic arteries, the following suggestions deserve especial concern:

1. Long term effects:

According to Green et al. the intimal lesions were not associated with inflammatory cells either within or adjacent to vessels showing the lesion. This finding when compared to another study, which showed that remodeling in the airway wall in patients with asthma is associated with infiltration and activation of inflammatory cells¹⁹, it can be concluded that humeral inflammatory factor(s) cannot be ruled out as the cause of these permanent vascular lesions. This is because the intima is in closer contact with the circulating blood than the unaffected media. These findings suggest that similar intimal lesion may compromise the arterioles in systemic circulation but to a lesser extent as humeral inflammatory factors will be diluted as they reach the general circulation. This could partially explain the mild increase in diastolic blood pressure secondary to the expected mild increase in the peripheral vascular resistance of asthmatic patients.

2. Short term effects:

Although the bronchial circulation has extensive collateral communications, it is likely that the arterial luminal narrowing observed by Green et al is physiologically significant. A major function of the airway circulation is to provide an essential route for clearance of smooth muscle bronchoconstrictor mediators. Csete et al tested the hypothesis that airway perfusion modifies the contractile response of airway smooth muscle to allergen challenge by influencing the clearance of locally released spasmogens²⁰. This study proved that antigen-induced airway smooth muscle contraction in vivo was due to alterations in airway blood flow rather than to alterations in airway smooth muscle responsiveness to chemical mediators. This finding can also explain why the degree of response of bronchial smooth muscles to chemical mediators (marked bronchoconstriction) is far more than vascular smooth muscles (mild diastolic hypertension) i.e. because a relatively small amount of

chemical mediators (smooth muscles constrictors) will reach the general circulation.

On the other hand, the renin-angiotensin system was found to be activated in patients with asthma during severe acute attacks⁷. In addition, there is evidence of synergy in bronchoconstriction between Angiotensin II and some other bronchoconstrictors like methacholine²¹. The results of other studies indicate that endogenous angiotensin II promotes antigen-induced airway hyperresponsiveness and eosinophil accumulation by acting at type-1 receptors⁸. Angiotensin II is a potent vasoconstrictor and can therefore explain increased diastolic blood pressure discussed above.

The mechanism of activation of the renin-angiotensin system in asthma is uncertain. High level of angiotensin II may be a pathological phenomenon or it may represent a physiological response to asthma attack²². According to Ramsay et al, plasma renin and angiotensin II in asthmatics were strongly correlated; implying renin-dependent angiotensin II formation. However, the above study failed to demonstrate correlation between catecholamines, endothelin-1, histamine, serum angiotensin converting enzyme activity, total immunoglobulin E (as indicators of the severity of an asthma attack), renal function and renin or angiotensin II levels. Interestingly, Ramsay et al also did not demonstrate a relationship between blood pressure and renin or angiotensin II levels²².

Conclusion

In contrast to systolic and mean arterial blood pressures, diastolic blood pressure was significantly elevated in asthmatics compared with non-asthmatics. Further studies are needed to identify possible causes of increased diastolic blood pressure in asthmatics. Research areas in this field include looking for evidences suggesting systemic arteries remodeling as result of chronic intimal contact with inflammatory mediators released from the lungs as well as searching for a common pathology that can explain bronchoconstriction and peripheral vasoconstriction simultaneously

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References

1. Carey O, Locke C and Cookson J. Effects of alterations of dietary sodium on the severity of asthma in men. *Thorax*. 1993;48:714-8.
2. Burney P, Neild J, Twort C, Chinn S, Jones T, Mitchell W et al. Effect of changing dietary sodium on the airway response to histamine. *Thorax*. 1989;44:36-41.
3. Chideckel E, Frost J, Mike P and Fedan J. The effect of ouabain on tension in isolated respiratory tract smooth muscle of humans and other species. *1987;92(3):609-14*.
4. Mickleborough T, Gotshall R, Rhodes J, Tucker A and Cordain L. Elevating dietary salt exacerbates hyperpnea-induced airway obstruction in guinea pigs. *J Appl Physiol*. 2001;91: 1061-1066.
5. Eggleston P, Kagey-Sobotka A, Schleimer R and Lichtenstein L. Interaction between hyperosmolar and IgE-mediated histamine release from basophils and mast cells. *Am Rev Respir Dis*. 1984;130: 86-91.
6. Mickleborough T. Salt intake, asthma, and exercise-induced bronchoconstriction: a review. *Phys Sportsmed*. 2010 Apr;38(1):118-31.
7. Millar E, Angus R, Hulks G, Morton J, Connell J and Thomson N. Activity of the renin-angiotensin system in acute severe asthma and the effect of angiotensin II on lung function. *Thorax* 1994; 49:492-495.
8. Myou S, Fujimura M, Kurashima K, Tachibana H, Watanabe K and Hirose T. Type 1 Angiotensin II Receptor Antagonism Reduces Antigen-induced Airway Reactions. *Am. J. Respir. Crit. Care Med.*, 2000; 162, 45-49.
9. Salako B and Ajayi S. Bronchial asthma: a risk factor for hypertension? *Afr J Med Med Sci*. 2000 Mar;29(1):47-50.
10. Kojima K, Hirata K, Higuchi S, Akazawa K and Tashiro N. The relation of emotional behavior to plasma catecholamines, cortisol and ventricular arrhythmia. *Journal of the autonomic nervous system*. 1995; 55, 57-64.
12. Nakada T and Yokoyama M. Blood pressure and Plasma Catecholamines in Secondary School Students. *Pediatric Cardiology and Cardiac Surgery*. 1989; 4, 394-399.
13. McCrory W, Klein A and Rosenthal R. Blood pressure, heart rate, and plasma catecholamines in normal and hypertensive children and their siblings at rest and after standing. *Hypertension*. 1982; 4, 507-513.
14. Yernault J, Leclercq R, Schandevyl W, Virasoro E, De Coster A and Copinschi G. The endocrinometabolic effects of beclomethasone dipropionate in asthmatic patients. *Chest*. 1977; 71: 698-702.
15. Saetta M, DiStefano A, Rosina C, Thiene G and Fabbri LM. Quantitative structural analysis of peripheral airways and arteries in sudden fatal asthma. *Am Rev Respir Dis* 1991;143,138-143
16. Carroll N, Cooke C, James A. Bronchial blood vessel dimensions in asthma. *Am J Respir Crit Care Med*, 1997;155,689-695
17. Cudkowicz, L, Armstrong J. The bronchial arteries in pulmonary emphysema. *Thorax* 1953;8,46-58.
18. Rydell-Törmänen K, Uller L, Erjefält J. Remodeling of extra-bronchial lung vasculature following allergic airway inflammation. *Respir Res*. 2008 Feb 8;9:18.
19. Green F, Butt J, James A and and Carroll N.. Abnormalities of the Bronchial Arteries in Asthma. *Chest*. 2006;130:1025-1033.
20. Djukanovic R, Lai C, Wilson J, Britten K, Wilson S, Roche W et al. Bronchial mucosal manifestations of atopy: a comparison of markers of inflammation between atopic asthmatics, atopic nonasthmatics and healthy controls. *Eur Respir J* 1992; 5: 538-544
21. Csete M, Chediak A, Abraham W and Wanner A. Airway blood flow modifies allergic airway smooth muscle contraction. *Am Rev Respir Dis* 1991;144,59-63
22. Millar E, Nally J, Thomson N. Angiotensin II potentiates methacholine-induced bronchoconstriction in human airway both in vitro and in vivo. *Eur Respir J* 1995; 8,1838-1841
23. Ramsay S, Dagg K, McKay I, Lipworth B, McSharry C and Thomson N. Investigations on the renin-angiotensin system in acute severe asthma. *Eur Respir J* 1997; 10: 2766-2771.

