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Bronchial asthma could belong to the group of systemic inflammatory diseases

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ABSTRACT

Introduction: hypertensive cardiovascular disease is a complex, multifactorial, and chronic illness, frequently beginning during childhood or adolescence, that could lead to functional and/or structural organ damage by increase in arterial stiffness and the volume/pressure curve, that in turn can increase the stress into the ventricular-arterial coupling and could produce the appearance of arrhythmias such as atrial fibrillation.

This study **aims** to evaluate patients with bronchial asthma with non-invasive arterial tonometry to determine its possible similarity with systemic inflammatory diseases and also the capability of presenting brief episodes of atrial fibrillation.

Materials and Methods: this was a retrospective, cross-sectional study of 435 patients, of whom 93 were chronic asthmatics and the rest had systemic inflammatory diseases such as psoriasis, rheumatoid arthritis, celiac disease, Sjögren's syndrome and Crohn's disease, ulcerative colitis, endometriosis, and polycystic ovary syndrome. General and anthropological data, blood pressure, and central hemodynamic parameters were recorded using noninvasive arterial tonometry. Episodes of atrial fibrillation were recorded during 24-hour ambulatory electrocardiographic Holter monitoring.

Results: statistically comparing the data of asthmatics with all systemic inflammatory diseases and in both sexes separately, no significant differences were observed.

Conclusions: According to these observations, bronchial asthma presents a similarity with systemic inflammatory diseases due to damage to the arterial wall and the presence of brief phases of atrial fibrillation.

INTRODUCTION

Although Rudolph Virchow defined atherosclerosis as a chronic inflammatory pathology more than a century ago, decades of clinical investigation were necessary to confirm this remarkable intuition.

Different inflammatory pathways present pro-atherogenic and pro-thrombotic effects that may vary from patient to patient, and according to the different phases of natural history of atherosclerotic cardiovascular disease.[1]

There are increasingly more proofs that, besides the traditional risk factors, vascular wall inflammation plays a key role in the pathogenesis of vascular diseases and atherosclerotic and atherothrombotic processes. In spite of optimal control of traditional risk factors, cardiovascular events, even fatal ones, persist in some patients.[2] Chronic systemic inflammatory diseases are associated with premature atherosclerosis and hypertension.[3] The links between the immunological system and atherogenesis are properly established. Atherosclerosis is a systemic inflammation state of low grade, associated with immune system activation in the presence of classical risk factors. This chronic inflammation of low grade is different from the severe chronic inflammatory state associated with autoimmune diseases (for instance, rheumatoid arthritis and psoriasis).[4] It has been proven that chronic systemic inflammation, as for example in patients with psoriasis, psoriatic arthritis and rheumatoid arthritis can cause accelerated atherosclerosis and is associated with higher cardiovascular risk.[5,6] Recently, an extensive population study led by Conrad N, et al. confirmed the evidence of an association between autoimmune diseases and cardiovascular risk.[7]

OBJECTIVE

To study patients with bronchial asthma to establish a possible similarity with the more widely known systemic inflammatory diseases, mainly assessing by noninvasive arterial tonometry, measuring central hemodynamic parameters, and also to observe the presence of brief episodes of atrial fibrillation as an important cardiovascular complication.

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MATERIALS AND METHODS

To develop this retrospective and cross-sectional study, there were 435 patients registered; 328 were females (75.4%) and 107 were males (24.6%), of whom 93 (21.4%) were chronic asthmatic patients: 66 females (20.1%) and 27 males (25.2%). The age range is between 19 and 88 years, with an average age of 46.4 years, both genders. Gender, anthropological, blood pressure and heart rate data were recorded, as well as central hemodynamic parameters recorded with noninvasive arterial tonometry, and the prevalence of each of the systemic inflammatory diseases in total, separately, and bronchial asthma.

The measurements of blood pressure were made according to standard methods with ERKA sphygmomanometers (N° 7102869 – 18031068). The presence of brief episodes of atrial fibrillation were recorded during 24 h Holter ambulatory monitoring (Spacelabs Healthcare Ltd, USA. Evo N° 001877 - 014012).

Noninvasive arterial tonometry

Central hemodynamic parameters were measured by the SphygmoCor device, model PVX (AtCor-Medical, Australia). Noninvasive arterial tonometry is a valid instrument, using a high-fidelity technique, with software adequate for generalized transfer functions use for pulse wave analysis made on the radial artery, to estimate aortic augmentation index as a substitute measure for arterial stiffness. Central aortic pressure, end of systole pressure, mean blood pressure, pulse pressure and augmentation pressure were measured and expressed in mmHg. Likewise, the augmentation index was measured (AIx) adjusted to 75 beats per minute expressed in percentage (AIx@HR75), with a fidelity index of >85%, being the most commonly used index to measure pressure wave reflections. AIx and pulse wave velocity are closely correlated, in a significant and positive way ($r=0.29$, $p<0.005$). The differences in AIx were estimated between the values observed in regard to normal maximal levels, according to established protocols, according to gender and age.

Statistical analysis

Continuous variables were summarized by descriptive statistics. Data are expressed as mean+standard deviation. Categorical variables were summarized using count of patients and percentages. The differences between the means of central hemodynamic parameters in male and female patients were compared by Student's t-test for independent samples. Statistical tests were bilateral and alpha level was established in 0.05. Statistical analyses were carried out using the SAS system, version 9.2.

RESULTS

The patients with different systemic inflammatory diseases were 342 (78.6%), such as: psoriasis (125), rheumatoid arthritis (27), celiac disease (13), Sjögren's syndrome (9), Crohn's disease (7), ulcerative colitis (10), endometriosis (10) and polycystic ovary syndrome (141).

In *Table 1,* each of the systemic diseases and asthma are represented, with the number of patients who presented brief episodes of atrial fibrillation recorded in 24 h Holter.

From all systemic diseases between men, there was a predominance of psoriasis (59), and polycystic ovary syndrome between women (141), so the mean age in this gender is lower, while in asthmatic patients, the mean age was similar in both genders.

In most of the groups, body mass index was at the limit between overweight and obesity, except in the celiac disease group being much lower, with this difference maybe being caused by a possible limitation in therapeutic food ingestion by patients because of their base pathology.

Systolic and diastolic blood pressure figures of systemic diseases were in the 120/70 mmHg limit, which is the threshold pointed out as "elevated" blood pressure by the last guidelines on hypertension, observing the most elevated recordings in rheumatoid arthritis.[8] The criterion applied in this study was that the normal blood pressure level should be the one not producing functional and/or structural alterations on the cardiovascular system *(Table 2).*

Likewise, central hemodynamic parameters, whether between the systemic diseases or in asthma, were always elevated; for instance, central systolic pressure and end systolic pressure exceeding 110 and 100 mmHg, respectively. Also, the augmentation index presented figures above normal levels in all groups and in both genders *(Table 3).*

In a second analysis, the figures of all systemic inflammatory diseases were unified (considering them as a single entity due to their characteristics of producing endothelial damage, and subsequently, arterial stiffness) to be compared with the figures from asthmatic patients, whether by blood pressure, hemodynamic parameters and percentages of brief episodes of atrial fibrillation found in 24 h Holter.

TABLE 1.
Patients with atrial fibrillation according to underlying pathology

AF	Psor	RA	Celiac	End	Sjögren	Crohn	PCOS	UC	Asthma	Total
Women	9	3	1	1	0	0	3	2	6	25
Men	3	1	0		0	1		0	5	10
Total	12	4	1	1	0	1	3	2	11	35

AF: atrial fibrillation; **Psor:** psoriasis; **RA:** rheumatoid arthritis; **Celiac:** celiac disease; **End:** endometriosis; **PCOS:** polycystic ovary syndrome; **UC:** ulcerative colitis.

The mean pressures of asthmatic patients and those of the sample of all patients with systemic inflammatory diseases, in both genders, were higher than the figure of guidelines for hypertension *(Table 4)*.[8]

Once these figures were obtained, they were compared statistically, by contrasting the data from asthmatic patients with all systemic inflammatory diseases, and in both genders separately. No significant difference was observed *(Table 5)*.

DISCUSSION

According to scientific literature, this would be the first study evaluating bronchial asthma as a disease similar to those called chronic systemic inflammatory diseases, such as psoriasis, rheumatoid arthritis, Crohn's disease, Sjögren's syndrome, etc., taking central hemodynamic parameters, blood pressure and the presence of brief episodes of atrial fibrillation, as an important complication for hypertension, recorded in 24 h Holter, as reference point.

Several patients in this registry presented two inflammatory pathologies simultaneously, or in different periods of life, as for instance psoriasis and Sjögren's syndrome, which led to consider that the base of the disease is a single chronic inflammatory condition, frequently including the arteries. This manifested through the analysis of pulse wave with noninvasive arterial tonometry; so, we can assume that this systemic disease could be a single entity, which according to the response of the target organ where lesions occurred has received a different name in scientific literature.

The relationship in arterial stiffness and the presence of brief phases of atrial fibrillation, as well as its possible prevention, has been expressed in a study with 1500 patients comparing 3 groups of therapy: one group with angiotensin II receptor blockers (ARBs) associated to mineralocorticoid receptor antagonists (MRA), a second group with just ARBs and the third with ARBs associated to hydrochlorothiazide. It was observed that in the first group, lower systolic and diastolic blood pressures were obtained, and that the presence of brief phases of atrial fibrillation were virtually nil, with a statistically significant difference in relation to the other two therapy groups.[9]

TABLE 2.
Anthropometric data, age, blood pressure and heart rate of systemic inflammatory diseases and asthma

Men	n	Age	BMI	WC	SBP	DBP	HR
Asthma	27	52.4	30.2	105.7	139.1	84.6	69.4
Psoriasis	59	53.3	31.7	108.2	134.8	85.3	73.7
Rheumatoid arthritis	6	48.7	35.0	112.0	149.3	99.2	79.5
Celiac disease	5	47.0	27.8	101.0	133.4	83.4	65.0
Crohn	5	43.2	29.0	95.5	125.6	75.4	70.4
Sjögren	1	51.0	31.5	105.0	120.0	82.0	75.0
Ulcerative colitis	4	42.8	28.2	101.5	131.8	88.8	76.8

Women	n	Age	BMI	WC	SBP	DBP	HR
Asthma	66	52.2	30.3	95.7	136.3	82.7	73.9
Psoriasis	66	55.7	31.3	100.0	142.8	84.0	73.5
Rheumatoid arthritis	21	62.2	30.5	97.8	144.5	83.8	66.6
Celiac disease	8	39.3	22.5	83.4	121.9	76.9	74.6
Crohn	2	59.0	33.7	109.0	135.0	82.5	72.5
Sjögren	8	56.9	29.4	93.3	136.3	80.6	62.8
Ulcerative colitis	6	58.8	31.4	99.0	139.7	82.5	72.7
PCOS	141	39.6	30.9	96.8	130.6	83.0	78.4
Endometriosis	10	40.9	26.6	88.0	128.6	77.8	73.6

PCOS: polycystic ovary syndrome; **BMI:** body mass index; **WC:** waist circumference; **SBP**: systolic blood pressure; **DBP:** diastolic blood pressure; **HR:** heart rate.

TABLE 3.
Central hemodynamic parameters of systemic inflammatory diseases and asthma

Men	CAP	ESP	MBP	PP	AP	AIx	AIx Dif
Asthma	126.3	116.7	103.1	40.8	9.6	19.3	2.9
Psoriasis	123.6	115.1	102.8	37.0	9.0	22.0	4.8
Rheumatoid arthritis	136.0	126.0	116.5	35.3	6.7	18.8	5.0
Celiac disease	123.8	114.2	101.8	39.4	10.4	20.2	5.7
Crohn	113.2	104.4	94.4	34.6	8.0	21.0	9.1
Sjögren	112.0	107.0	95.0	29.0	7.0	24.0	6.5
Ulcerative colitis	121.3	113.8	104.5	31.3	5.8	20.5	8.3

Women	CAP	ESP	MBP	PP	AP	AIx	AIx Dif
Asthma	127.1	116.8	103.0	43.1	13.3	29.0	4.1
Psoriasis	133.0	121.2	106.2	48.0	15.8	31.0	3.6
Rheumatoid arthritis	136.3	124.5	106.2	50.8	19.3	33.9	4.8
Celiac disease	113.4	105.4	90.1	35.4	10.6	26.1	6.8
Crohn	126.0	117.0	101.0	43.0	14.5	33.5	3.5
Sjögren	127.9	116.9	101.0	46.4	17.1	29.6	1.6
Ulcerative colitis	130.3	121.2	104.7	46.0	16.2	34.0	6.8
PCOS	119.8	111.4	100.0	35.3	9.2	25.5	5.5
Endometriosis	117.1	108.6	96.0	38.3	9.4	22.8	1.2

PCOS: polycystic ovary syndrome: **CAP:** central aortic pressure; **ESP:** end-systolic pressure; **MBP:** mean blood pressure; **PP:** pulse pressure; **AP:** augmentation pressure; **AIx:** augmentation index; **Aix Dif:** AIx difference (difference between the figures observed and normal maximal figures).

Subsequently, in a substudy of the latter study with 500 patients, it was also observed that up to a mean level of 121/73 mmHg of blood pressure measured by sphygmomanometer and an age less than 65 years, treated with the therapeutic association ARBs + MRA, did not present the brief episodes of atrial fibrillation in 24 h Holter monitoring.[10]

This observation allows associating arterial wall inflammatory phenomena with the development of hypertension, and one of its most frequent complications such as atrial fibrillation, present in patients with chronic systemic inflammatory diseases and in asthmatic patients.

In regard to systemic diseases, premature atherosclerosis in patients with systemic lupus erythematosus and rheumatoid arthritis has been increasingly observed, which may lead to early coronary death in comparison with the general population.[11]

Rheumatoid arthritis is the most frequent manifestation of chronic inflammatory polyarthritis, which is present between the third and fifth decade of life, and with an increase in prevalence of atherosclerotic CAD. This chronic inflammation state has been related with an acceleration of the atherosclerotic process with a rapid increase in the risk of myocardial infarction.[12]

Psoriasis is a chronic inflammatory skin disorder, affecting approximately 1.5-3% of the general population, and seems to be linked to an increase in cardiovascular morbidity and mortality, sharing with atherosclerosis several similar inflammatory mechanisms, with a greater risk of clinical and subclinical CAD.[13,14] Moreover, it is a well-known independent determinant for myocardial infarction.[15]

Coronary flow reserve is often reduced in patients with psoriasis, suggesting a deterioration in preclinical endothelial dysfunction. It was also proven that an increase in intima-media thickness of the common carotid artery in psoriatic arthritis is a marker of early atherosclerosis in the absence of signs and symptoms of cardiovascular compromise and traditional cardiovascular risk factors. This microvascular dysfunction seems to be related with severity, extension and duration of psoriasis.

TABLE 4.
Central hemodynamic parameters, systolic and diastolic pressure figures, and the percentage of brief phases of atrial fibrillation observed between asthmatic patients and in systemic inflammatory diseases

Asthma	n	Age	AIx	CAP	ESP	MBP	PP	AP	SBP	DBP	AF	%
Total	93	52.2	3.8	127.8	117.7	103.7	42.9	12.4	138.1	83.8	11	11.8
δ		17.1	8.1	20.6	16.8	13.1	16.6	8.5	20.6	10.5		
Women	66	52.2	4.1	127.1	116.8	103.0	43.1	13.3	136.3	82.7	6	9.1
δ		17.4	8.6	20.7	17.5	14.1	15.0	7.8	20.8	11.0		
Men	27	52.4	2.9	126.3	116.7	103.1	40.8	9.6	139.1	84.6	5	18.5
δ		16.7	7.0	20.7	15.5	10.5	20.1	10.0	20.7	9.4		
SID	**n**	**Age**	**AIx**	**CAP**	**ESP**	**MBP**	**PP**	**AP**	**SBP**	**DBP**	**AF**	**%**
Total	342	46.4	5.0	122.4	113.3	100.6	38.4	10.9	132.7	82.6	24	7.0
δ		15.8	7.6	19.3	16.8	13.6	14.9	7.6	20.2	10.5		
Women	262	45.2	4.8	122.4	113.0	100.0	39.6	11.8	132.5	81.6	19	7.3
δ		16.3	7.4	20.2	17.4	13.6	15.9	7.9	20.8	9.9		
Men	80	51.4	5.3	123.6	115.0	103.2	36.5	8.6	134.9	85.9	5	6.3
δ		13.2	8.4	16.4	14.8	13.3	10.8	5.6	18.0	12.0		

SID: systemic inflammatory diseases; **Aix:** augmentation index; **CAP:** central aortic pressure; **ESP:** end-systolic pressure; **MBP:** mean blood pressure; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure; **AF:** atrial fibrillation.

TABLE 5.
P values between central hemodynamic parameters, systolic and diastolic pressures, and the percentages of patients with brief episodes of atrial fibrillation.

	SBP	DBP	CAP	ESP	MBP	PP	AP	AIx	AF	Total AF
Women	0.2	0.5	0.1	0.1	0.1	0.1	0.2	0.5	0.2	0,2
Men	0.4	0.6	0.5	0.6	0.9	0.3	0.6	0.1	0.1	

SBP: systolic blood pressure; **DBP**: diastolic blood pressure; **CAP:** central aortic pressure; **ESP:** end-systolic pressure; **MBP:** mean blood pressure; **PP:** pulse pressure; AP: augmentation pressure; AIx: augmentation index; **AF:** atrial fibrillation.

Polycystic ovary syndrome (PCOS) affects between 6 and 16% of women, with a marked ethnical variation in a reproductive age, frequently associated to hyperandrogenism, with a high prevalence of dyslipidemia, obesity, glucose intolerance, resistance to insulin and diabetes mellitus.[16]

Diagnosis is based, most commonly, in the Rotterdam criteria, requiring 2 to 3 data: oligoovulation or anovulation, clinical or biochemical evidence of hyperandrogenism and polycystic ovaries in ultrasound.[17] Also, endothelial dysfunction has been described in these women. In spite of presenting cardiometabolic changes, the American Heart Association has not established PCOS as a factor increasing the risk of atherosclerotic cardiovascular disease.[18] However, other authors have observed that women with PCOS present a significantly higher risk of cardiovascular disease.[19]

Endometriosis belongs to a complex interaction between endocrine, immunological, inflammatory and pro-angiogenic processes, and was also defined as an estrogen-dependent inflammatory condition.[20] Growing evidence has highlighted a concerning link between endometriosis and cardiovascular disease. Recent guidelines and position statements have provided limited commentaries on the correlation between endometriosis and adverse cardiovascular outcomes, although other studies have proven an association between endometriosis and a greater risk of atherosclerotic cardiovascular disease, particularly CAD and stroke.[21]

Recently, a Danish study of national scope, of the case-control type, has shown that women with endometriosis present a greater risk in the long term, of suffering adverse cardiovascular events in comparison with the general population, such as acute myocardial infarction, ischemic stroke, arrhythmias (including atrial fibrillation and different degrees of blocks) and heart failure.[22]

In this study, it was timely to emphasize some investigations that entail a moderate association between bowel inflammation and CAD.

Inflammatory bowel disease, including ulcerative colitis, Crohn's disease and inflammatory bowel disease unclassified, is a chronic inflammatory disorder, affecting mainly the gastrointestinal tract, but that often also presents extra-intestinal manifestations and complications.[23]

Some studies have suggested a link between inflammatory bowel disease and cardiovascular diseases, including acute arterial events, venous thromboembolism, hypertension and arrhythmias.[24,25,26,27]

In Crohn's disease and ulcerative colitis, elevated coagulation factors are observed, such as factor V, factor VIII, fibrinogen and Von Willebrand factor.[28]

Although thrombocyte and fibrinogen levels increased both in patients with ulcerative colitis and with Crohn's disease, levels of prothrombin times, factor V and factor VIII only increased in ulcerative colitis. On the other hand, plasminogen only increased in Crohn's disease. The difference between control subjects and patients was more marked in those with Crohn's disease in comparison with patients with ulcerative colitis.

Sjögren's syndrome is frequently a secondary phenomenon in patients with lupus, rheumatoid arthritis or scleroderma, or it may present with no other systemic rheumatic disease (primary Sjögren's syndrome). Sjögren's syndrome is associated to lymphocyte infiltration that may present even in kidneys.[29]

Bronchial asthma is a heterogeneous disease of the respiratory airways, where genetic and environmental factors converge, characterized by inflammation and greater responsiveness to a variety of stimuli. Atopy is the main risk factor of asthma, and non-atopic people have a very low risk of developing asthma.

This observation suggests that other environmental or genetic factors predispose to the development of asthma in atopic individuals.

Asthma is one of the most extended chronic diseases, and it currently affects approximately 300 million people all over the world. In industrialized countries, the prevalence of asthma has increased in the last 30 years, and now it seems to be stabilizing with a prevalence of 10-12% in adults. Respiratory airway mucosa is infiltrated by eosinophils and activated T-lymphocytes, and mastocyte activation is observed in mucosa. The degree of hyperresponsiveness is closely linked to the intensity of inflammation.[30]

CONCLUSIONS

According to these observations, bronchial asthma presents similarities with systemic inflammatory diseases, whether by damage on the arterial wall, contributing to developing hypertensive cardiovascular disease, or by the presence of one of its most frequent and important complications, namely brief phases of atrial fibrillation that precede its definitive establishment. Patients with bronchial asthma would have a cardiovascular risk similar to patients with systemic diseases.

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