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Research Article

Evaluation of Arterial Stiffness in Patients with Bronchial Asthma and Co-Existent Chronic Obstructive Pulmonary Disease

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Abstract

T**he objective of the research** was to determine the characteristics of arterial stiffness and cardiovascular risk in patients with co-existence of asthma and chronic obstructive pulmonary disease.

Materials and methods. The study included patients with symptoms of chronic obstructive pulmonary disease, those with asthma and chronic obstructive pulmonary disease and the group of apparently healthy individuals.

Results. In patients with obstructive lung disease, the parameters of vascular stiffness and central blood pressure reflecting the degree of cardiovascular risk were significantly higher as compared to those in apparently healthy individuals. They were significantly elevated in patients with chronic obstructive pulmonary disease and asthma-chronic obstructive pulmonary disease overlap. The indicators of central blood pressure were significantly higher in patients with asthma-chronic obstructive pulmonary disease overlap and more pronounced bronchial obstruction, and in patients with more obvious symptoms of obstructive pathology. Excess body weight or obesity had a strong and pronounced effect on the parameters of central blood pressure in patients with asthma-chronic obstructive pulmonary disease overlap. In patients with a comorbidity, a reliable correlation between the indicator of the presence of pulmonary hyperinflation and the degree of arterial stiffness was revealed.

Keywords

asthma-COPD overlap; arterial stiffness; cardiovascular risk

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Problem statement and analysis of the recent research

Both asthma and chronic obstructive pulmonary disease (COPD) are common among the population. Although they have different specific characteristics, some patients develop the signs of both diseases, and they have asthma-COPD overlap (ACO). To diagnose ACO is a challenging task considering the clinical similarity of two diseases and various phenotypes [1]. COPD is a disease that can be prevented and treated, and is characterized by persistent airflow limitation that is usually progressive being associated with an enhanced chronic inflammatory response of the lungs to harmful particles and gases [2]. In this definition, the main emphasis is on bronchopulmonary manifestations. However, in recent years, non-pulmonary manifestations of COPD, such as systemic inflammation, muscle dysfunction, cardiovascular disorders, body weight loss, osteoporosis, anemia have been increasingly discussed [3].

A number of epidemiological studies have shown that the leading cause of mortality in mild to moderate COPD is not respiratory failure, but cardiovascular pathology, namely coronary heart disease (CHD) and heart failure (HF) [4-7]; in such patients, the risk of cardiovascular death accounting for nearly 50% of all deaths increases by 2-3 times [5].

Increased vascular stiffness being one of the markers of subclinical atherosclerosis is associated with the development of cardiovascular complications (myocardial infarction, stroke, HF, kidney disease, and high rates of overall mortality) [8-11].

Changes in elastic vessels (the aorta and pulmonary artery) play a significant role in the pathogenesis of hypertension. Normally, the elastic properties of these blood vessels facilitate absorption stroke volume and can transfer large part of energy reduction during cardiac diastole. This leads to the reduction in aortic systolic blood pressure (SBP) and the increase in diastolic blood pressure (DBP), thereby decreasing damaging effect of pulse wave on the blood vessels in the brain, heart and kidneys and improving blood flow to these organs. Pulse wave velocity (PWV) reflects central and peripheral arterial stiffness. The determination of PWV is an informative and safe method of non-invasive assessment of central vascular stiffness. In particular, PWV in elastic arteries is the current gold standard for evaluating arterial stiffness and a strong predictor of future cardiovascular events and the overall death rate being of great importance in clinical research and general practice [12, 13, 14].

PWV is known to be more important than SBP marker of increased cardiovascular risk. It is an independent predictor of all-cause and cardiovascular mortality, particularly in patients with CHD and hypertension [12, 13, 14, 15, 16]. Previous studies have demonstrated increased arterial stiffness in patients with COPD compared to ex-smokers without bronchial obstruction and apparently healthy individuals irrespective of smoking status [17, 18, 19].

Previous studies have demonstrated that during the 9-year follow-up period, in patients with persistent asthma, the risk of cardiovascular events, namely myocardial infarction, heart failure and cardiovascular death increased by 60% as compared to individuals without asthma. In patients with persistent asthma, the levels of C-reactive protein and fibrinogen were significantly higher as well that indicated the relation between the inflammatory processes and cardiovascular diseases in asthma [20, 21]. These preliminary studies have pointed out increased arterial stiffness in patients with asthma as compared to healthy individuals [22, 23].

The augmentation index (AIx) is a more indirect indicator of arterial stiffness as compared to PWV and reflects the combined effect of PWV in large arteries, peripheral wave reflection and vascular properties. The assessment of the AIx is simpler as compared to the determination of PWV [24, 25]. Previous studies have demonstrated independent prognostic features of this index as a predictor of acute cardiovascular events [26]. The AIx varies depending on heart rate (HR); the AIx adjusted to a standard heart rate of 75 bpm (AIx75) is commonly used (AIx75). Previous studies have demonstrated that in patients with COPD, the AIx was higher as compared to apparently healthy individuals [17, 27].

Left ventricular (LV) ejection duration (ED) is the ratio of ventricular systole to the total duration of the cardiac cycle. In patients with LV systolic dysfunction, according to previous studies, ED rate was higher compared to patients with LV diastolic dysfunction. Subendocardial viability ratio (SEVR) reflects the state of subendocardial viability and in presence of subendocardial ischemia it falls below 50% [28].

According to previous studies, there have been revealed significant properties of central pressure, in particular, central SBP, in predicting the development of LV hypertrophy, LV systolic dysfunction, left atrial dilatation, the onset of atrial fibrillation and LV diastolic dysfunction [29, 30]. The results of the Conduit Artery Function Evaluation (CAFE) study, a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) have confirmed that central aortic pressure is a stronger predictor of stroke and CHD complications as compared to peripheral blood pressure (BP) in the brachial artery [31].

The objective of the research was to determine the characteristics of arterial stiffness and cardiovascular risk in patients with co-existence of asthma and COPD.

1. Materials and methods

The study included patients with symptoms of ACO over the age of 30 years. ACO diagnosis was verified by the Global Initiative for Asthma (GINA) criteria and the Global Initiative for Obstructive Lung Disease (GOLD) criteria [32-34]. All the patients had persistent, albeit variable symptoms of asthma and COPD. The patients' condition was stable; none of them had exacerbations 2 months prior to the study. The study included patients with asthma and COPD and the group of apparently healthy individuals as well. The most common comorbid conditions in patients with ACO were found to be hypertension (65%), CHD (37%), diabetes mellitus (DM) (12%), and gastrointestinal diseases (19%). Characteristics of patients are given in Table 1.

All the patients underwent the following examinations: height and weight measurements, determination of body mass index (BMI), spirometry, whole body plethysmography and pulse wave analysis.

Spirometry was performed using the MasterScreen Pneumo system (Cardinal Health, Germany). To determine total airway resistance (Rtot), total lung capacity (TLC), intrathoracic gas volume (ITGV) that includes residual volume (RV) and expiratory reserve volume (ERV), whole body plethysmography was performed using the Master Screen PFT system (Cardinal Health, Germany).

PWV measurements were performed using the SphygmoCor Px system (Atcor Medical Blood Pressure Analysis System, Sydney, Australia). PWV was evaluated between the carotid and femoral artery with the participant lying in the supine position. Pulse measurements were performed non-invasively using the SphygmoCor probe over the carotid and femoral artery with simultaneous ECG recording. The distance from the carotid artery to the femoral artery was measured directly between each artery location and the suprasternal notch and the values were entered in the SphygmoCor software database. The parameters of central aortic hemodynamics were measured using radial artery applanation tonometry.

In order to evaluate the elastic properties of elastic arteries, carotid-femoral artery PWV (PWVe) was determined; in order to evaluate the elastic properties of muscular arteries carotid-radial PWV (PWVm) was measured.

There were determined the following parameters: central SBP, central DBP, central pulse pressure (PP), augmentation pressure (AP), heart rate normalized AIx (AIx75), LVED, SEVR, LV end-systolic pressure (ESP).

The accumulation of data and their mathematical processing were carried out using licensing software products included in the package Microsoft Office Professional 2007 Russian Academic OPEN No Level No 43437596. Statistical processing was performed using mathematical and statistical functions of MS Excel. The studied parameters were evaluated using the mean value (M), the error of the mean value (m), test of statistical significance (t), significance value (p), followed by the comparison using the Student's t-test and the

Table 1. Characteristics of patients

Indices	Asthma (n=17)	COPD (n=10)	ACO (n=111)
Gender, (n)	14 women, 3 men	4 women, 6 men	54 women, 57 men
Age, years	51.0±1.75	68.3±2.7	58.13±0.93
BMI, kg/m^2	30.32±1.52	30.4±1.7	28.86±0.49
Ex-smokers (%)	71	60	64
Smokers (%)	29	40	36
Asthma severity degree			
mild, (%)	23		7
moderate, (%)	65		80
severe, (%)	12		13
Groups of patients with COPD			
A (%)		20	14
B (%)		20	21
C (%)		20	21
D (%)		40	44
GOLD COPD stage			
1, (%)		50	32
2, (%)		10	56
3, (%)		30	11
4, (%)		10	1

Mann-Whitney U test depending on the type of data distribution. Correlation analysis was performed calculating the Pearson correlation coefficient.

2. Results and discussion

Central SBP, PP, ESP and PWVm were higher in patients with asthma as compared to the control group. Central SBP, DBP, PP, AP, AIx, ESP and PWVe were significantly higher in patients with COPD. Moreover, in these patients, the rate of PWVe was significantly higher as compared to both the control group and patients with asthma.

In patients with ACO, central SBP, DBP, PP, ED, SEVR, ESP, and PWVe were significantly different from those in apparently healthy individuals. When comparing the indices in patients with COPD and those with ACO, significantly higher ESP and PWVe were found in patients with COPD.

SERV, which is an index characterizing the state of coronary perfusion, was significantly lower in patients with ACO as compared to the control group. Therefore, a significant deterioration of coronary perfusion was observed in patients with co-existent pathology, although the index remained within the normal range. The data are presented in Table 2.

The increase in central SBP, PP and AIx75 indicates an increase in cardiovascular risk. The value of central PP characterizes the degree of pulse wave activity effect on the vessels of target organs. Central PP is an independent predictor of cardiac and cerebral events. Thus, in comorbid pathology and COPD, cardiovascular risk and arterial stiffness were more pronounced as compared to those in healthy individuals and patients with asthma.

In patients with COPD, there was found a higher degree of arterial stiffness as compared to apparently healthy individuals. In guidelines for management of hypertension, arterial stiffness is included in the number of target organs that are investigated for determining subclinical organ damage in hypertension, and factors having a significant effect on the prognosis of patients. Thus, in previous studies, there was found a relation between PWV and stroke development in hypertension. The increase in PWV by 1 m/s increased all-cause and cardiovascular mortality by 15% [11, 13, 35].

Potential factors affecting the development of central hemodynamic disturbances and increased arterial stiffness in patients with obstructive lung disease are the effects of smoking, bronchial obstruction, hypodynamia, age-related factors, systemic inflammation, and oxidative stress which are typical for this disease. The presence of systemic inflammation and oxidative stress in such patients may explain the appearance of numerous comorbidities. The results of previous studies have demonstrated the relation between systemic inflammation and arterial stiffness [18, 19].

The next task of our research was to evaluate arterial stiffness and the state of central hemodynamics in patients with ACO depending on the degree of bronchial obstruction.

Patients with ACO and higher degree of bronchial obstruction (GOLD 2 and GOLD 3, 4) had higher indicators of central SBP, DBP and PP: in patients with GOLD 2 COPD, they were significantly higher compared to those with GOLD 1 COPD. PWVm was the highest in patients with a low degree of bronchial obstruction, while PWVe was the highest in patients with more pronounced bronchial obstruction. These features indicated a more pronounced cardiovascular risk in

Table 2. Indices of vascular stiffness and central BP in patients with asthma, COPD, ACO and healthy individuals

Indices	Apparently healthy individuals (n = 35)	Asthma (n=17)	COPD (n=10)	ACO (n=111)
Central SBP, mm Hg	110.97±1.69	124.29±3.82**	127.8±2.07**	123.24±1.32**
Central DBP, mm Hg	80.14±1.01	85.76±2.19	85.4±2.18*	85.15±0.86*
Central PP, mm Hg	30.83±1.07	39.59±2.71**	46.6±4.7**	39.5±1.01**
ED, ms	322.51±3.59	308.65±7.12	297.9±6.17*	309.82±2.9*
ED, %	35.8±0.84	36.0±1.11	35.3±1.37	36.66±0.44
AP, mm Hg	7.97±0.94	11.24±1.27	12.3±1.08*	10.68±0.57
AIx75, %	20.34±2.06	25.82±1.5	27.1±1.54*	24.99±1.01
SEVR, %	158.74±4.9	154.88±8.52	156.6±10.17	149.67±2.82**
ESP, mm Hg	102.4±1.77	113.47±3.54*	117.1±1.93**	111.26±1.58* β
PWVm, m/s	3.05±0.13	4.25±0.44*	3.69±0.37	3.69±0.1
PWVe, m/s	3.02±0.12	4.0±0.29	5.63±0.34**$\gamma\gamma$	4.88±0.19* γ β

Note.
* p <0.05;
** p <0.01 compared to the control group;
γ p <0.05; $\gamma\gamma$ p <0.01 compared to patients with asthma;
β p <0.05; $\beta\beta$ p <0.01 compared to patients with COPD.

patients with ACO and a high degree of bronchial obstruction.

According to previous studies, bronchial obstruction is an independent predictor of arterial stiffness. Previously, there was a significant correlation between forced expiratory volume in the first one second (FEV1), forced vital capacity (FVC) and PWVe in men with hypertension. One of the potential factors of the reduction in pulmonary function and high vascular stiffness may be change in the elastic properties of the alveoli and the vascular wall [19]. The data are presented in Table 3.

When comparing the indices of vascular stiffness in different clinical groups of patients with ACO (GOLD classification), in patients with more pronounced symptoms (Group B and Group D), there were found significantly higher levels of central PP and AIx75 and significantly lower level of SEVR as compared to patients with minor symptoms (Group A and Group C) (p<0.05). The data are demonstrated in Fig. 1.

Increased arterial stiffness, central BP, and higher cardiovascular risk were found in patients with severer course of ACO.

The importance of smoking as a risk factor for developing cardiovascular disease and premature death has been proven in numerous studies and is universally accepted. According to preliminary data, tobacco smoking doubles the risk of developing angina pectoris and myocardial infarction and increases the risk of sudden cardiac death by almost 5 times. Approximately one-third of deaths from coronary heart disease was found to be associated with tobacco smoking [36, 37].

The next task of our study was to determine the effect of active tobacco smoking on central BP and the state of the vascular wall in patients with ACO. In active smokers with ACO, the level of central DBP was significantly higher, while ED and AIx75 were lower. Thus, the negative impact of smoking on the indices of central BP was noted. There were no convincing data on the effect of active tobacco smoking on the parameters of arterial stiffness in patients with ACO. The data are shown in Table 4.

Obesity is the most common metabolic disease in the world. Numerous studies have proven the independent influence of excess body weight and obesity on the development of hypertension, myocardial hypertrophy, dyslipidemia and DM. The presence of obesity increases the risk of coronary heart disease, ischemic stroke and death from cardiovascular disease [38, 39].

The objective of this study was to detect the effect of body mass on the parameters of central BP and vascular properties in patients with ACO. Most patients with ACO included in our study had metabolic disorders of varying degrees of severity (30% of patients had excess body weight and 45% had obesity).

In patients with ACO and excess body weight, central DBP was significantly higher in comparison with those having normal body weight. In patients with obesity, the indicators of central SBP, DBP were the highest, and ED was lower as compared to patients with normal body mass. In patients with obesity, the index of SEVR was significantly lower in comparison with patients having excess body weight. Therefore, the negative effect of metabolic disorders on the parameters of central BP and the overall cardiovascular risk in patients with ACO was revealed. The data are presented in Table 5. One of the signs of the severity of bronchial obstructive disease clinical course is the development of pulmonary hyperinflation (i.e., an increase in the residual volume). The ratio of the residual volume to total lung capacity (RV/TLC) is an

Table 3. Indices of arterial stiffness and central BP in patients with ACO and different degrees of bronchial obstruction

Indices	GOLD 1 (n=36)	GOLD 2 (n=62)	GOLD 3, 4 (n=13)
Central SBP, mm Hg	119.08±2.45	125.24±1.76*	125.23±3.04
Central DBP, mm Hg	82.75±1.69	86.58±1.09*	85.0±2.23
Central PP, mm Hg	36.33±1.27	40.81±1.5*	42.0±3.18
ED, ms	317.36±5.27	304.77±3.87*	313±7.67
ED, %	36.14±0.83	37.03±0.57	36.31±1.34
AP, mm Hg	10.11±1.13	10.71±0.73	12.15±1.46
AIx75, %	22.97±2.04	25.82±1.31	26.69±2.08
SEVR, %	154.19±5.25	147.03±3.8	149.69±7.34
ESP, mm Hg	105.26±3.73	114.27±1.64*	113.54±2.81*
PWVm, m/s	3.83±0.23	3.72±0.13	3.19±0.21* γ
PWVe, m/s	4.49±0.26	4.98±0.28	5.55±0.68

Note.
*p <0.05;
** p <0.01 as compared to patients with GOLD 1 COPD;
γ p <0.05;
γγ p <0.01 compared to patients with GOLD 2 COPD.

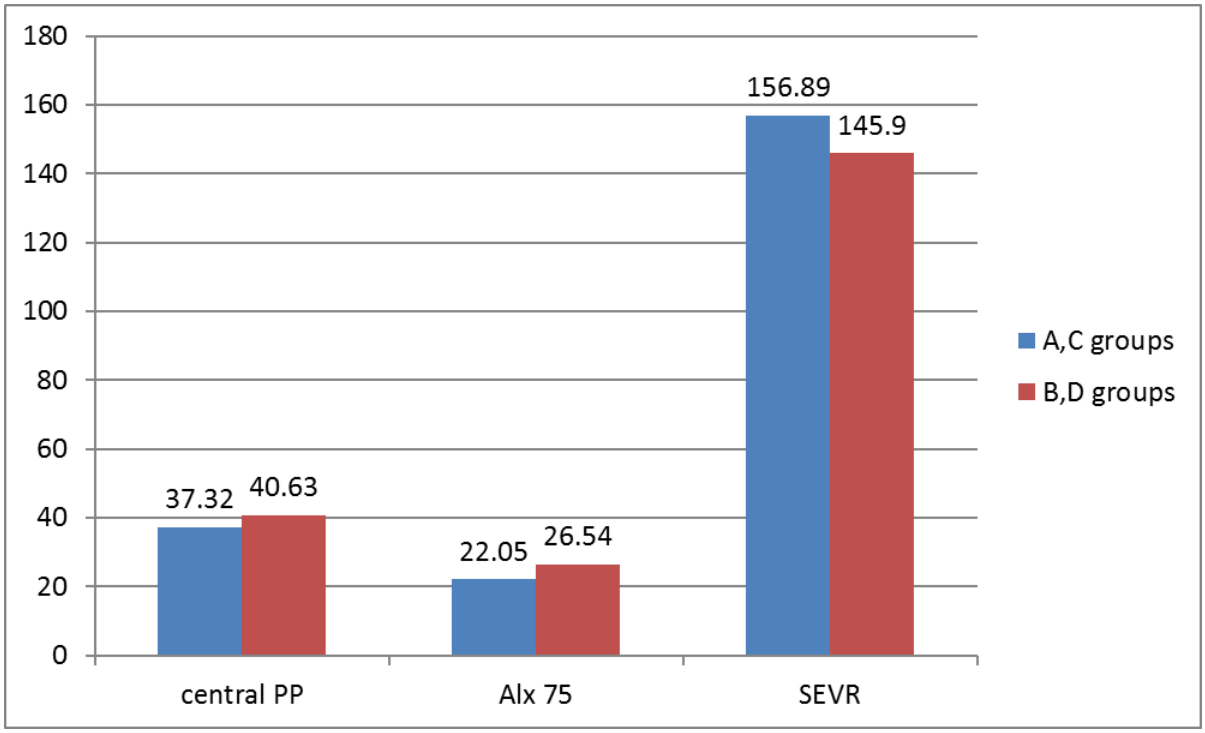

Figure 1. Indices of arterial stiffness and central BP in patients with ACO

Table 4. Indices of arterial stiffness and central BP in patients with ACO depending on smoking status

Indices	Ex-smokers (n=71)	Active smokers (n=40)
Central SBP, mm Hg	122.25±1.72	125.0±2.07
Central DBP, mm Hg	83.75±1.14	87.65±1.2*
Central PP, mm Hg	39.61±1.17	39.3±1.92
ED, ms	315.42±3.84	299.88±3.94**
ED, %	36.52±0.52	36.9±0.81
AP, mm Hg	11.79±0.72	8.73±0.87**
AIx75, %	26.83±1.19	21.78±1.76*
SEVR, %	150.34±3.62	148.48±4.6
ESP, mm Hg	109.86±2.21	113.75±1.96
PWVm, m/s	3.67±0.15	3.73±0.14
PWVe, m/s	4.92±0.26	4.8±0.25

Note.
* $p < 0.05$;
** $p < 0.01$ as compared to ex-smokers

Table 5. Indices of arterial stiffness and central BP in patients with ACO depending on BMI

Indices	Patients with normal body weight (n = 28)	Patients with excess body weight (n = 33)	Obese patients (n = 50)
Central SBP, mm Hg	119.25±2.68	122.27±2.69	126.12±1.78*
Central DBP, mm Hg	81.11±1.72	85.48±1.66*	87.2±1.18**
Central PP, mm Hg	38.14±1.8	39.15±1.98	40.48±1.56
ED, ms	320.68±6.11	309.3±6.11	304.08±3.63*
ED, %	36.11±1.02	35.85±0.75	37.5±0.62
AP, mm Hg	11.18±0.88	11.03±1.12	10.18±0.92
AIx75, %	25.39±1.8	25.84±2.21	24.22±1.45
SEVR, %	152.75±6.58	156.06±5.56	143.72±3.52 γ
ESP, mm Hg	107.64±2.68	112.82±2.56	112.27±2.71
PWVm, m/s	3.45±0.18	3.74±0.22	3.8±0.17
PWVe, m/s	4.61±0.38	5.04±0.37	4.92±0.27

Note.
* $p < 0.05$;
** $p < 0.01$ compared to patients with normal body weight;
γ $p < 0.05$;
$\gamma\gamma$ $p < 0.01$ compared to patients with excess body weight.

important prognostic marker, and its increase by more than 73% is a sign of a high risk of death [40]. There was a reliable correlation between the RV/TLC ratio and the AIx in patients with ACO ($r = 0.37$; $p < 0.05$) (Fig. 2). Therefore, in patients with ACO, one of the main indicators of arterial stiffness was associated with the development of pulmonary hyperinflation. This association may be the result of systemic effects of ACO (systemic inflammation, hypoxia, oxidative stress, etc.), the impact of negative environmental factors, changes in the elastic properties of the lungs and the vascular wall [18].

3. Conclusions

In patients with bronchial obstructive pathology, the parameters of vascular stiffness and central BP reflecting the degree of cardiovascular risk were significantly higher compared to those in apparently healthy individuals. They were significantly elevated in patients with COPD and ACO.

The indicators of central BP were significantly higher in patients with ACO and more pronounced bronchial obstruction, and in patients with more obvious symptoms of the underlying disease.

Excess body weight or obesity had a strong and pronounced effect on the parameters of central BP in patients with ACO.

In patients with a comorbidity, a reliable correlation between the indicator of the presence of pulmonary hyperinflation and the degree of arterial stiffness was revealed.

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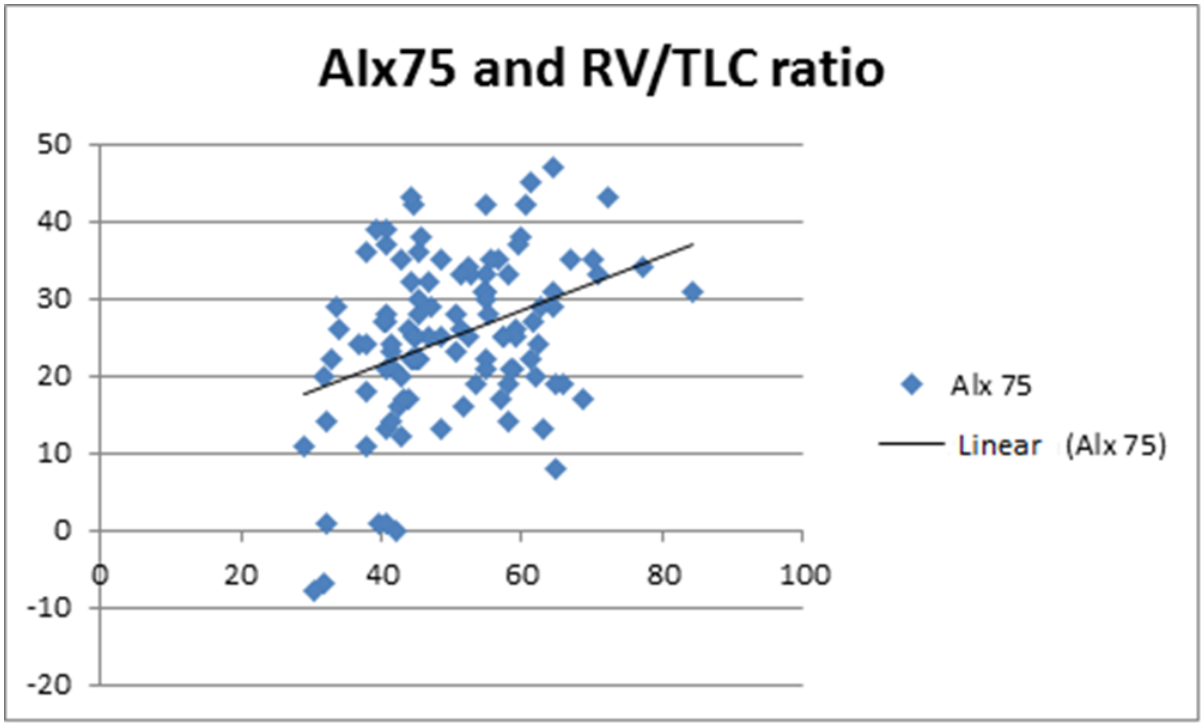

Figure 2. Relationship of arterial stiffness and the RV/TLC ratio in patients with ACO (r=0.37; p<0.05)

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