EVALUATION OF ATRIAL CONDUCTION FEATURES IN STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS AND ITS RELATIONSHIP WITH NEUTROPHIL TO LYMPHOCYTE RATIO

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ABSTRACT

Aims*: Chronic obstructive pulmonary disease (COPD) has been associated with a high frequency of cardiac arrhythmia. While many studies have examined the development of atrial fibrillation (AF) in COPD patients, there is insufficient data about atrial conduction time (ACT) and its relationship with the Neutrophil to Lymphocyte ratio (NLR) in these patients. The aim of the present study was to evaluate atrial conduction features and its relationship with NLR.*

Materials and methods*: The study groups comprised 40 patients with COPD and 40 healthy subjects, who were subjected to pulmonary function tests, 12-lead surface electrocardiograms, echocardiographic examinations and blood sample tests. ACT was measured through tissue Doppler imaging, while NLR was measured by dividing the neutrophil count by the lymphocyte count.*

Results*: Pulmonary function values were significantly lower in COPD patients than in the control group, as would be expected (p<0,001). According to the ACT measurements, tricuspid ACT was significantly longer in COPD patients than in the controls (26.4 ± 11.4 ms vs 17.7 ± 7.7 ms, p<0.001). Also, NLR was higher in COPD patients than in the control group (2.4 ±1.2 vs 1.94 ±0.8 p=0.009). A negative correlation was observed between tricuspid ACT and the percent of forced expiratory volume in one second (FEV1 %) (r = – 0.45; p <0.001), and a significant positive correlation was identified between tricuspid ACT and NLR (r=+0.38; p< 0.001).*

Conclusion*: Our study revealed prolonged tricuspid ACT and increased NLR in COPD patients, and the existence of a relationship between these parameters was identified. Previous studies claim that hypoxia and chronic inflammation may be the underlying mechanisms explaining arrhythmia in patients with COPD, while many studies also show that a prolongation of ACT and increased NLR is associated with atrial arrhythmias. In the light of our findings and previous data, the assessment of ACT and NLR can be considered a clinically useful approach to detecting the risk of AF development in the population.*

Key words*: Atrial conduction time, atrial fibrillation, chronic obstructive pulmonary disease, neutrophil to lymphocyte ratio.*

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Introduction

Chronic obstructive pulmonary disease (COPD) is a global health problem that has been defined as being partially characterizable by poor reversible airway obstruction[(1)]. The effects of COPD are not limited to the lungs, as COPD is documented to have significant systemic outcomes that may affect morbidity and mortality. COPD is a heterogeneous collection of syndromes with overlapping conditions, which causes major difficulties in obtaining an acceptable description for pathogenesis. Typically, patients show a chronic inflammation of the airways, lung tissue and pulmonary blood vessels from the start of the disease[(2)]. The abnormal inflammatory response in COPD is triggered by the inhalation of such noxious substances as tobacco smoke, and leads to structural changes and a narrowing of the small airways[(3)]. Systemic inflammation is considered a hallmark of COPD, and one of the key responsible mechanisms in the increased rate of comorbidities, including cardiovascular events[(4)]. The spectrum of cardiovascular disease includes right ventricular (RV) dysfunction, pul-

monary hypertension, coronary artery disease (CAD) and arrhythmia[5]. Cardiac arrhythmias, including atrial premature beats, multifocal atrial tachycardia, atrial flutter and atrial fibrillation (AF) occur frequently in patients with COPD, but are rarely fatal, and can generally be treated medically[6,7]. As with COPD, the development of AF is thought to be involved in systemic inflammation, and known risk factors include aging, cardiac disease, hypertension, obesity, smoking and hypoxia[8].

Atrial conduction delay is strongly associated with underlying diseases affecting the atria, either directly or indirectly[9-11], and any pathological process impairing atrial conduction may result in reentrant atrial arrhythmias[12]. The frequency of AF is increased in patients with impaired interatrial conduction. Atrial conduction time (ACT) has been proposed as a marker of atrial remodeling[13], and so the prevention or amelioration of atrial conduction delay may prevent the development of such atrial arrhythmias as AF. Indeed, previous studies suggest that the ACT may be a useful target of therapy[14-16].

Leukocyte count and its subtypes are also well-known inflammatory markers (17). With one of the key inflammatory cells in COPD being neutrophils, which are increased in sputum and their numbers grow with the progression of the disease[3]. Several studies have found that systemic inflammatory markers, such as C-reactive protein (CRP), fibrinogen and leukocyte count and its subtypes are higher in patients with COPD when compared with subjects without COPD, and is related to mortality in COPD patients[18,19]. The neutrophil to lymphocyte ratio (NLR), which can be derived from the white blood cell (WBC) count, is a novel marker of prognosis in patients with cardiovascular disease. Furthermore, several recent studies have shown that NLR is an indicator of systemic inflammation, and that a relationship exists between NLR and the presence of AF[20].

In recent years, many studies have examined the development of AF in COPD patients, but there is insufficient data about ACT and its relationship with NLR in these patients. The aim of the present study was to evaluate atrial conduction features, NLR and their possible relationship in stable COPD patients.

Materials and methods

Study population

A total of 80 subjects, including 40 healthy control and 40 COPD patients who were followed up at chest disease out-patient clinic of the department of pulmonary diseases were recruited in the study. The diagnosis of COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD)[3] criteria was confirmed by spirometry where the criterion is a ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC), FEV1 / FVC < 0.70. FEV1 % was expressed as the % of expected normal value. In addition, patients with COPD were classified according to their airflow limitation severity: GOLD1 (mild) was FEV1 ≥ 80% predicted; GOLD2 (moderate) was 50% ≤ FEV1 < 80% predicted; GOLD3 (severe) was 30% ≤ FEV1 < 50% predicted; and GOLD4 (very severe) was FEV1 < 30% predicted. In the COPD patient group, typical pharmacological treatment was used: inhaled steroids, beta-2 agonists, theophylline medications. Controls were not treated pharmacologically. None of patients was receiving pharmacological cardiovascular drugs.

Patients with diagnosed right or left ventricular failure, AF, right or left bundle branch block, moderate-severe valve abnormalities, known coronary artery disease, systemic arterial hypertension, diabetes mellitus, chronic renal failure, anemia, acute infectious disease, hematological disease, thyroid dysfunction and rheumatic diseases were excluded from the study.

Blood Sample Analysis

The blood samples were collected in calcium ethylenediaminetetraacetic acid (EDTA) tubes. Whole blood counts were evaluated using an autoanalyzer Sysmex XT-1800i Hematology Analyzer (Sysmex Corporation, Kobe, Japan). Baseline NLR was measured by dividing neutrophil count by lymphocyte count.

Electrocardiography

Standard ECGs were acquired from all patients with sweeping rate of 50 mm/s and amplitude of 20 mm/mV. A cardiologist who was blind to conduction times, measured by other methods, evaluated all ECGs. The values were calculated by taking the average of three consecutive complexes in each lead. The maximum and minimum durations of P waves (Pmax and Pmin, respectively) were detected, and the difference between Pmax and Pmin was defined as P wave dispersion. (Pwd)

Echocardiographic examination

The echocardiographic examination consisted of a standard two dimensional echocardiogram, including M-mode and Doppler echocardiography (Vivid S5, General Electric Horten, Norway) during continuous ECG monitoring according to the recommendations as described in the American Society of Echocardiography guidelines[21]. Left ventricular (LV) wall thickness (Interventricular septum-IVS and Posterior wall-PW) and LV end-diastolic/end-systolic diameters (LVEDD / LVESD) were measured by M-mode echocardiography. Left atrial (LA) and right atrial (RA) diameters were measured from apical four-chamber view. LV ejection fraction (EF) was calculated using apical four-chamber views by Simpson's method. Pulmonary acceleration time (PAAT) was measured using pulse wave Doppler in the parasternal short-axis view. LA maximum volume at the end-systolic phase was measured and calculated index by dividing the volumes to body surface area. Because of inadequate tricuspid regurgitation (TR) or absence of Doppler-detected TR, mean pulmonary artery pressure (mPAP) was estimated by using Mahan's equation (79 - 0.45* PAAT)[22].

Tissue Doppler echocardiography

Tissue Doppler echocardiography was performed by transducer frequencies of 3.5-4.0 MHz, adjusting the spectral pulsed Doppler signal filters until a Nyquist limit of 15-20 cm/s and using the minimal optimal gain. ACT was defined as the time between the beginning of the P-wave on the monitor's ECG to the start of the late diastolic wave (Am). It was obtained from lateral mitral annulus, septal mitral annulus, and RV tricuspid annulus and named as lateral ACT, septum ACT and tricuspid ACT respectively. The difference between lateral ACT and tricuspid ACT was defined inter-atrial ACT; the difference between septal ACT and tricuspid ACT was defined as intra-right atrial ACT; the difference between lateral ACT and septal ACT was defined as intra-left ACT.

All measurements were repeated three times, and average values were received for each of the atrial conduction delay times. Two experienced investigators unaware of the subject's clinical status performed all measurements. If a difference of > 5% in any of the variables measured by both investigators was found, the patient was not included, whereas if the difference was < 5%, the measurements were averaged.

Statistical analysis

All analyses were performed using the statistical package for the social sciences (SPSS for Windows 15.0) software package. Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as percentage. All the numerical variables of the study groups presented a normal distribution, and the variances between the groups were equal. The results obtained in the COPD patients group and in the control group were compared by means of the independent simple T-test. The relationships between variables were examined with Pearson correlation coefficients. Results were evaluated at 95% confidence interval and p value less than 0.05 was accepted significant.

Results

Patient characteristics

The baseline demographic parameters, leukocyte counts and spirometry results of the two groups are set out in Table 1.

	COPD Patients n= 40	Control Group n= 40	p value
Age (years)	54.8±9.6	51.0±8.5	0.062
Male	28 (70%)	26 (65%)	
Female	12 (30%)	14 (35%)	
BMI, (kg/m2)	27.3±3.2	25.7±4.7	0.101
BSA, (m^2)	1.88±0.16	1.81±0.18	0.093
HR (1/min)	75.3±13.3	74.2±11	0.71
Current Smoking	23 (57,5%)	17 (42%)	0.07
Laboratory findings			
Neutrophil, 10^9/L	4.9±1.9	3.8±1	**0.004**
Lymphocyte, 10^9/L	2.21±0.7	2.11±0.5	0.675
NLR	2.4±1.2	1.94±0.8	**0.009**
Spirometric Paramaters			
FEV_1 (lt)	2.0±0.6	3.3±0.8	**<0.001**
FEV_1 (%)	64±16.3	104±11.5	**<0.001**
FEV_1/ FVC	65.5±9.4	88.2±3.5	**<0.001**
Severity of COPD (%)			
GOLD1	4 (10%)		
GOLD2	27 (67.5%)		
GOLD3	7 (17.5%)		
GOLD4	2 (%5)		

Table 1: Baseline demographic parameters, leukocyte counts, and spirometry results in COPD patients and control group.

COPD - chronic obstructive pulmonary disease, BMI- body mass index, BSA- body surface area, HR (1/min)- heart rate per minute NLR- Neutrophil to lymphocyte ratio FEV_1- forced expiratory volume in one second, FEV_1 %- forced expiratory volume in one second %, FEV_1/FVC - forced expiratory volume in one second /vital capacity ratio, GOLD- Global Initiative for Chronic Obstructive Lung Disease Criteria, NS- statistically nonsignificant.

Statistically important differences with respect to age, sex, body mass index (BMI), BSA, smoking in COPD patients and in the control group were not found. Pulmonary function values of FEV_1, FEV_1%, FEV_1/FVC measured with the spirometer were significantly lower in COPD patients than the control

group. The spirometry results showed bronchial obstruction in COPD patients (FEV1 64 ±16.3%, FEV1/FVC 65.5 ±9.4%) and no ventilation effectiveness impairment in the control group. In laboratory results, Neutrophil count and NLR were significantly higher in patients with COPD (4.9 ±1.9 vs 3.8 ±1 p=0.004 2,4 ±1.2 vs 1.94 ±0.8, p=0.009 respectively)

Echocardiographic examination

All groups were similar in terms of conventional echocardiographic parameters. No difference was found between the groups regarding LVEDD, LVESD, IVS, PW, EF, LA max volume index. Only statistically important differences concerned RA diameter, PAAT and mPAP. As assessed from the PAAT, mPAP was significantly higher in COPD patient (p <0,001). Echocardiography data are presented in Table 2.

	COPD Patients n= 40	Control Group n= 40	p value
LVEDD (mm)	48.4±3.4	46.9±2.7	0.06
LVESD (mm)	31.8±3.5	30.4±3.1	0.081
IVS (mm)	10±1.0	9.7±0.7	0.180
PW (mm)	10±0.9	9.7±0.9	0.117
LVEF (%)	64.1±3.2	64.9±2.9	0.337
LA (mm)	35.6±2.5	35.7±1.9	0.803
LA Vmax (ml/m^2)	21.6±3.7	20.7±4.5	0.055
RA (mm)	32.6±2.1	31.1±3.6	**0.033**
PAAT (ms)	99.7±19.9	130.7±13.2	**<0.001**
mPAP (mmHg)	34.1±8.9	20.1±5.9	**<0.001**

Table 2: Conventional echocardiographic parameters in COPD patients and control group.
LVEDD- left ventricular end-diastolic diameter, LVESD- left ventricular end-sistolic diameter, IVS- interventricular septum, PW- posterior wall, LV EF -left ventricular ejection fraction, LA- left atrial diamater, LA Vmax index- left atrial maximal volume index, RA- right atrial diamater, PAAT-pulmonary accelaration time, mPAP-mean pulmonary artery pressure, NS- statistically nonsignificant.

Atrial conduction parameters

Atrial conduction times and P wave analysis are set out in Table 3. The tricuspid ACT was significantly higher in patients with COPD than the control group (26.4 ± 11.4 ms vs 17,7 ± 7.7 ms, p<0.001) (Figure 1). There was no difference in lateral ACT and septal ACT between the two groups. There were no differences intra-atrial and inter-atrial ACT between COPD patients and control group. Pmax and Pwd were significantly higher in patients with COPD than the control group (107,7±11,8 vs 93,6±9,4 p<0,001, 50,2±14 vs 40,8±10,2 p= 0,001 respectively).

	COPD Patients n= 40	Control Group n= 40	p value
Lateral ACT(ms)	35.5±10.9	31.5±10.5	0.10
Septal ACT (ms)	25.9±10.7	22.3±8.4	0.095
Tricuspid ACT (ms)	26.4±11.4	17,7±7.7	**<0,001**
Intra-atrial Left ACT (ms)	9.6±9.2	12.7±7.7	0.106
Intra-atrial Right ACT (ms)	0.5±11.1	1.05±8.3	0.477
Interatrial ACT (ms)	9.1±12.0	13.8±9.1	0.052
Pmax (ms)	107,7±11,8	93,6±9,4	**<0,001**
Pmin (ms)	57,2±13,2	52,6±10,2	0.083
P wd (ms)	50,2±14	40,8±10,2	**0,001**

Table 3: Comparison of parameters of atrial conduction times and P wave dispersion between the groups.
ACT- atrial conduction time, ms- millisecond, Pmax- duration of the longest P wave, Pmin- duration of the shortest P wave, Pwd- P wave dispersion, NS- statistically nonsignificant.

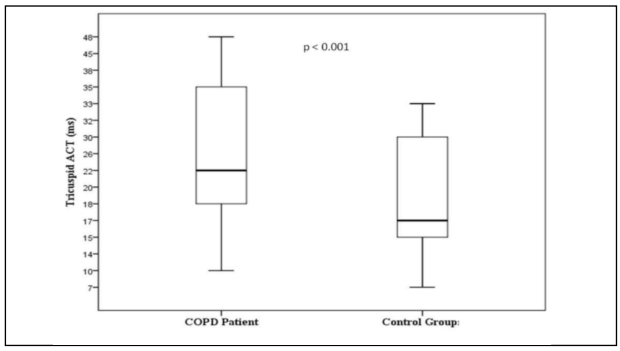

Figure 1: Tricuspid ACT is significantly longer in patients with COPD compared to the control group.

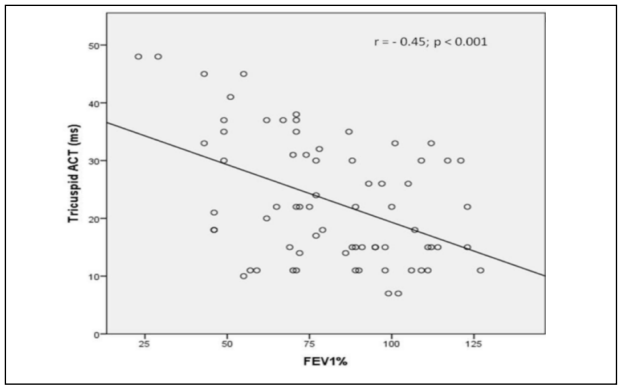

Figure 2: Scatter plot graph showing the negative correlation between tricuspid ACT and FEV_1% in patients with COPD.

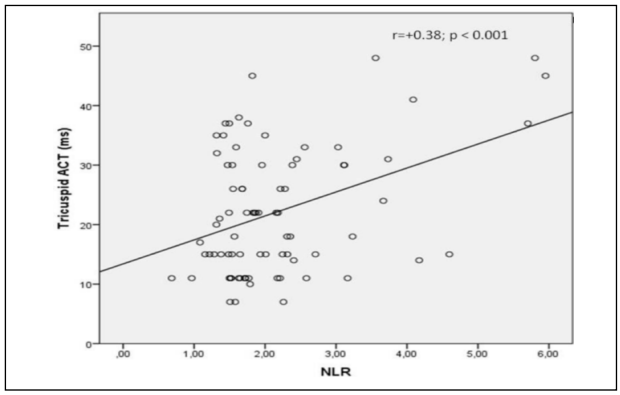

Figure 3: Scatter plot graph showing the positive correlation between tricuspid ACT and NLR in patients with COPD.

A negative correlation was observed between tricuspid ACT and FEV1 % (r = - 0.45; p <0.001) (Figure 2). A moderate positive correlation was found between tricuspid ACT and mPAP (r=+0.37; p=0,001). There was a significant positive correlation between tricuspid ACT and NLR (r=+0.38; p <0.001) (Figure 3)

Discussion

The present study demonstrated that COPD patients have longer tricuspid ACT and higher NLR when compared to healthy controls. Furthermore, a positive correlation was identified between NLR and tricuspid ACT. Previous studies have demonstrated that patients with longer ACT and higher NLR have increased atrial arrhythmia incidence, and these parameters may predict developing atrial fibrillation[12,21].

COPD has been associated with a high frequency of cardiac arrhythmia, and the risk of arrhythmia in patients with COPD is influenced by the state of the disease, with a higher frequency of supraventricular tachycardia during exacerbations[22]. Atrial arrhythmias are common in the population, but only a few studies have analyzed in detail the relationship between lung function and the risk of developing atrial arrhythmia. In recent studies it has been established declines in pulmonary function can be linked to increased inflammatory markers[23]. Furthermore, low-grade inflammations that have been demonstrated by an increase in blood leukocyte levels, acute-phase proteins and other inflammatory cytokines can also be associated with stable COPD[24]. NLR was introduced as a cost-effective, potential inflammatory marker with prognostic and predictive values in cases of systemic inflammatory disease([16]. As with COPD, the development of AF is thought to be involved in systemic inflammation[7].

ACT has been proposed as a marker of atrial remodeling, and reflects the extent of both the electrical and structural remodeling of the atria[25]. Any pathologic process impairing atrial conduction may result in reentrant atrial arrhythmias, and the frequency of AF has been seen to increase in patients with impaired inter-atrial conduction time[11]. ACT, defined by TTE, could be useful in the noninvasive evaluation of atrial conduction disturbance[12]. As in previous studies, we used TDI echocardiographic method, and found that patients with COPD had similar lateral-septal ACT but prolonged tricuspid ACT, and that RA was also dilated in COPD patients. There was no statistically significant difference in the intra-atrial and inter-atrial conduction times of the groups. Furthermore, we have demonstrated that the prolongation of ACT can be related to spirometric parameters in stable COPD patients. These results suggest a relationship between COPD and right atrial electromechanical delay. Caglar et al.[26] also showed that a right atrial mechanical delay was significantly correlated with right atrial area and PAP, and negatively correlated with FEV1 measurements. Omi et al.[27] showed that patients with PAF had longer tricuspid ACT and greater right atrial dimensions than the control group. Karapınar et al.[28] reported a significant difference between PAF patients and the control group with regard to tricuspid ACT. Furthermore, previous electrophysiological studies have documented that RA conduction is prolonged and fractioned in patients with paroxysmal AF[29,30]. The findings of this investigation concur with the data from recent electrophysiological works and the noninvasive expressions of RA conduction disturbance that have been documented invasively in those studies. There are two possible theories that may be deduced from this finding, being a different localization of the conduction pathways, or different degrees of conduction disturbance in different localizations of the RA.

We found that tricuspid ACT was negatively correlated with FEV1 %. To date, there have been few epidemiological studies analyzing the relationship between the incidence of AF and pulmonary function, and the results of these studies are controversial. In Takahata study[7], Cardiovascular Health study[32] and Copenhagen City Heart Study[33], it was demonstrated that impaired pulmonary function was an independent risk factor for AF, and that AF was significantly associated with the degree of predicted FEV1 %. However, in the Framingham Heart Study[34], they concluded that the incidence of AF did not correlate with FEV1. Similarly Renfrew/Paisley study[35] found no relationship between FEV1 % and AF, while the present study found that tricuspid ACT was positive correlated with NLR. Several studies have shown a relationship between NLR and the presence of AF. Of note, Im et al.[36] demonstrated that NLR is an independent predictor of an early recurrence after radiofrequency catheter ablation in patients with AF. Gibson et al.[37] showed that NLR is a predictor of new-onset AF after coronary artery bypass grafting,

and in our study, we also found higher NLR in stable COPD patients, and an association with longer tricuspid ACT.

Previous studies have indicated that the mechanisms involved in the relationship between AF and COPD are hypoxia, elevated pulmonary pressure and chronic inflammation. First, subjects with severely-impaired pulmonary function may have hypoxia, which reportedly induces sympathetic drive and results in the incidence of AF[7]. This may be one of the mechanisms whereby AF is induced in subjects with airflow limitations. Second, subjects with reduced pulmonary function may have elevated PAP, which can be attributed to pulmonary arterial intimal and medial cellular hypertrophy, and hyperplasia in COPD patients[38]. Kang et al.[39] demonstrated the elevation of PAP and reduced pulmonary function in AF patients. Similarly in our study, decreased FEV1 was associated with a higher PAP. Pulmonary hypertension leads to a remodeling and structural changes in RV- RA[38,40], and in addition, atrial tension is increased secondary to high PAP levels. Third, chronic systemic inflammation is reported to be involved in the pathogenesis of some chronic respiratory disease, and the involvement of systemic inflammation was also suggested in the pathogenesis of AF[19]. As a result of all these factors, impairments to the electrical conduction pathways leads to slow down and delay atrial depolarization, which may explain why tricuspid ACT prolongs and NLR increases in our study.

Study Limitations

The main limitation of our study is related to its cross-sectional design and the lack of follow-up with the patients, while a further limitation is the small study population. For these reasons, long-term follow-up and large-scale prospective studies are needed to determine the predictive value of prolonged ACT and NLR in this population.

Conclusions

Our study revealed prolonged tricuspid ACT and increased NLR in COPD patients, and identified a relationship between these parameters. Based on previous studies and our own results, an assessment of ACT and NLR may be considered a clinically useful approach to detecting the risk of AF in this population. However, larger prospective long-term follow-up studies are warranted so as to come up with a precise definition.

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