Atrial electromechanical delay, neutrophil-to-lymphocyte ratio, and echocardiographic changes in patients with acute and stable chronic obstructive pulmonary disease

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Background: Atrial electromechanical delay (AEMD) is the time interval between the beginning of *P* wave on surface electrocardiography and starting of the late diastolic wave on tissue Doppler imaging. We investigated the prolongation of AEMD, echocardiographic changes, and correlation of these findings with neutrophil-to-lymphocyte ratio (NLR) in patients with chronic obstructive pulmonary disease (COPD). **Materials and Methods:** The study consisted of 105 (49 females and 56 males; mean age: 65.1 ± 9) patients with COPD exacerbation and 104 (21 females and 83 males; mean age: 64.8 ± 9.6) stable COPD outpatients. Demographics, body mass index, pulmonary function tests, and transthoracic echocardiography of the patients were evaluated. Echocardiography was performed in the first 6 h for stable COPD outpatients and in the first 24 h for COPD exacerbation patients. Diameters of right ventricle (RV), left ventricle (LV) and left atrium, aortic root diameters, left ventricular ejection fraction (LVEF), E_{max}, A_{max}, E_{max}/A_{max}, tricuspid annular plane systolic excursion (TAPSE), Ea, Aa, Ea/Aa, E_{max}/Ea, and tricuspid regurgitation velocity (TRV) were evaluated. AEMD measurements were obtained from lateral/tricuspid, lateral/mitral, and septal annulus from apical four-chamber views with tissue Doppler imaging and corrected for heart rate. Complete blood count including NLR was also assessed. **Results:** The mean age of patients in exacerbation period (65.1 ± 9) was higher than the stable group (64.8 ± 9.6). RV basal and mid diameters ($P < 0.001$), A_{max} ($P < 0.001$), Ea tricuspid ($P = 0.040$), Aa tricuspid ($P < 0.001$), TRV, and systolic pulmonary artery pressure ($P < 0.001$) were higher; TAPSE and tricuspid E_{max}/A_{max} ($P < 0.001$) were significantly lower in patients with COPD exacerbation. LV end-diastolic diameter ($P = 0.002$) and LVEF ($P = 0.005$), E_{max}/A_{max} mitral ($P < 0.001$), Ea/Aa mitral ($P < 0.001$), and Ea/Aa septal ($P < 0.001$) were significantly lower; A_{max} mitral ($P = 0.002$), Aa mitral ($P < 0.001$), Aa septal ($P < 0.001$), and systolic motion mitral ($P = 0.011$) were significantly higher in patients with exacerbation. AEMD lateral/tricuspid ($P < 0.001$), lateral/mitral ($P < 0.001$), and septal ($P < 0.001$) were significantly higher in patients with COPD exacerbation. Neutrophil and lymphocyte count ($P < 0.001$) and NLR ($P = 0.003$) were significantly higher in the acute group. A weak correlation of NLR with LV end-diastolic diameter ($P = 0.003$; $r = 0.357$), E_{max}/Ea mitral ($P = 0.019$; $r = 0.285$), E_{max} tricuspid ($P = 0.045$; $r = -0.244$), and systolic motion septal ($P = 0.003$; $r = 0.352$) was detected in patients with stable COPD. **Conclusion:** In COPD exacerbation patients, prolongation of AEMD intervals was determined. Acute period of COPD may trigger atrial dysrhythmias including atrial fibrillation and flutter, multifocal atrial tachycardia, premature beats, and both systolic and diastolic dysfunctions frequently.

Key words: Atrial electromechanical delay, chronic obstructive pulmonary disease, echocardiography, prolongation

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by commonly progressive airflow limitation and directly associated with an increased chronic inflammatory response in the airways. COPD affects primarily lungs, but it has some important extra pulmonary effects including cardiovascular system abnormalities that contribute to disease severity.[1] Cardiovascular diseases are the leading causes of mortality in patients with mild-to-moderate COPD and many of these patients remain undiagnosed.[2] The development, evaluation, and prevalence of cardiovascular comorbidities in COPD patients have not been totally clarified, but COPD may affect right ventricle (RV) and atrium, pulmonary blood vessels, and left ventricle (LV) and cause pulmonary hypertension, cor pulmonale, and RV-LV dysfunctions.[2,3] The important clinical manifestations of COPD are myocardial infarction, heart failure, atrial arrhythmias such as atrial fibrillation (AF) and flutter, multifocal atrial tachycardia, and premature beats.[2,3]

AF is the most commonly encountered arrhythmia in clinical practice and is related to increased mortality and morbidity.[4] COPD is independently associated with AF, but the pathophysiological mechanism is not completely determined.[4] Increased atrial automaticity, trigger activity, microreentry, and abnormal atrial tissue are possible stimulating mechanisms of AF.[4,5] Atrial electromechanical delay (AEMD) is the time interval between the beginning of *P* wave on surface electrocardiography (ECG) and starting of the late diastolic wave (Am-wave) on tissue Doppler imaging (TDI).[5] The structural changes of atrial tissue may cause delay between the electrical stimulation and mechanical contraction.[5] Atrial tissue changes can cause prolongation of *P* wave on surface ECG.[6] Prolongation of *P* wave can be seen in patients undergoing coronary artery bypass surgery and patients with hypertrophic cardiomyopathy, right atrial dilatation, atrial septal defect, hypertension, and COPD due to affected atrial tissue.[6]

COPD is a common progressive inflammatory disease, and therefore a simple, widely available, and cost-effective biomarker is needed to reveal inflammation, particularly during periods of exacerbation.[7,8] Neutrophil-to-lymphocyte ratio (NLR) is a rapid and easy inflammatory marker which can be obtained from complete blood count and it has been shown to be an independent risk factor for tumors, cardiovascular diseases, sepsis, inflammatory, and infectious diseases such as COPD.[7,8]

We thought that the echocardiographic findings that occur in two different periods (exacerbation and stable) of COPD will give detailed information about the cardiac effects of the disease. The aims of the study were to compare AEMD intervals, echocardiographic changes of acute and stable periods of COPD, and correlation of these findings with NLR. We especially focused on the prolongation of AEMD intervals of the patients during two periods of this condition.

METHODS

Study design and population
This prospective cross-sectional study was conducted with the approval of Kafkas University Medical Faculty Ethics Committee (REF: 80576354-050-99/63) between March and July 2018**.** The sample size was estimated as 46 per group and 106 for total patients based on the results of a similar studies, and the formula was used for comparing two groups ([Z1 − a/2 + Z1 − b] p1 [1 − p1] × p2 [1 − p2]/ [p1 − p2]2), with a confidence coefficient of 95% and test power of 80% for reaching better outcomes. A written informed consent form was obtained before the initiative of the research protocol.

Inclusion and exclusion criteria
The study included 105 (49 females and 56 males) patients with COPD exacerbation who admitted to the emergency department and 104 (21 females and 83 males) stable COPD outpatients who admitted to the respiratory medicine unit, Stages I-IV, for both groups. COPD outpatients were stable with no exacerbation of disease for at least 1 month prior to admission and they were under regular treatment. The exclusion criteria were as follows: under age of 18 years, patients with no previous COPD diagnosis, patients with valvular heart disease, wall motion abnormality, uncontrolled hypertension, insulin-dependent diabetes mellitus, hypo- and hyperthyroidism, anemia, acid–base disorders, electrolyte disorders, renal impairment, lipid abnormalities, coronary artery disease, acute coronary syndrome, heart failure, structural heart diseases, atrioventricular conduction abnormalities, ejection fraction (EF) <50%, pulmonary embolism, pneumonia, malignancy, systemic inflammatory response syndrome, intubated patients after admission, and patients using two or more oral antidiabetic drugs. The patients who had a history of AF and prior use of antiarrhythmic drugs were also excluded. The diagnosis of acute COPD exacerbation and stable COPD were in accordance with the criteria established by the European Respiratory Society and American Thoracic Society.[9,10]

Design
The following parameters of all patients were evaluated: age, gender, body mass index, pulmonary function tests, and transthoracic echocardiography. Forced expiratory volume in the 1st s (FEV$_1$) and forced vital capacity (FVC) were measured at baseline using a spirometer (Spirolab

III-MIR, Italy). The most appropriate expiratory maneuver was used recording of FEV_1 and FVC results.

Echocardiography was performed in the first 6 h for stable COPD outpatients and in the first 24 h for COPD exacerbation patients who admitted to emergency department. All patients and their relatives were informed about the aims of the study. Written and verbal consent was obtained for all procedures and then the patient's signature was accepted.

Blood samples
All blood samples were drawn from the vein in the forearm and collected into 2 mL Lavender (EDTA) top tube and were analyzed with Pentra DF Nexus, Horiba Medical, Japan, with Automated Cell Counter Methodology. The blood samples were stabilized optimally when run within in 4 h of collection, stable for 24 h at room temperature, and stable for 36 h at 2°C–8°C.

Echocardiography
Transthoracic echocardiography (Epiq 7; Philips) was evaluated by a cardiologist experienced with 7 years in a standard protocol in all patients. Patients were monitored using electrocardiographic leads and were placed in the left lateral decubitus position. Echocardiographic images were obtained from the parasternal views (long axis and short axis), the apical four-chamber view, and the subcostal view. Echocardiographic measurements were performed at the end of expiration according to the recommendations of the American Society of Echocardiography/European Association of Echocardiography.[11] (1) Diameters of RV were measured in the apical view. (2) LV diameters and wall thickness were measured in the parasternal view. (3) Left atrial diameter was measured in the parasternal view. (4) Aortic root diameters were measured at the sinus of Valsalva. (5) Left ventricular EF (LVEF) was measured in the apical four-chamber view by modified Simpson method. (6) RV and LV functions were evaluated as follows: (a) maximal peak velocity of early diastolic flow (E_{max}), maximal peak velocity of atrial contraction (A_{max}), and ratio of these (E_{max}/A_{max}) were measured over the mitral and tricuspid valves; (b) TDI was measured in the mitral and tricuspid lateral annulus (tricuspid annular plane systolic excursion [TAPSE]) at early diastole (Ea), atrium systole (Aa), and ratio of these (Ea/Aa); (c) the ratio of $E_{max}/$Ea.[3] (7) Aortic, tricuspid, mitral, and pulmonary valvular evaluation. (8) tricuspid regurgitation velocity (TRV) was recorded by continuous wave Doppler.

AEMD was calculated from colored-TDI recordings; it was determined as the time interval between the beginning of echocardiographic *P* wave to the initial of Am-wave (late diastolic wave) in TDI recordings and measured from lateral/tricuspid, lateral/mitral, and septal annulus from apical four-chamber views.

Statistical analysis
All statistical calculations were performed with IBM SPSS Statistics software (version 22, IBM Corporation, Armonk, NY, USA). All continuous variables were expressed as mean ± standard deviation; categorical variables were defined as percentages (%). The categorical parameters were compared with Chi-square test and Fisher's exact test. The normal distribution was determined by histogram and Kolmogorov-Smirnov test. The mean values of continuous variables were compared between the groups using Mann-Whitney *U*-test. A nonparametric (distribution free) test known as Spearman's rank correlation coefficients were used to measure the strength of the associations between two variables. A *P* level of < 0.05 was considered statistically significant. This significance threshold was <0.01 for Spearman's rank correlation. Univariate and multivariable logistic regression analyses were used determining risk factors. All statistical analyses were performed by a blind statistician about details of the study. The study was cross-sectional and it did not include a long-term interval follow-up and therefore any missing data was recorded. In the study, the effect of NLR on cardiac functions was not examined, only the relationship between them was detailed, and therefore, logistic regression analysis was not performed.

RESULTS

In the study, 214 patients including acute and stable period participated, but 209 cases completed it. Figure 1 demonstrates the flow chart of the study.

First, 33.5% (*n* = 70) of all patients were female and 66.5% (*n* = 139) of them male. The mean age of patients in exacerbation period (65.1 ± 9) was higher than the stable group (64.8 ± 9.6), but it was not statistically significant (*P* = 0.253). Clinical characteristics and spirometric findings for the two groups are presented in Table 1. Heart rate was higher in patients with COPD exacerbation group (*P* < 0.001). FEV_1 and FVC were significantly higher in stable COPD outpatients (*P* < 0.001)

Conventional and tissue Doppler echocardiographic parameters of the right heart for the two groups are shown in Table 2. RV basal (*P* < 0.001) and mid (*P* < 0.001) diameters, A_{max} (*P* < 0.001), Ea (*P* = 0.040), Aa tricuspid (*P* < 0.001), TRV (*P* < 0.001), and systolic pulmonary artery pressure (SPAP) (*P* < 0.001) were significantly higher in COPD exacerbation patients. TAPSE (*P* < 0.001) and E_{max}/A_{max} tricuspid (*P* < 0.001) were significantly lower in the exacerbation group.
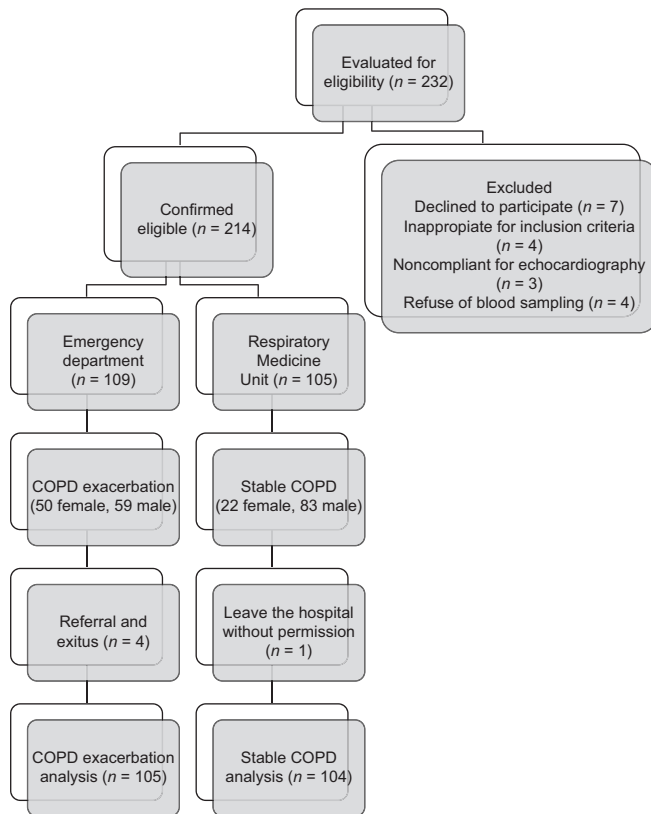
Figure 1: Study flow diagram

Table 1: Demographics and spirometric characteristics of the patients

	COPD exacerbation (*n*=105)	Stable COPD (*n*=104)	*P*
Age (years)	65.1±9	64.8±9.6	0.253
BMI (kg/m²)	28.47±6.09	27.23±5.09	0.130
Heart rate (beats/min)	97.4±13.9	78.9±11.6	<0.001
FEV₁ (%)	33.8±12.3	56.7±16.4	<0.001
FVC	34.2±13.2	55±12.9	<0.001

*Mann-Whitney *U*-test. Continuous variables are expressed as mean±SD.
COPD=Chronic obstructive pulmonary disease; BMI=Body mass index;
FEV₁=Forced expiratory volume in the 1st s; FVC=Forced vital capacity;
SD=Standard deviation

Table 2: Echocardiographic findings of the right heart in both groups

Dimensions	Right heart		*P*
	COPD exacerbation	Stable COPD	
RV (mm)			
Basal	37.5±5.9	35.2±5	<0.001
Mid	28.5±6	24.3±3.9	<0.001
Vertical	47.6±7	49.1±5.9	0.065
TAPSE (mm)	20.7±3.7	24±3.4	<0.001
Ventricular function			
Diastolic function			
E_{max} tricuspid (cm/s)	52.98±16.05	48.2±10.66	0.070
A_{max} tricuspid (cm/s)	70.98±18.36	54.67±12.94	<0.001
E_{max}/A_{max} tricuspid	0.77±0.22	0.92±0.27	<0.001
Ea (TDI tricuspid) (cm/s)	8.68±2.72	7.93±2.35	0.040
Aa (TDI tricuspid) (cm/s)	18.74±5.06	15.24±3.39	<0.001
Ea/Aa tricuspid	0.49±0.22	0.54±0.18	0.008
E_{max}/Ea	6.61±3.01	6.56±2.27	0.347
Assessment of pulmonary hypertension			
TRV (m/s)	3.085±0.381	2.759±0.387	<0.001
SPAP (mmHg)	38.4±9.2	30.7±8.5	<0.001
Systolic motion tricuspid	12.7±3.07	11.99±2.53	0.056

*Mann-Whitney *U*-test. Continuous variables are expressed as mean±SD.
COPD=Chronic obstructive pulmonary disease; TAPSE=Tricuspid annular plane
systolic excursion; E_{max}=Maximal peak velocity of early diastolic flow; A_{max}=Maximal
peak velocity of atrial contraction; Ea=Early diastole; Aa=Atrium systole;
TDI=Tissue doppler imaging; TRV=Tricuspid regurgitation velocity; SPAP=Systolic
pulmonary artery pressure; SD=Standard deviation; RV=Right ventricle

Conventional and tissue Doppler echocardiographic parameters of left heart and septum for the two groups are shown in Table 3. LV end-diastolic diameter ($P = 0.002$) and LVEF ($P = 0.005$), Ea/Aa mitral ($P < 0.001$), and Ea/Aa septal ($P < 0.001$) were higher and A_{max} ($P = 0.002$), Aa mitral ($P < 0.001$), Aa septal ($P < 0.001$), and systolic motion mitral ($P = 0.011$) were significantly lower in patients with COPD exacerbation.

Measurements of AEMD, complete blood count, and NLR for the two groups are presented in Table 4. AEMD lateral/tricuspid ($P < 0.001$), lateral/mitral ($P < 0.001$), and septal ($P < 0.001$) were significantly higher in patients with acute COPD exacerbation compared with the stable outpatients. WBC ($P = 0.045$), neutrophil count ($P < 0.001$), lymphocyte count ($P < 0.001$), NLR ($P = 0.003$), and eosinophil ($P = 0.005$) were significantly higher in patients with exacerbation ($P < 0.05$). In addition, a weak correlation of NLR with LV end-diastolic diameter ($P = 0.003$; $r = 0.357$), E_{max}/Ea mitral ($P = 0.019$; $r = 0.285$), E_{max} tricuspid ($P = 0.045$; $r = -0.244$), and systolic motion septal ($P = 0.003$; $r = 0.352$) was detected in patients with stable COPD [Table 5].

The independent risk factors affecting the acute and stable period of COPD are demonstrated in Table 6 by logistic regression analysis including adjusted and unadjusted odds ratio (95% confidence interval) values. Accordingly, NLR, TAPSE, Ea tricuspid, and AEMD lateral/tricuspid were independent risk factors for COPD periods.

DISCUSSION

Cardiovascular diseases including dysrhythmias are common causes of mortality in COPD, and systemic inflammation, vascular dysfunction, and lung hyperinflation are responsible mechanisms for these kinds of comorbidities.[3] Early prediction of cardiovascular complications in patients with COPD exacerbation may

increase the survival and improve poor outcomes.[3] In the study, prolongation of AEMD interval which is the AF predictor and cardiac changes of heart caused by COPD were evaluated by echocardiography.

Table 3: Echocardiographic findings of the left heart and septum in both groups

Dimensions	Left heart		P
	COPD exacerbation	Stable COPD	
Left atrium (parasternal long axis)			
Diameter (mm)	36.9±4	36.4±4	0.253
LV (mm) (parasternal long axis)			
End-diastolic diameter	44.7±4.1	46.2±3.9	0.002
End-systolic diameter	27.9±4	28.6±3.8	0.129
LV wall thickness (mm)			
Interventricular septum	12.4±7.7	11.6±1.2	0.397
Posterior wall	11.2±7.7	10.3±1	0.726
Ventricular function			
Systolic function			
LVEF (%)	65.89±5.58	68.18±7.78	0.005
Diastolic function			
E_{max} mitral (cm/s)	64.41±17.48	63.97±15.04	0.983
A_{max} mitral (cm/s)	96.49±35.7	85.08±19.11	0.002
E_{max}/A_{max} mitral	0.7±0.19	0.77±0.19	0.001
Ea (TDI lateral mitral) (cm/s)	8.55±2.43	8.68±2.24	0.620
Aa (TDI lateral mitral) (cm/s)	13.89±3.33	11.7±2.69	<0.001
Ea/Aa mitral	0.65±0.24	0.78±0.29	<0.001
Aortic root diameter (cm)	3.47±0.37	3.47±0.31	0.914
Septum			
Ea (TDI septal) (cm/s)	6.18±1.74	6.43±1.64	0.243
Aa (TDI septal) (cm/s)	11.93±2.62	10.69±2.12	0.001
Ea/Aa septal	0.53±0.15	0.62±0.17	<0.001
E_{max}/Ea	11±3.63	10.24±2.92	0.326
Systolic motion mitral	10.4±11.44	8.24±2.02	0.011
Systolic motion septal	7.49±1.75	7.34±1.61	0.561

*Mann-Whitney *U*-test. Continuous variables are expressed as mean±SD. LV=Left ventricle; COPD=Chronic obstructive pulmonary disease; E_{max}=Maximal peak velocity of early diastolic flow; A_{max}=Maximal peak velocity of atrial contraction; Ea=Early diastole; Aa=Atrium systole; SD=Standard deviation; TDI=Tissue doppler imaging, LVEF=Left ventricular ejection fraction

Our results suggest that RV basal-mid diameters, TRV, and SPAP were significantly higher in patients with acute COPD patients. TAPSE, E_{max}/A_{max} tricuspid ratio known as maximal peak velocity of early diastolic flow/atrial contraction and Ea/Aa tricuspid ratio known as early diastole/atrium systole were significantly lower in the COPD exacerbation group. Increased SPAP is caused by hypoxia, mechanical stress induced by hyperinflated lungs, inflammation, the toxic impact of smoking, and impaired endothelial dysfunction in patients with COPD.[12] Enlargement and impaired RV diameters in patients with COPD are associated with reduced exercise capacity and progressive disease stages.[3] In these patients, increased TRV is an inevitable outcome of higher SPAP.[13,14]

In COPD patients, the pressure caused by remodeling in the lung parenchyma may cause changes in the RV and TAPSE which is used for evaluating degree of RV dysfunction.[15] Decreased TAPSE in patients with COPD exacerbation is an indicator of decreased RVEF.[16] In patients with COPD and pulmonary hypertension, the rate of E_{max}/A_{max} and Ea/Aa indicating RV diastolic function is expected to decrease.[3] The RV systolic and diastolic functions which are thought to be more impaired in the COPD exacerbation patients may cause the dysfunction.

In this study, LV end-diastolic diameter and systolic motion mitral were increased in COPD exacerbation group. LVEF, E_{max}/A_{max} mitral, Ea/Aa mitral, and Ea/Aa septal were decreased in patients with COPD exacerbation compared with stable outpatients. The systemic inflammatory response of COPD can lead to atherosclerotic plaque formation, which is associated with myocardial ischemia, and LV diastolic dysfunction. Impaired LV diastolic function is associated with increased RV pressure and volume load, showing that LV diastolic functions are affected by

Table 4: Atrial conduction times, complete blood counts and neutrophil-to-lymphocyte ratio in both groups

	COPD exacerbation (*n*=105)	Stable COPD (*n*=104)	P
Lateral/tricuspid (msec)	42.3±12.9	23.3±8.8	<0.001
Lateral/mitral (msec)	72.1±13.3	53.4±11.4	<0.001
Septal (msec)	49.6±12.3	34.5±9.9	<0.001
	Median (minimum-maximum)	Median (minimum-maximum)	P
Hemoglobin (mg/dL)	15.91 (9.27-21.59)	15.88 (9.55-22.01)	0.898
Hematocrit (%)	48.7 (17.6-63.6)	48.4 (31.5-64.7)	0.547
WBC (10^9/L)	8.5 (3.9-23.1)	7.95 (3.5-19.8)	0.045
Platelet count (10^9/L)	227 (67-416)	237 (11-513)	0.264
Neutrophil count (10^3 µL)	5.94 (1.96-17.6)	4.56 (1.71-10.4)	<0.001
Lymphocyte count (10^3 µL)	1.6 (0.03-10.7)	2.13 (0.53-20.9)	<0.001
NLR	3.83 (0.75-197.1)	2.24 (0.08-8.87)	0.003
Eosinophil count (10^3 µL)	0.13 (0.02-0.97)	0.19 (0-0.79)	0.005

*Mann-Whitney *U*-test. Continuous variables are expressed as mean±SD. Median (minimum-maximum), SD were too high as data did not conform the normal distribution. Therefore, the median, minimum and maximum values of the data were used. SD=Standard deviation; COPD=Chronic obstructive pulmonary disease; WBC=White blood cell; NLR=Neutrophil/lymphocyte ratio

Table 5: Spearman's correlation coefficient (r) and its level of significance for neutrophil-to-lymphocyte ratio and cardiac parameters

Variables	NLR			
	COPD exacerbation		Stable COPD	
	R	*P*	*R*	*P*
RV basal diameter	0.036	0.769	−0.052	0.671
RV mid diameter	−0.1	0.471	0.097	0.432
RV vertical diameter	−0.067	0.587	0.057	0.643
TAPSE	−0.02	0.874	−0.136	0.270
LV end-diastolic diameter	−0.014	0.912	0.357	0.003
LV end-systolic diameter	0.1	0.415	−0.171	0.163
LV interventricular septum	−0.017	0.888	0.036	0.768
LV posterior wall	−0.062	0.613	−0.043	0.728
Left atrium diameter	0.133	0.279	0.024	0.844
Aortic root diameter	0.063	0.611	−0.163	0.184
EF	−0.056	0.652	−0.201	0.101
E_{max} mitral	−0.043	0.730	−0.186	0.128
A_{max} mitral	−0.036	0.773	−0.046	0.711
Ea mitral	0.105	0.392	0.108	0.392
Aa mitral	0.078	0.529	0.087	0.479
E_{max}/A_{max} mitral	−0.024	0.847	0.032	0.793
Ea/Aa mitral	−0.005	0.971	0.086	0.484
E_{max}/Ea mitral	0.147	0.232	0.285	0.019
Ea septal	0.08	0.636	−0.082	0.508
Aa septal	−0.065	0.599	0.021	0.862
Ea/Aa septal	−0.052	0.673	0.092	0.456
E_{max}/Ea septal	0.04	0.745	0.005	0.967
E_{max} tricuspid	0.068	0.581	−0.244	0.045
A_{max} tricuspid	−0.116	0.347	0.2	0.101
Ea tricuspid	0.088	0.477	0.127	0.304
Aa tricuspid	−0.014	0.910	−0.059	0.633
E_{max}/A_{max} tricuspid	−0.139	0.258	0.189	0.123
Ea/Aa tricuspid	−0.019	0.880	−0.143	0.244
E_{max}/Ea tricuspid	0.111	0.366	0.07	0.572
TRV	−0.028	0.823	0.019	0.876
SPAP	0.074	0.546	−0.057	0.645
AEMD lateral/mitral	−0.115	0.349	0.034	0.784
AEMD septal	0.085	0.491	−0.086	0.484
AEMD lateral/tricuspid	−0.093	0.452	−0.012	0.923
Systolic motion mitral	−0.002	0.988	−0.103	0.403
Sytolic motion septal	0.073	0.553	0.352	0.003
Sytolic motion tricuspid	0.078	0.525	−0.164	0.182

*Spearmen's correlation. Correlation is significant at 0.01 level (*P*<0.01). Correlation is significant at 0.05 level (*P*<0.05). NLR=Neutrophil/lymphocyte ratio; COPD=Chronic obstructive pulmonary disease; E_{max}=Maximal peak velocity of early diastolic flow; A_{max}=Maximal peak velocity of atrial contraction; Ea=Early diastole; Aa=Atrium systole; LV=Left ventricle; RV=Right ventricle; TAPSE=Tricuspid annular plane systolic excursion; EF=Ejection fraction; TRV=Tricuspid regurgitation velocity; SPAP=Systolic pulmonary artery pressure; AEMD=Atrial electromechanical delay

RV loading conditions.[17,18] Impaired LVEF, altered LV diameter, and decreased LV diastolic functions such as peak velocity of an early diastolic transmitral and peak velocity of atrial systolic transmitral flow were reported in patients with COPD.[3,17-20] On the contrary, in our study, inflammation was not correlated with echocardiographic changes. We only used NLR as an inflammatory marker,

using a more specific biomarker could perhaps change the results.

In the present study, we found that lateral/tricuspid, lateral/mitral, and septal AEMD and NLR increased in patients with acute COPD exacerbation compared with COPD outpatients. NLR is an important, inexpensive, and easily available marker that shows an increasing acute inflammation.[7,21] Lee *et al.*, Yousef *et al.*, and Kocak *et al.* reported that NLR can predict acute COPD exacerbation, as well as cardiovascular diseases.[7,21-23] During inflammation, endothelial dysfunction related to atherosclerotic plaque, is usually associated with neutrophilia and lymphopenia.[24] Although inflammation is a common cause of arrhythmias in patients with COPD, hypoxemia, hypercapnia, cardiac autonomic dysfunction, and structural and functional changes of myocardium may cause cardiac conduction abnormalities. AF is the most common cardiac rhythm disorder for COPD patients.[25,26] The prolongation of AEMD is a prominent electrophysiological quantity, resulting from new onset or recurrence of AF.[27] TDI is a noninvasive and simple method to measure AEMD and this interval is measured from the onset of the *P* wave on ECG to the beginning of the atrial contraction.[28] Many diseases affecting the heart may cause prolongation of AEMD.[29] Similarly, Caglar *et al.* and Acar *et al.* compared AEMD intervals between COPD patients and healthy subjects and also they reported that AEMD intervals prolonged patients with COPD.[6,30] It is observed that AEMD is an expected finding in patients with COPD. In this study, AEMD was measured at different periods of the same disease and more patients were compared, unlike them.

This study shows that AEMD intervals measured from RV and LV in patients with COPD exacerbation were prolonged compared to stable period. The acute period of COPD may be an early predictor of AF. There is no doubt that AF is the most common dysrhythmia in the community and therefore it is important for clinicians to diagnose earlier, follow-up, and treat of this condition since it causes mortality.

This single-center study had some limitations. We merely used NLR as an inflammatory marker to evaluate relationship between inflammation and cardiac parameters. High sensitive biomarkers for measurement of inflammation and multicenter patient populations are needed for a clear determination of COPD's cardiac affects.

CONCLUSION

AEMD intervals are prolonged in patients with acute COPD compared with stable COPD outpatients. COPD

Table 6: Univariate and multivariable logistic regression analysis of variables

Variables	Univariate				Multivariable			
	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
NLR	1.463 (1.24-1.726)	0.000	1.49 (1.254-1.771)	0.000	1.662 (1.042-2.653)	0.033	1.9 (1.064-3.392)	0.030
RV basal diameter	2.312 (1.317-4.059)	0.003	3.72 (1.926-7.186)	0.000	0.355 (0.012-10.653)	0.551	0.382 (0.007-21.506)	0.640
RV mid diameter	5.574 (2.901-10.711)	0.000	8.089 (3.827-17.097)	0.000	90.592 (1.141-7192.353)	0.043	141.688 (0.837-23985.514)	0.058
RV vertical diameter	0.692 (0.45-1.064)	0.093	0.831 (0.527-1.311)	0.426				
TAPSE	0.076 (0.031-0.188)	0.000	0.081 (0.031-0.208)	0.000	0.004 (0-0.203)	0.006	0.005 (0-0.283)	0.010
LV end-diastolic diameter	0.389 (0.19-0.796)	0.010	0.57 (0.268-1.21)	0.143	0.111 (0.007-1.806)	0.122	0.083 (0.004-1.806)	0.113
LV end-systolic diameter	0.652 (0.323-1.316)	0.233	1.031 (0.485-2.194)	0.937				
LV interventricular septum	1.97 (0.333-11.642)	0.455	1.553 (0.612-3.938)	0.354				
LV posterior wall	2.661 (0.284-24.968)	0.391	1.671 (0.518-5.386)	0.390				
Left atrium diameter	1.436 (0.724-2.85)	0.301	1.119 (0.541-2.317)	0.762				
Aortic root diameter	1.021 (0.459-2.27)	0.960	1.439 (0.592-3.495)	0.422				
EF	0.95 (0.911-0.991)	0.017	0.947 (0.906-0.99)	0.016	1.064 (0.913-1.239)	0.427	1.094 (0.92-1.301)	0.310
E_{max} mitral	1.002 (0.985-1.019)	0.845	1 (0.982-1.018)	0.968				
A_{max} mitral	1.024 (1.008-1.039)	0.002	1.014 (0.999-1.029)	0.074	1.002 (0.95-1.058)	0.928	0.986 (0.929-1.047)	0.643
Ea mitral	0.977 (0.869-1.098)	0.696	1.052 (0.924-1.198)	0.446				
Aa mitral	1.278 (1.152-1.417)	0.000	1.278 (1.147-1.424)	0.000	1.021 (0.676-1.541)	0.923	1.101 (0.691-1.756)	0.685
E_{max}/A_{max} mitral	0.119 (0.025-0.556)	0.007	0.198 (0.039-1.005)	0.051	0.381 (0.001-240.434)	0.769	0.614 (0-903.469)	0.896
Ea/Aa mitral	0.118 (0.033-0.416)	0.001	0.194 (0.053-0.705)	0.013	0.086 (0.001-14.288)	0.347	0.058 (0-16.12)	0.321
E_{max}/Ea mitral	1.014 (0.915-1.123)	0.797	0.943 (0.842-1.057)	0.315				
Ea septal	0.914 (0.776-1.076)	0.281	0.963 (0.81-1.143)	0.664				
Aa septal	1.253 (1.105-1.422)	0.000	1.318 (1.147-1.515)	0.000	1.369 (0.825-2.272)	0.224	1.355 (0.757-2.426)	0.306
Ea/Aa septal	0.038 (0.006-0.242)	0.001	0.047 (0.007-0.329)	0.002	0.079 (0-100.929)	0.487	0.093 (0-111.482)	0.512
E_{max}/Ea septal	1.074 (0.987-1.168)	0.099	1.044 (0.955-1.141)	0.349				
E_{max} tricuspid	1.027 (1.005-1.05)	0.015	1.024 (1-1.047)	0.049	1.119 (0.766-1.634)	0.561	1.003 (0.665-1.514)	0.987
A_{max} tricuspid	1.068 (1.045-1.091)	0.000	1.062 (1.039-1.086)	0.000	0.913 (0.686-1.215)	0.531	0.996 (0.728-1.361)	0.979
Ea tricuspid	1.128 (1.008-1.262)	0.036	1.147 (1.016-1.295)	0.027	2.116 (1.247-3.593)	0.006	2.401 (1.343-4.293)	0.003
Aa tricuspid	1.221 (1.13-1.32)	0.000	1.204 (1.112-1.304)	0.000	1.186 (0.941-1.494)	0.148	1.206 (0.954-1.525)	0.118
E_{max}/A_{max} tricuspid	0.071 (0.019-0.257)	0.000	0.087 (0.023-0.333)	0.000	0 (0-46734.544)	0.348	0.029 (0-51421221.571)	0.744
Ea/Aa tricuspid	0.289 (0.064-1.304)	0.106	0.397 (0.086-1.838)	0.237				
E_{max}/Ea tricuspid	1.007 (0.91-1.116)	0.888	0.994 (0.89-1.109)	0.908				
TRV	1.022 (1.014-1.031)	0.000	1.022 (1.013-1.03)	0.000	1.053 (0.892-1.241)	0.544	1.022 (0.858-1.217)	0.809
SPAP	1.105 (1.065-1.146)	0.000	1.099 (1.058-1.142)	0.000	0.841 (0.417-1.693)	0.627	0.923 (0.442-1.928)	0.831
AEMD lateral/mitral	1.143 (1.101-1.187)	0.000	1.14 (1.097-1.184)	0.000	1.138 (1.01-1.281)	0.033	1.116 (0.985-1.264)	0.085
AEMD septal	1.131 (1.092-1.172)	0.000	1.138 (1.095-1.183)	0.000	1.011 (0.889-1.151)	0.864	1.023 (0.885-1.183)	0.757
AEMD lateral/tricuspid	1.193 (1.138-1.25)	0.000	1.191 (1.134-1.25)	0.000	1.218 (1.086-1.366)	0.001	1.259 (1.091-1.453)	0.002
Systolic motion mitral	1.171 (1.019-1.346)	0.026	1.233 (1.061-1.433)	0.006	1.111 (0.599-2.062)	0.738	1.227 (0.581-2.589)	0.592
Systolic motion septal	1.054 (0.896-1.241)	0.523	1.131 (0.95-1.347)	0.167				
Systolic motion tricuspid	1.096 (0.992-1.21)	0.072	1.09 (0.981-1.21)	0.107				

*Logistic regression analysis. NLR=Neutrophil/lymphocyte ratio; E_{max}=Maximal peak velocity of early diastolic flow; A_{max}=Maximal peak velocity of atrial contraction; Ea=Early diastole; Aa=Atrium systole; LV=Left ventricle; RV=Right ventricle; TAPSE=Tricuspid annular plane systolic excursion; EF=Ejection fraction; TRV=Tricuspid regurgitation velocity; SPAP=Systolic pulmonary artery pressure; AEMD=Atrial electromechanical delay; OR=Odds ratio; CI=Confidence interval

exacerbation may lead to right-left ventricle systolic and diastolic impairment, but increased NLR during this period is not associated with cardiac dysfunction.

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Conflicts of interest

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