

# Pulmonary arterial hemodynamic assessment by a novel index in systemic lupus erythematosus patients: pulmonary pulse transit time

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## ABSTRACT

**Objective:** Systemic lupus erythematosus (SLE) is a chronic, inflammatory, and autoimmune connective tissue disease. One of the leading causes of mortality among SLE patients is pulmonary hypertension. The aim of this study was to evaluate the association between echocardiographic findings, including the pulmonary pulse transit time and pulmonary hypertension parameters, in SLE patients.

**Methods:** Thirty SLE patients (aged 39.9±11 years, 28 females) as the study group and 34 age- and sex-matched healthy volunteers (aged 37.9±11.5 years, 31 females) as the control group were included in the study. After detailed medical histories were recorded, 12-lead electrocardiography, blood tests, and echocardiography were performed in the groups. In addition to basic echocardiographic measurements, other specialized right ventricular indicators [i.e. Tricuspid Annular Plane Systolic Excursion (TAPSE), estimated pulmonary artery systolic pressure (ePASP), right ventricular dimensions, and myocardial performance index (MPI)] were measured. The pulmonary pulse transit time was defined as the time interval between the R-wave peak in ECG and the corresponding peak late-systolic pulmonary vein flow velocity.

**Results:** The mean disease duration was 121.1±49.9 months. The mean age at diagnosis was 35.0±15.4 years. The mean RV MPI was higher (p=0.026), mean TAPSE measurements were shorter (p=0.021), and mean ePASP was higher (p=0.036) in the SLE group than in the control group. In addition, pPTT was significantly shorter in the SLE group (p=0.003). pPTT was inversely correlated with disease duration (p<0.001), MPI (p=0.037), and ePASP (p=0.02) and positively correlated with TAPSE (p<0.001).

**Conclusion:** SLE patients have higher pPTT values than controls. Further, pPTT shows an inverse correlation with disease duration, MPI, and ePASP and a positive correlation with TAPSE. (*Anatol J Cardiol* 2017; 17: 000-00)

**Keywords:** pulmonary pulse transit time, systemic lupus erythematosus, pulmonary hypertension

## Introduction

Systemic lupus erythematosus (SLE) is associated with multisystem involvement, which affects women 9-fold higher than men. The skin, joints, serous membranes, kidney, central nervous system, heart, and lungs are the most involved organs and systems. One of the leading causes of mortality among SLE patients is pulmonary hypertension (PH) (1, 2). PH frequency varies between 1.8% and 14% in SLE patients (3, 4). PH has been shown to be related to poor prognosis among these individuals (5, 6). In SLE patients with PH, the 2-year mortality has been found more than 50% in some studies, and right heart failure is an important contributor to this result (7, 8).

Right heart catheterization is the gold-standard method that exactly establishes a hemodynamic diagnosis of PH (9, 10). However, it is susceptible to serious complications because of its

invasive nature. Instead of catheterization, echocardiographic evaluation is more feasible owing to its easy availability, inexpensiveness, repeatability, and most importantly, noninvasive nature. Nevertheless, traditional echocardiographic measurements have some limitations as well: standardization of measurement techniques has not been well established and there is no exact echocardiographic parameter in PH diagnosis and prognosis (11, 12). Thus, novel developments for pulmonary hemodynamic assessment are required.

Current guidelines classify PH into 5 categories, namely pulmonary arterial hypertension, PH due to heart diseases, PH due to lung diseases, PH due to a thromboembolic etiology, and PH due to unclear/multifactorial mechanisms. Although these categories have very different pathophysiological pathways, vascular wall changes are considered to be a common pathology of PH (10, 13). Recently, Wibmer et al. (10) have suggested

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a new echocardiographic indicator of vascular alterations in PH: “pulmonary pulse transit time” (pPTT). They showed that pPTT was shorter in PH patients than in controls and claimed that pPTT is associated with pulmonary hemodynamic and vascular changes. Shorter pPTT means that the time needed for the pressure pulse wave to travel from the pulmonary valve to the left atrium is lesser, and this may indicate increased pulmonary vascular stiffness (10). The aim of this study was to evaluate the association between echocardiographic findings, including pPTT and PH parameters, in SLE patients.

## Methods

### Study design

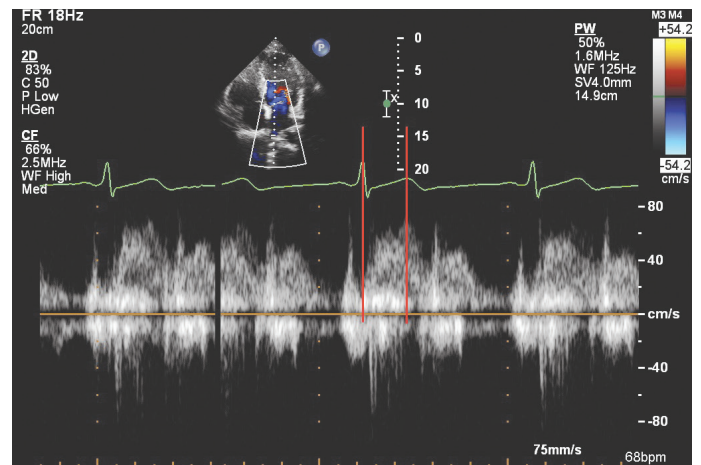
Thirty SLE patients (aged  $39.9 \pm 11$  years, 28 females) (study group) who were admitted to the Dışkapı Yıldırım Beyazıt Training and Research Hospital Rheumatology outpatient clinic and 34 age- and sex-matched healthy volunteers (aged  $37.9 \pm 11.5$  years, 31 females) (control group) were included in the study. SLE patients were included if the disease duration was longer than 1 year and if they were being followed-up in our rheumatology department regularly. In total, 104 patients were considered for inclusion in this study; 30 of these were free of the exclusion criteria mentioned below. After detailed medical histories were recorded, 12-lead electrocardiography, blood tests, and echocardiography were performed in the groups. Among SLE patients, during the visit, 18 were asymptomatic, 10 were complaining of arthralgia, 4 were suffering from myalgia, and 3 were complaining of headache. The American College of Rheumatology criteria were used for SLE diagnosis (14). There was musculoskeletal involvement in 22 patients, renal involvement in 4, mucosal ulcers in 6, and blood cell abnormalities in 3. The control group consisted of individuals who had no history of pulmonary disease, systemic disorders, or major cardiovascular diseases in addition to exclusion criteria.

All 30 SLE patients were taking hydroxychloroquine (100%), 5 (16.6%) of them were undergoing immunosuppressive therapy (azathioprine or methotrexate), 4 (13.3%) were taking nonsteroidal anti-inflammatory drugs, and 14 (46.6%) were taking steroids.

The exclusion criteria were as follows: coronary artery disease, moderate or severe left-sided valve pathologies, ejection fraction less than 60%, New York Heart Association functional status  $\geq 2$ , chronic obstructive pulmonary disease, pulmonary thromboembolism history, atrial fibrillation, malignancy, acute or chronic renal insufficiency, and pregnancy.

### Laboratory testing

Blood samples were obtained from all participants in the morning after 8 h of fasting. Hemogram, erythrocyte sedimentation rate (ESR), C-reactive protein level, fasting glucose level, and thyroid and renal functions were assessed. The body mass index was calculated according to the weight and height mea-



**Figure 1.** Pulmonary pulse transit time is defined as the time interval between the R-wave peak in the ECG and corresponding peak late-systolic pulmonary vein flow velocity. It is depicted in the figure between 2 parallel vertical red lines

surements and expressed as  $\text{kg/m}^2$ . The disease duration was recorded as months for each patient.

### Echocardiography

Transthoracic echocardiographic examination was performed in the standard left lateral decubitus position on a Philips IE33 commercially available device (Philips Electronics, Washington, USA) by an experienced cardiologist who was blinded to patient data. After continuous single-lead ECG monitoring, standard 2-dimensional, M-mode, and color-Doppler evaluations were performed. Left ventricular (LV) and right ventricular (RV) ejection fractions (EF) were obtained using the modified Simpson’s method. In addition to basic echocardiographic measurements such as left atrial dimensions, LV end-systolic/end-diastolic dimensions, and ventricular septal and posterior wall thickness, other specialized RV indicators [i.e., Tricuspid Annular Plane Systolic Excursion (TAPSE), estimated pulmonary artery systolic pressure (ePASP), RV dimensions, and myocardial performance index (MPI)] were measured. The estimated pulmonary artery systolic pressure was calculated by the sum of the Doppler derived from the transtricuspid gradient and the estimated right atrial pressure, as assessed by the inspiratory collapse of the inferior vena cava. ePASP greater than 36 mm Hg was considered as PH. MPI was calculated as “(isovolumetric contraction time + isovolumetric relaxation time)/RV ejection time” using the tissue Doppler method. This index incorporates both systolic and diastolic time intervals; thus, it expresses global systolic and diastolic ventricular functions.

Pulmonary vein flow was studied by pulse wave Doppler of the right superior pulmonary vein from the apical 4-chamber view according to guidelines of the American Society of Echocardiography (15). pPTT was defined as the time interval between the R-wave peak in ECG and the corresponding peak late-systolic pulmonary vein flow velocity (R-PVs2 interval, Fig. 1). Three separate measurements in the same procedure were used for the calculation of the mean pPTT.

The protocol was approved by the Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee. All the participants gave written consent before data collection.

### Statistical analyses

The data were analyzed using SPSS 18.0 statistics package (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as means±standard deviations, and categorical variables were reported as percentages. Student's t-test was used for the comparison of normally distributed variables. Categorical variables were compared by  $\chi^2$  test or Fisher's exact test as appropriate. A p value less than 0.05 was considered statistically significant. Pearson's correlation coefficients were used to assess the significance of relationship between continuous variables, and Spearman correlation analysis was used to assess the significance of relationship between noncontinuous and categorical variables.

## Results

### Clinical characteristics of patients

Characteristics of patients compared with those of healthy controls are given in Table 1. There was no statistically significant difference between the groups in terms of age, sex, body mass index, hemoglobin levels, fasting glucose levels, and creatinine levels (Table 1). Distribution of SLE disease activity indexes (SLEDAI) is shown in Table 2 (16). The mean disease duration was 121.1±49.9 months. The mean age at diagnosis was 35.0±15.4 years. The heart rate and systolic and diastolic blood pressure were not significantly different between the SLE and control groups ( $p>0.05$ ). In total, 26.7% of SLE patients (8 of 30 patients) and 26.5% of controls (9 of 34 individuals) were smokers. Two SLE patients (6.7%) and 3 controls (8.8%) were males.

### Echocardiographic findings

Five SLE patient and 1 control were excluded from the study because of poor echocardiographic visualization. LV systolic functions were similar in both the groups (SLE group ejection fraction 66.8%±3.7, control group ejection fraction 67.1%±3.5,  $p>0.05$ ). Similarly, LV septum, posterior wall, and left atrial diameters were not statistically different among groups. On the other hand, the mean RV MPI was higher in SLE patients than in controls (0.48±0.07 vs. 0.43±0.09,  $p=0.026$ ); MPI values of both the groups were found to be in the normal range using the tissue Doppler method. Mean TAPSE measurements were shorter in SLE patients than in controls (2.34±0.37 cm vs. 2.53±0.24 cm,  $p=0.021$ ). In addition, mean ePASP was higher in SLE patients than in controls (23±3.3 mm Hg vs. 20.9±4.3 mm Hg,  $p=0.036$ ). However, this increase did not reach the pathological level; all measurements were under 31 mm Hg. One of the main purpose of this study was to evaluate the "pPTT" differences in SLE patients. pPTT was significantly shorter in SLE patients (SLE

**Table 1. Demographic and clinical features of the SLE and control groups**

Variables	SLE group (n=30)	Control group (n=34)	P
Age, years	39.9±11	37.9±11.5	0.47
Fasting glucose, mg/dL	87.4± 8.2	94.1±27.7	0.18
Hemoglobin, g/dL	13.3±1.1	13.2±1.1	0.75
Creatinine, mg/dL	0.79±0.13	0.82±0.12	0.37
BMI, kg/m <sup>2</sup>	25.1±4.9	25.6±4.5	0.65
Age at diagnosis	35.0 ±15.4		
Disease duration, month	121.1±49.9		
Hydroxychloroquine	100% (30)		
Steroids	46.7% (14)		
NSAIDs	13.3% (4)		
Immunosuppressive	16.7% (5)		

BMI - body mass index; N - number; NSAIDs - nonsteroidal anti-inflammatory drugs

**Table 2. Distribution of SLE disease activity index (SLEDAI)\***

SLEDAI Score	Percentage (N)
1	16.7% (5)
2	43.3% (13)
3	6.7% (2)
4	23.3% (7)
5	6.7% (2)
6	3.3% (1)

N: Number; \*Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992; 35: 630-640. PMID: 1599520

**Table 3. Echocardiographic features of the SLE and control groups**

Variables	SLE group (n=30)	Control group (n=34)	P
EF, %	66.8±3.7	67.1±3.5	0.73
IVSd, mm	9.1±1.4	9.5±1	0.22
LVPWd, mm	9±1.5	9.4±1.1	0.26
LA, mm	31.6±4.7	31.2±3.7	0.71
RV MPI	0.48±0.07	0.43±0.09	0.026*
TAPSE, mm	23.4±3.7	25.3±2.4	0.021*
ePASP, mm Hg	23±3.3	20.9±4.3	0.036*
pPTT, ms	174.1±30.1	196.1±27.8	0.003*
HR, bpm	80.6±7.3	77.5±10.2	0.17

EF - ejection fraction; ePASP - estimated pulmonary artery systolic pressure; HR - heart rate; IVSd - diastolic interventricular septum diameter; LA - left atrial diameter; LVPWd - diastolic left ventricular posterior wall diameter; pPTT - pulmonary pulse transit time; RV MPI - right ventricular myocardial performance index; TAPSE - Tricuspid Annular Plane Systolic Excursion. \*Statistically significant

group =174.1±30.1 ms, control group=196.1±27.8 ms,  $p=0.003$ , Table 3). Further, pPTT was inversely correlated with disease

**Table 4. Correlation coefficients between echocardiographic parameters and pulmonary pulse transit time**

	<b>r</b>	<b>P</b>
BMI	-0.143	0.260
Disease duration	-0.593	0.001
MPI	-0.262	0.037
ePASP	-0.423	0.020
TAPSE	0.525	<0.001
SLEDAI2	0.249	0.185
Age	0.034	0.787

BMI - body mass index; ePASP - estimated pulmonary artery systolic pressure; MPI - right ventricular myocardial performance index; SLEDAI2 - SLE disease activity index; TAPSE - Tricuspid Annular Plane Systolic Excursion

duration ( $p < 0.001$ ), MPI ( $p = 0.037$ ), and ePASP ( $p = 0.020$ ) and positively correlated with TAPSE ( $p < 0.001$ , Table 4, Fig. 2 a, b).

### Discussion

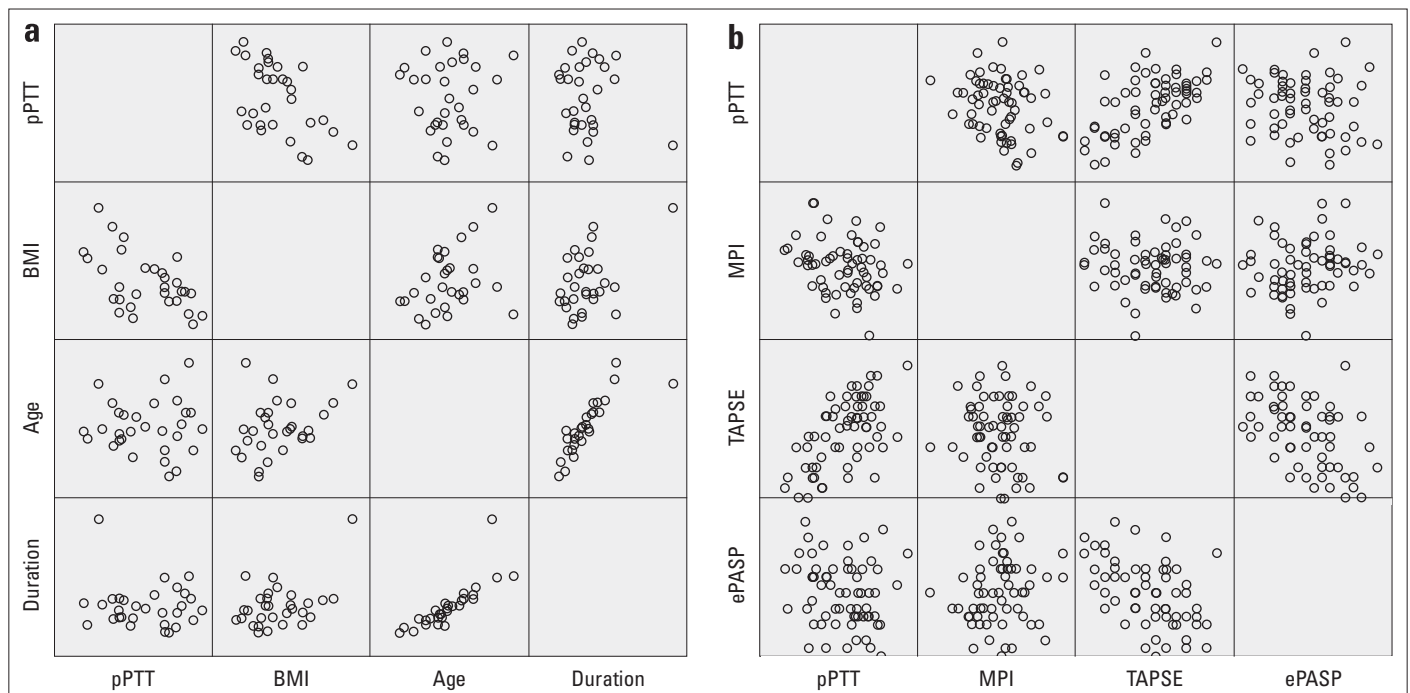
The present study has showed that SLE patients have a higher RV MPI, shorter TAPSE, higher ePASP and shorter pPTT than controls. Previous studies have shown that SLE negatively affects the RV functions and results in higher values of RV MPI and ePASP and shorter TAPSE (17, 18). Our findings are consistent with those of previous studies with regard to these parameters. However, the relationship between SLE and pPTT has not been investigated to date. According to our findings, shorter pPTT values may provide additional information about pulmonary hemodynamics in cardiac asymptomatic SLE patients. These findings support the hypothesis

that pulmonary vascular and RV changes occur early before clinical manifestation in SLE patients.

MPI is a reproducible and easily measurable index that provides information about both systolic and diastolic global RV function. It has shown that MPI has a greater prognostic value than other RV function parameters in PH patients (19). Moreover, Tannus-silva et al. (20) have demonstrated that MPI values are correlated with worse quality of life parameters. In our study, mean MPI values were higher in the SLE group, and they were correlated with pPTT. This findings support the hypothesis that shortening of pPTT is a novel prognostic factor for RV global dysfunction.

TAPSE provides information about RV function by measuring the longitudinal movement of the lateral tricuspid annulus on M-mode echocardiography. It has been shown that TAPSE is associated with the prognosis of PH patients (21, 22). In our study, the mean TAPSE values were significantly lower in SLE patients than in controls, although all of them were in normal limits. Moreover, TAPSE was correlated with pPTT and inversely correlated with ePASP and disease duration ( $p < 0.001$  for all). These relationships between TAPSE and ePASP and disease duration are consistent with those observed in previous studies, but to the best of our knowledge, a positive correlation between pPTT and TAPSE has not been shown yet. This result strengthens the value of pPTT in pulmonary vascular changes and/or PH manifestation in SLE patients.

Previously, Wibmer et al. (10) have demonstrated that pPTT is shortened in PH patients. Our results support the hypothesis that pPTT is correlated with pulmonary vascular changes and associated with disease duration in SLE patients.



**Figure 2.** Matrix scatter plot graph representing correlation between clinical /echocardiographic parameters and pulmonary pulse transit time

Arterial stiffness is related to functional and structural arterial wall changes and is considered to be a major risk factor for cardiovascular diseases (23). Similarly, increased pulmonary arterial stiffness is shown to be associated with high mortality rates in PH patients (24, 25). In order to determine pulmonary arterial stiffness, pPTT may be used just as pulse wave velocity. These inversely related echocardiographic parameters are promising noninvasive indicators of pulmonary arterial stiffness, and consequently, PH evaluation and progression. As mentioned previously, Wibmer et al. (10) have showed that pPTT decreases in PH patients. In our study, we found that pPTT was shortened in asymptomatic SLE patients. These results may indicate that shorter pPTT values are related to early pathophysiological changes in the pulmonary vascular bed. The positive correlation between pPTT and disease duration supports this findings. Because PH is associated with poor prognosis of SLE patients, early diagnosis of PH in asymptomatic SLE patients is promising for reducing mortality and morbidity.

### Study limitations

The most important limitation of our study was the relatively small number of patients. Further, pulmonary pressures could not be measured invasively; thus, the pulmonary hemodynamics may not have been determined exactly. We could not record the excluded patients' data; therefore, we cannot re-analyze the alterations in symptomatic patients. Moreover, 40% of data regarding drug use durations was missing; therefore, we could not determine the long-term effects of the drugs.

The term "asymptomatic SLE patients" refers to patients who were not symptomatic in terms of cardiac complaints. Thus, cardiac symptomatic patients were excluded from the study. Unfortunately, asymptomatic-symptomatic subgroup analyses were not performed with regard to SLE symptoms. Long-term follow-up of SLE patients would provide more precise information about pulmonary hemodynamic alterations.

### Conclusion

We revealed for the first time that SLE patients have higher pPTT values than controls. Further, pPTT shows an inverse correlation with disease duration, MPI, and ePASP and a positive correlation with TAPSE. More comprehensive studies are required for evaluation of pulmonary changes in asymptomatic SLE patients.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – T.H.E., C.Ö.; Design – T.H.E.; Supervision – T.Ç., M.A.F.; Funding – T.Ç., A.G.E., E.A.; Materials – C.Ö., T.Ç.; Data collection &/or processing – S.A., A.G.E., E.A.; Analysis &/or interpretation – T.H.E., M.D.; Literature search – C.Ö., S.A.; Writing – M.D., A.G.E.; Critical review – M.D., M.A.F., E.A.; Other- M.A.F., S.A.

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