

# Is early diagnosis of pulmonary arterial hypertension possible in inflammatory rheumatic diseases? Experience from a single center in Turkey

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## Abstract

**Objective:** Pulmonary arterial hypertension (PAH) is a devastating complication of inflammatory rheumatic diseases. The aim of this study was to determine the role of screening for the early diagnosis of pulmonary hypertension (PH) in inflammatory rheumatic diseases.

**Material and Methods:** Data of patients with inflammatory rheumatic diseases and PH who had no obvious cause of PH and who were evaluated by Working Group for Pulmonary Hypertension in Hacettepe University were investigated retrospectively. All patients with inflammatory disease were evaluated by right heart catheterization (RHC) to check if they had systolic pulmonary arterial pressure (sPAP)  $\geq 40$  mmHg and/or symptoms related to PH unless explained by other causes.

**Results:** RHC was performed in 47 patients with inflammatory rheumatic diseases and PH out of 50 patients who were to be evaluated by RHC based on clinical and Doppler echocardiographic findings. There was a positive correlation between sPAP estimated by Doppler echocardiography and sPAP determined by RHC in patients with inflammatory rheumatic diseases ( $r=0.66$ ;  $p<0.001$ ). The mean pulmonary arterial pressure (mPAP) was found to be  $<25$  mmHg in 27.7% of the patients. New York Heart Association functional capacity (NYHA FC) was class III or IV in 79.0% of the patients with PAH. PAH was more frequent in patients with NYHA FC III-IV compared with patients with NYHA FC I-II [58.7% (15) patients vs. 19.0% (4) patients;  $p=0.009$ ].

**Conclusion:** In this study, approximately 80% of the patients with inflammatory disease-associated PAH were diagnosed late in NYHA FC III or IV. There are still unresolved issues in the diagnosis and treatment of PH in inflammatory diseases. Collaboration and multidisciplinary approach are the key points to overcome the challenges in this field.

**Keywords:** Pulmonary hypertension, pulmonary arterial hypertension, inflammatory rheumatic diseases

## Introduction

Inflammatory rheumatic diseases, especially systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and mixed connective tissue disease, are at an increased risk for pulmonary hypertension (PH). Various complications of inflammatory rheumatic disease can lead to PH (1). Therefore, it is challenging to accurately determine the exact cause of PH in inflammatory rheumatic diseases. PH is a poor prognostic factor regardless of its cause (2-4). Early diagnosis and proper treatment may provide a better clinical outcome in patients with pulmonary arterial hypertension (PAH) (5). For this purpose, annual screening of patients with SSc and symptomatic patients with other connective tissue diseases by transthoracic echocardiography for the presence of PH is recommended (6, 7). The aim of this study was to determine the role of screening for the early diagnosis of PH in inflammatory rheumatic diseases.

## Material and Methods

Data of the Working Group for Pulmonary Hypertension in our university, which was established four years ago to evaluate PH patients in a multidisciplinary approach, were reviewed retrospectively. Demographic data and clinical and laboratory features of the patients with inflammatory rheumatic diseases who were investigated for PH were noted. Additional data on disease course of the patients were obtained from hospital file records. All patients with inflammatory rheumatic diseases were evaluated at least once by transthoracic echocardiography prior to right heart catheterization (RHC). If the patients had an elevated systolic pulmonary arterial pressure (sPAP) due to an obvious pulmonary and/or left-sided heart disease and if hemodynamic evaluation was not necessary for their treatment plan, they did not undergo RHC. All the other patients with inflammatory disease were evaluated with RHC if they had  $sPAP \geq 40$  mmHg and/or symptoms related to PH unless explained by other causes. PH was defined as increased mean pulmonary arterial pressure (mPAP)  $\geq 25$  mmHg at rest and PAH as  $mPAP \geq 25$  mmHg together with pulmonary



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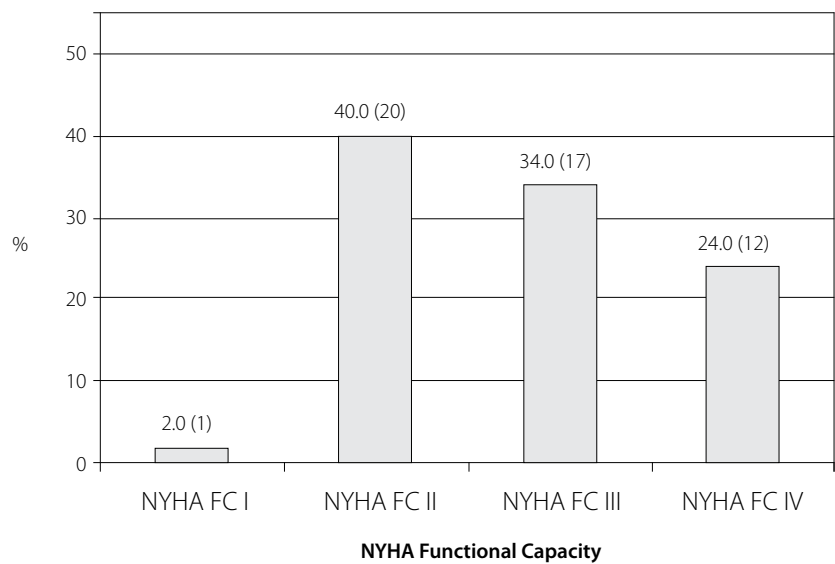
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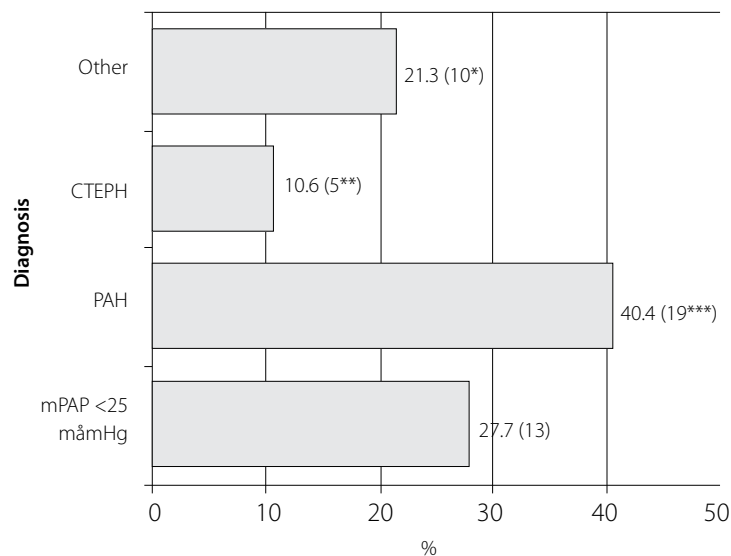
Submitted: 14.05.2014

Accepted: 19.09.2014

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**Figure 1.** NYHA functional capacity of patients with inflammatory rheumatic diseases who were to be evaluated by RHC (n=50)  
NYHA: New York Heart Association; NYHA FC: New York Heart Association functional class; RHC: right heart catheterization



**Figure 2.** Final diagnosis of patients with inflammatory rheumatic diseases after RHC (n=47)  
\*Diagnoses of patients: interstitial lung disease in 4, left ventricular diastolic dysfunction in 2, atrial septal defect and left ventricular diastolic dysfunction in 1, heart involvement and left ventricular diastolic dysfunction in 1, and mitral valve stenosis in 2 patients.  
\*\* Diagnoses of patients with CTEPH: systemic lupus erythematosus in 3 (two had antiphospholipid syndrome), rheumatoid arthritis in 1, and systemic sclerosis in 1 patient.  
\*\*\*Diagnoses of patients with PAH: systemic sclerosis in 15, systemic lupus erythematosus in 1, rheumatoid arthritis in 1, Sjogren's syndrome in 1, Takayasu's arteritis in 1 patient  
RHC: right heart catheterization; CTEPH: chronic thromboembolic pulmonary hypertension; PAH: Pulmonary arterial hypertension; mPAP: mean pulmonary arterial pressure

capillary wedge pressure $\leq$ 15 mmHg in the absence of other PH causes. Acute vasodilator testing was performed using adenosine or inhaled iloprost during RHC if indicated. An acute vasoreactive response was defined as a reduction in mPAP $\geq$ 10 mmHg to reach an absolute value of mPAP $\leq$ 40 mmHg with increased or unchanged cardiac output. To

determine the exact cause of PH, a diagnostic work-up procedure including laboratory and imaging methods useful for evaluation of PH such as pulmonary function tests, ventilation/perfusion scan, and lung computed tomography were performed in all patients according to the guidelines (8). The study was approved by the local ethics committee of our university.

**Statistical analysis**

For statistical comparison of clinical and laboratory features, chi-square test and Mann-Whitney U test were performed. Values were expressed as the mean $\pm$ SD. Correlation was tested using Spearman's rank order or Pearson correlation coefficient. Results were considered statistically significant when p values were  $<0.05$ .

**Results**

There were 56 patients with inflammatory rheumatic diseases who were investigated for the presence of PH. Among them, 50 patients were to be evaluated by RHC; in the remaining 6 patients, PH causes were clearly identified (interstitial lung disease in 3, interstitial lung disease and left ventricular diastolic dysfunction due to coronary heart disease in 1, and acute pulmonary thromboembolism in 2).

In total, 50 (Female/Male: 42/8) patients were enrolled in the study. The mean age of the patients was 52.1 $\pm$ 12.8 years. The diagnoses of the patients were as follows: SSc and related diseases in 34 (68.0%; 2 patients with scleromyxedema), SLE in 7 (14.0%), rheumatoid arthritis (RA) in 4 (8.0%), sarcoidosis in 2 (4.0%), Sjogren's syndrome in 1 (2.0%), undifferentiated collagen tissue disease in 1 (2.0%), and Takayasu's arteritis in 1 (2.0%). All patients were symptomatic except 1. The New York Heart Association Functional Class (NYHA FC) of the patients is shown in Figure 1. Mean sPAP measured by Doppler echocardiography of the patients was 59.9 $\pm$ 27.6 mmHg. In 4 patients, sPAP was  $<40$  mmHg. Left ventricular ejection fraction was  $\geq 50\%$  in all subjects. In 31 (62.0%) patients, the right ventricular diameter was increased ( $>2.5$  cm), and in 19 (38.0%), there was pericardial effusion on transthoracic echocardiography.

In 47 (94.0%) patients, RHC was performed. Two patients died before RHC [1 with RA who was considered to have PAH and was on bosentan (Tracleer; Actelion Pharmaceuticals, Allschwil, Switzerland) treatment; 1 with SSc who had pulmonary hemorrhage] and 1 did not consent. Mean pulmonary artery pressures were found to be  $<25$  mmHg in 13 (27.7%) patients by RHC. Final diagnosis of the patients is shown in Figure 2. PAH and chronic thromboembolic pulmonary hypertension were the causes of PH in 19 (40.4%) and 5 (10.6%) patients, respectively. Mean sPAP, mPAP, cardiac output, and pulmonary vascular resistance of the patients with PAH were 67.3 $\pm$ 26.6 mmHg, 44.7 $\pm$ 17.5 mmHg, 5.4 $\pm$ 1.1 L/min, and 536.3 $\pm$ 304.1 dyn/cm $^2$ , respectively. NYHA FC was III or IV (79.0%) in most of the patients with

PAH at the time of diagnosis. A positive acute vasoreactivity response was found in 2 (10.5%) patients. The patient with Sjogren's syndrome (vasoreactivity test performed by adenosine) was on calcium channel blocker (CCB) treatment, and the other patient was put on bosentan when the acute phase response was found to be negative (both vasoreactivity tests were performed by inhaled iloprost) one year later. PAH was more frequent in patients with NYHA FC III-IV compared with patients with NYHA FC I-II [58.7% (15) patients vs. 19.0% (4) patients;  $p=0.009$ ]. The number of patients with an enlarged right ventricle or with pericardial effusion was not different between patients who had PH by RHC and patients who had normal hemodynamic findings ( $p$ : NS; for all). Mean sPAP determined by Doppler echocardiography was higher in the patients who had PH by RHC than in the patients who had normal hemodynamic findings ( $64.4 \pm 29.9$  mmHg vs.  $43.5 \pm 13.7$  mmHg;  $p=0.002$ ). There was a positive correlation between sPAP estimated by Doppler echocardiography and sPAP determined by RHC in patients with inflammatory rheumatic diseases ( $r=0.66$ ;  $p<0.001$ ).

## Discussion

In this study, approximately 80% of the patients with inflammatory disease-associated PAH were diagnosed late in NYHA FC III or IV. The presence of right ventricular enlargement or pericardial effusion was not different between patients whose PH was confirmed by RHC and those who had normal findings by RHC. The patients with inflammatory rheumatic diseases were at increased risk for PAH. PAH prevalence is 8%-12% in SSc patients; this is the highest prevalence among inflammatory rheumatic diseases (9, 10). In accordance, most studies in literature on PAH-associated with inflammatory rheumatic diseases were conducted in SSc patients. Transthoracic echocardiography is a non-invasive tool that is considered to be the first step in the detection of PH in SSc (9, 11). Annual screening of patients with SSc for the presence of PH is recommended (6, 7). Furthermore, it was postulated that earlier diagnosis of PAH is possible by a diagnostic strategy based on echocardiographic estimation of sPAP and symptoms (9, 10, 12). In our study with a similar diagnostic approach, the patients with inflammatory disease-associated PAH were still diagnosed in late stages as reported previously (13). This result may be due to the abrupt onset of PAH in these groups of patients or the inadequate screening of patients by echocardiography or the late referral of these patients. Systolic PAP estimated by Doppler echocardiography and measured during RHC was highly correlated in this study

in agreement with previous data (14). On the other hand, it was found that 45% of cases of echocardiographic diagnosis of PH were false positive according to RHC results in SSc patients (15). This necessitates the need for improved diagnostic strategies. In this study, 27% of the patients had a false positive diagnosis of PH by Doppler echocardiography, supporting data in literature. Evaluation of the patients using additional parameters that had been shown to be useful in the diagnosis, prognosis, and/or follow-up of PAH such as serum brain natriuretic peptide levels (BNP), diffusing capacity of carbon monoxide (DLCO), and six minute walk distance before RHC may improve the diagnostic approach (16-18). Currently, new algorithms for the diagnosis of PH that include components such as patient's clinical features, BNP levels, and DLCO have been suggested (19-22). DETECT (DETECTion of PAH in SSc) algorithm in SSc patients with  $DLCO<60\%$  and disease duration  $>3$  years may be useful for early diagnosis (22). An additional current problem is the timely initiation of treatment in PAH patients with inflammatory rheumatic diseases. Treatment with PAH-specific agents is recommended in all PAH patients with NYHA FC II (6). Despite accumulating data on the course of PAH in inflammatory rheumatic diseases, most recommendations are established on the basis of studies related mainly to idiopathic pulmonary arterial hypertension (IPAH) patients. The pathogenesis of PH is complex in rheumatic diseases; vasculopathy-endothelial dysfunction, inflammation, hypoxia, pulmonary venous changes, cardiac involvement, hypercoagulability, and platelet activation are the contributing mechanisms in PAH (23-25). The complexity of the pathogenesis of PH in rheumatic disease could be the cause for lower response rate to PAH-specific treatments and poor prognosis in this patient group compared with IPAH patients. The systemic nature of this group of disease not only challenge the assessment of the severity of PH related symptoms but also obscures the findings that are useful for determining the prognosis and severity of PAH such as right ventricular enlargement and/or pericardial effusion. In this study, the number of patients with an enlarged right ventricle or pericardial effusion was not different between the groups with and without PH by RHC. In this situation, it is hard to decide to initiate PAH-specific treatment in patients with SSc who have mildly elevated mPAP and mild dyspnea in the presence of interstitial lung disease or subclinical cardiac involvement that are frequent (17, 26). The presence of left ventricular diastolic dysfunction should be rigorously investigated in patients with SSc with PH (12). Treatment options may also vary according to

the different types of rheumatic diseases. For instance, immunosuppressive treatment has been shown to be effective in SLE-associated PAH and the response to CCB is poor in rheumatic disease-associated with PAH particularly in SSc (19, 27). The response to CCB is poorly defined in other rheumatic diseases. One of our patients with Sjogren's syndrome and PAH has been doing well under CCB treatment. Therefore, we think that the response to CCB should be evaluated with an acute vasoreactivity test in other connective tissue-associated PAH patients not having SSc. The importance of reactive PH, borderline PH (mPAP between 21 and 24 mmHg), and the prognosis of patients with mildly elevated mPAP in connective tissue diseases has yet to be defined (6, 28). In a recent study, SSc patients with borderline PH and an elevated trans-pulmonary gradient were found to be more likely to develop PH than patients with  $mPAP \leq 20$  mmHg (29). As a result, these patients should be followed-up by experienced centers. There are still unresolved issues in the diagnosis and treatment of PH in inflammatory diseases. PH has numerous causes, and the diagnosis is incomplete without determining the cause and its severity (30). PAH is one of the leading disease-related cause of mortality in SSc and a rare but devastating complication of other inflammatory rheumatic diseases (24, 31). Early diagnosis and treatment of PH may provide better clinical outcomes in this patient group (5). Furthermore, the early diagnosis of PAH in this group of patients will provide more data about the pathogenesis, mainly the role of inflammation in PH (32). Genetics may be helpful for the diagnosis of PAH in the future in this patient group (32).

In conclusion, despite the limited number of patients with a variety of rheumatological diseases in the present study, we underlined the limitations of screening-confirming workup for the early diagnosis of PAH in these patients. Until more precise diagnostic tools are adopted, we believe that awareness, collaboration, and multidisciplinary approach are the key points to overcome the challenges in this field.

**Ethics Committee Approval:** Ethics committee approval was obtained.

**Informed Consent:** Written informed consent was obtained from patients who participated in this case.

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

**Author Contributions:** Concept - A.A., S.O., B.K.; Design - A.A., B.K.; Supervision - K.A., L.C., I.E., M.C., A.O., L.T.; Materials - A.A., S.O., B.E., B.K., K.A.; Data Collection and/or Processing - A.A., L.K., S.O., B.E., B.K.; Analysis and/or Interpretation - A.A., L.K.S.O.; Literature Review - A.A., L.K., B.K., S.O., B.E.; Writer - A.A., S.O., L.K., B.K., B.E.; Critical Review - K.A., L.C., I.E., M.C., A.O., L.T.

**Conflict of Interest:** The authors declared no conflict of interest.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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