CLINICAL INVESTIGATION

Selection of Patients at Risk for Pulmonary Artery Hypertension Using a Clinical and Echocardiographic Assessment in Patients With Systemic Sclerosis

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ABSTRACT

Background: Prognosis of systemic sclerosis (SSc) is affected by pulmonary artery hypertension (PAH).

Methods: Among 202 patients (mean age: 46.1 ± 13.3 years; 177 women) with SSc, those with a tricuspid regurgitation (TR) jet maximal velocity at 2D-echocardiography (2DE) < 2.8 m/second were not considered at high risk for PAH, whereas those with a TR velocity >3 m/second or between 2.8 and 3 m/second and associated with dyspnea were.

Results: Among 22 patients at risk, 15 (mean age: 50.4 ± 14.3 years) had definite precapillary PAH on right heart catheterization (RHC). The delay period between recognitions of SSc and PAH was 12.9 ± 5.2 years. Dyspnea was present in all 15 patients, 11 (73.3%) being in the New York Heart Association class III or IV. The 2DE showed normal left ventricular geometrics and function ($n = 15$), enlargement of the right-sided cardiac chambers ($n = 12$), increased pulmonary arterial resistances with a TR velocity to pulmonary time-velocity integral ratio of > 0.2 ($n = 15$) and impaired right ventricle function ($n = 15$). RHC showed severe PAH in all 15 patients (mean pulmonary artery pressure: 48 ± 17 mm Hg and mean right atrial pressure: 11.8 ± 4.4 mm Hg) and a reduced cardiac index (2.2 L/m²). There was no statistical difference between patients with and without PAH regarding age, sex ratio, duration from onset of disease, diffuse or cutaneous limited type of SSc, Rodnan severity score and presence of digital ulcerations or autoantibodies. Telangiectasia ($P = 0.01$) and New York Heart Association class III or IV heart failure ($P = 0.001$) were more frequent in patients with PAH.

Conclusion: A combined clinical and Doppler-coupled 2DE screening of PAH risk in patients with SSc is useful to select those who can undergo RHC.

Key Indexing Terms: Systemic sclerosis; Pulmonary hypertension; Echocardiography. [Am J Med Sci 2016;▮(▮):▮▮▮–▮▮▮.]

INTRODUCTION

Pathogenesis of systemic sclerosis (SSc) includes autoimmune and vascular manifestations involving the microcirculation.[1] The disease accounts for 8-12% of patients with group 1 pulmonary artery hypertension (PAH) and ranks first among connective tissue diseases complicated with PAH.[2,3] When compared with patients without PAH, those with PAH-associated SSc have a 3-fold increase in mortality. In a recent registry of 131 patients with incident PAH, the 3-year cumulative survival rate was as low as 75%.[4] Prognosis and mortality of patients with SSc is largely effected by the severity of PAH and its related functional impairment.[4-8] Although recent studies showed that early recognition and treatment improve prognosis and survival,[9] most patients in whom PAH is detected are in a New York Heart Association (NYHA) functional class III or IV.[10,11] Accordingly, current guidelines emphasize early detection of this harmful complication to prevent further progression and right-sided heart failure.[12] Also, screening and early detection of PAH in patients with SSc who are at high risk of PAH have been recommended.[12] Doppler-coupled 2-dimensional echocardiography provides an easy and reliable approach to screen patients at increased risk for PAH. The present study is intended to provide data on the prevalence and severity of PAH, as assessed by a combined clinical and Doppler-coupled 2D-echocardiography, in a cohort of 202 patients hospitalized for SSc in the Mustapha Universitary Hospital, Algiers, Algeria.

PATIENTS AND METHODS

Patients aged ≥18 years referred to the Mustapha University Hospital for SSc between December 2010 and December 2013 were included. They had to fulfill the American College of Rheumatology criteria for diagnosis and classification of SSc.[13] Patients were either asymptomatic or evaluated for chest disease–related symptoms. Patients with any other cardiac disease (valvular heart disease or coronary artery disease) were excluded. Patients with other inflammatory diseases such as systemic diseases, vasculitides, dermatopolymyosistis,

systemic lupus erythematosus and rheumatoid arthritis and those with any overlap syndrome were excluded.

The following information was collected: demographics, physical examination findings, NYHA functional class assessment, electrocardiogram, pulmonary function tests (PFT) and transthoracic Doppler-coupled 2-dimensional echocardiographic examination. The later included left ventricular (LV) geometrics and function assessment, LV filling pressures, right ventricular geometrics and function, pulmonary Doppler-flow profiles, pulmonary artery pressure (PAP) and pulmonary artery resistances assessment.

Patients at high risk for pulmonary hypertension were identified using a stepwise echocardiographic approach after recording the maximum velocity of the tricuspid regurgitation (TR) jet. Those with a TR velocity $<$ 2.8 m/second were not considered at high risk for pulmonary hypertension, whereas those with a TR velocity $>$ 3 m/second were. A TR velocity between 2.8 and 3 m/second was considered as a high risk of PAH in patients with dyspnea (not related to other causes) only (Figure). To avoid inclusion of patients with pulmonary hypertension owing to other causes, including interstitial lung disease or SSc-related pulmonary fibrosis or both, patients must have fulfilled the following criteria: (1) forced vital capacity (FVC) $>$ 70% predicted and diffusing capacity for carbon monoxide (DLco) $<$ 55% predicted and (2) %FVC to %DLco ratio $>$ 1.6.

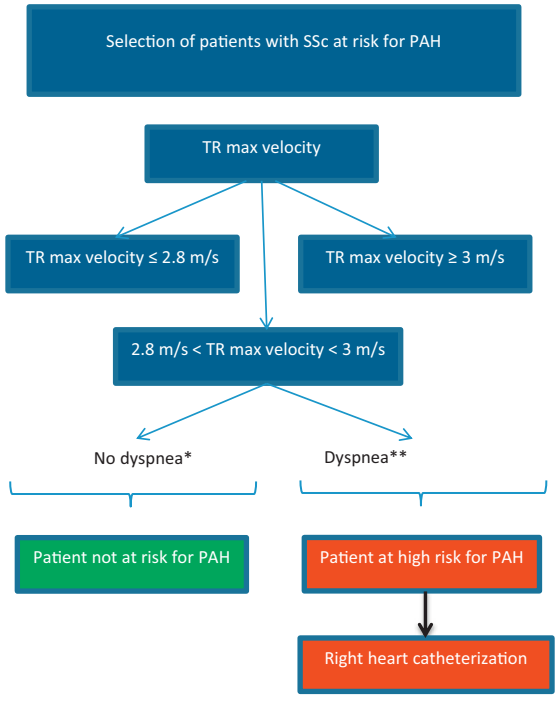

FIGURE. Screening algorithm for selection of patients with SSc at risk for PAH. TR max velocity: tricuspid regurgitation maximal velocity; * or dyspnea related to any other cause; ** not related to any other cause. PAH, pulmonary artery hypertension; SSc, systemic sclerosis; TR, tricuspid regurgitation.

Right heart catheterization (RHC) was performed in patients at high risk for PAH using a Swan-Ganz catheter. According to the World Health Organization criteria for group 1 PAH diagnosis, SSc-related PAH was confirmed in patients with a mean PAP $\geq$ 25 mm Hg and a capillary wedge pressure $\leq$ 15 mm Hg.

The investigation center obtained institutional review board approval, and all patients provided written informed consent before enrollment.

STATISTICAL ANALYSIS

Data were computed using a statistical package software—SPSS version 1.7 and EPI INFO TM version 6. Continuous variables were expressed as means with standard deviation (SDs) and categorical variables as frequencies and percentages. Means comparisons were done using the Student's t test. Percentages were compared using Pearson Chi-square test. $P < 0.05$ was considered as statistically significant.

RESULTS

Among 225 patients referred for SSc, 202 were included. The mean $\pm$ SD age was 46.1 $\pm$ 13.3 years. Most patients were women, with a women to men ratio of 7.08. The mean $\pm$ SD disease duration from the first Raynaud phenomenon and first non-Raynaud SSc symptoms was 10.7 $\pm$ 8.5 years. A limited cutaneous disease was observed in 120 patients (59.4%), 79 (39.1%) had diffuse cutaneous disease (39.1%) and the remaining 3 (1.5%) had a limited disease only.

There was no statistically significant difference between patients with SSc at risk for PAH and those not considered at risk regarding age, sex ratio, duration from onset of disease, type of SSc, diffuse or cutaneous limited, severity score of SSc, presence of digital ulcerations and presence of autoantibodies. Conversely, patients with PAH more frequently had telangiectasia ($P = 0.01$) and were more frequently in NYHA class III and IV ($P = 0.001$) (Table 1).

Using the aforementioned echocardiographic and clinical screening, 22 patients were considered at risk for pulmonary hypertension, among whom 15 had definite precapillary PAH based on RHC confirmation and 7 did not. Thus, the positive predictive value of screening for PAH detection was 68.1%. Prevalence of PAH among patients with SSC in our study reached 7.4%. The mean $\pm$ SD age of patients with PAH was 50.4 $\pm$ 14.3 years. Dyspnea was present in all 15 patients, 11 of them (73.3%) being in NYHA class III or IV. The mean $\pm$ SD 6-minute walk distance was 283.7 $\pm$ 52 m.

The mean duration $\pm$ SD from diagnosis of SSc to PAH recognition or screening was 12.9 $\pm$ 5.2 years in patients with subsequently RHC-confirmed PAH and 10.6 $\pm$ 6.9 years in those who were not at high risk for PAH. Only 4 of 15 patients (26.6%) with RHC-confirmed PAH were in NYHA class II when selected for RHC, whereas 176 of 187 patients (94.1%) not selected at risk for PAH were in class II ($P = 0.001$). In these 4 patients, the delay