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Determinants of exercise-induced pulmonary arterial hypertension in systemic sclerosis

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ABSTRACT

Background: Exercise-induced pulmonary arterial hypertension (EIPH) in systemic sclerosis (SSc) has already been observed but its determinants remain unclear. The aim of this study was to determine the incidence and the determinants of EIPH in SSc.

Methods and results: We prospectively enrolled 63 patients with SSc (age 54 ± 3 years, 76% female) followed in CHU Sart-Tilman in Liège. All patients underwent graded semi-supine exercise echocardiography. Systolic pulmonary arterial pressure (sPAP) was derived from the peak velocity of the tricuspid regurgitation jet and adding the estimation of right atrial pressure, both at rest and during exercise. Resting pulmonary arterial hypertension (PH) was defined as sPAP >35 mm Hg and EIPH as sPAP >50 mm Hg during exercise. The following formulas were used: mean PAP (mPAP) = 0.61 × sPAP + 2, left atrial pressure (LAP) = 1.9 + 1.24 × left ventricular (LV) E/e′ and pulmonary vascular resistance (PVR) = (mPAP–LAP) / LV cardiac output (CO) and slope of mPAP–LVCO relationship = changes in mPAP / changes in LVCO. Resting PH was present in 3 patients (7%) and 21 patients developed EIPH (47%). Patients with EIPH had higher resting LAP (10.3 ± 2.2 versus 8.8 ± 2.3 mm Hg; $p = 0.03$), resting PVR (2.6 ± 0.8 vs. 1.4 ± 1.1 Woods units; $p = 0.004$), exercise LAP (13.3 ± 2.3 vs. 9 ± 1.7 mm Hg; $p < 0.0001$), exercise PVR (3.6 ± 0.7 vs. 2.1 ± 0.9 Woods units; $p = 0.02$) and slope of mPAP–LVCO (5.8 ± 2.4 vs. 2.9 ± 2.1 mm Hg/L/min; $p < 0.0001$). After adjustment for age and gender, exercise LAP ($\beta = 3.1 \pm 0.8$; $p = 0.001$) and exercise PVR ($\beta = 7.9 \pm 1.7$; $p = 0.0001$) were independent determinants of exercise sPAP.

Conclusion: EIPH is frequent in SSc patients and is mainly related to both increased exercise LV filling pressure and exercise PVR.

1. Introduction

Systemic sclerosis (SSc) is a rare and complex disease, characterized by an extensive vasculopathy associated with auto-antibodies and fibrosis, with a multifactorial etiology [1]. Pulmonary arterial hypertension (PH), resulting from a pre-capillary mechanism, may be frequent in SSc with an approximated incidence of 8% to 13%, leading to an increased morbidity and mortality [2]. Echocardiography is an accurate non-invasive tool for the daily-life screening of patients at risk of PH [3]. Exercise echocardiography assessment of the pulmonary circulatory system has evolved over these last few years [4–6] and exercise-induced PH (EIPH) has recently been suggested as a potential useful tool for the early identification of patients with SSc at risk of developing resting PH [7,8]. It seems however, that the incidence of EIPH may overestimate the percentage of onset of resting PH during follow-up [9]. Some recent studies have underlined that the origin of EIPH in SSc could be secondary, not only to pulmonary vasculopathy, but also to myocardial [10] and/or pulmonary impairment [11,12]. Therefore, a post-capillary involvement in EIPH has been hypothesized in the literature [13,14]. Hitherto, the echocardiographic determinants of EIPH in SSc remain unclear. The present study sought to evaluate the incidence of EIPH and its determinants in patients with SSc.

Abbreviations: CO, cardiac output; EIPH, exercise-induced pulmonary arterial hypertension; LAP, left atrial pressure; LV, left ventricular; mPAP, mean pulmonary arterial pressure; sPAP, systolic pulmonary arterial pressure; PH, pulmonary arterial pressure; PVR, pulmonary vascular resistance; SSc, systemic sclerosis.

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2. Methods

We prospectively studied 68 consecutive patients from January 2008 to November 2012 with a diagnosis of SSc, followed in the rheumatology center of CHU Sart-Tilman in Liège. Five patients refused the study protocol. Exclusion criteria were: (1) inability to provide informed consent, (2) previous ischemic heart or valvular heart diseases and (3) inability to perform an exercise test. Eighteen patients were excluded, 15 due to

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poor echogenicity and unquantifiable sPAP secondary to severe thinness and/or pulmonary diseases, 1 for moderate mitral regurgitation and 2 for known coronary artery diseases. Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

All patients underwent a comprehensive resting echocardiography using conventional method with a Vivid 9 ultrasound system (General Electric Healthcare, Little Chalfont, UK). Offline analysis was performed retrospectively using a customized software package (EchoPac). Left ventricular (LV) stroke volume were calculated as the difference between LV end-diastolic and systolic volumes assessed by the bi-apical Simpson disk method and LV ejection fraction was derived as the ratio stroke volume/LV end-diastolic volume. Cardiac output (CO) was obtained by multiplying LV SV and heart rate. Left atrial area was measured in apical 4-chamber view at end-systole by planimetry. Peak E- and peak A-wave velocities of the mitral inflow were measured with pulsed-wave Doppler. Doppler tissue imaging was applied for measurement of the e′ wave at the lateral mitral annulus aspect.

The following right ventricular echocardiographic parameters were assessed: right ventricular end-diastolic and end-systolic areas, right ventricular fractional area change, tricuspid annular plane systolic excursion from an automated M-mode applied on the right ventricular apical 4-chamber view and maximal systolic velocity of the tricuspid annulus derived from Doppler tissue imaging pulsed-wave at the lateral tricuspid annulus.

The systolic pulmonary arterial pressure (sPAP) was derived from the maximal velocity of tricuspid regurgitant jet according to the simplified Bernoulli equation and adding right atrial pressure, estimated from the dimension and collapsibility of the inferior vena cava, according to the American guidelines [15]. A peak value >35 mm Hg was considered to define resting PH [16]. At peak exercise, sPAP was derived from the maximal velocity of tricuspid regurgitant jet and adding 10 mm Hg for the estimation of the right atrial pressure, as previously validated [17,18]. EIPH was defined as a sPAP >50 mm Hg [19]. The mPAP was estimated by the Chemla formula: $mPAP = 0.61 \times sPAP + 2$. As previously described [20,21], left atrial pressure (LAP) was assessed by 1.9 + 1.24 LV E/e′ and pulmonary vascular resistance (PVR) was estimated as the ratio between (mPAP–LAP) and LVCO, both at rest and at peak exercise. The slope of mPAP/LVCO relationship was estimated as the ratio between changes (peak–rest value) in mPAP and changes in LVCO [19]. All measurements were performed according to the current European Association of Echocardiography/American Society of echocardiography recommendations [22].

A symptom-limited graded bicycle exercise was performed in a semi-supine position on a tilted table. After an initial workload of 25 W maintained for 2 min, the workload was gradually increased by 25 W every 2 min. A 12-lead ECG was monitored continuously, and blood pressure was measured and rest and at each level of exercise. All patients presented normal tests, defined as the absence of the occurrence of 1) angina, 2) ≥2-mm ST-segment depression compared with baseline level or 3) complex ventricular arrhythmias.

All patients underwent standard pulmonary function tests with assessment of total lung capacity, vital capacity, forced vital capacity, forced expiratory volume in 1 s, ratio of forced expiratory volume in 1 s upon vital capacity and diffusing capacity of the lung for carbon monoxide.

Continuous variables are expressed as means ± standard deviation; categorical variables are presented as numbers and percentages. Data comparisons were performed according to the presence or absence of EIPH using Student unpaired and paired *t* test, χ^2 test or Fischer exact test as appropriate. The relationships between exercise sPAP and other continuous variables (i.e., demographic data, resting and exercise echocardiographic data) were evaluated by simple linear regression. Independent determinant of exercise sPAP were obtained with the use of multiple linear regression. Values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed with JMP version 10.0.2.

3. Results

3.1. Population characteristics

Fifteen patients were excluded due to unquantifiable sPAP, 1 for moderate mitral regurgitation and 2 for known coronary artery diseases. Among the remaining 45 patients, 47% developed EIPH (n = 21). The sPAP increased significantly during exercise (from 25 ± 7 to 46 ± 14 mm Hg; $p < 0.0001$). Patients with EIPH had higher resting sPAP (29 ± 6 vs. 21 ± 5 mm Hg; $p < 0.001$), resting mPAP (20 ± 4 vs. 14 ± 3 mm Hg; $p < 0.0001$), exercise sPAP (58 ± 9 vs. 36 ± 8 mm Hg; $p < 0.0001$, Fig. 1), exercise mPAP (37 ± 6 vs. 24 ± 5 mm Hg; $p < 0.0001$) and slope of mPAP–LVCO relationship (5.8 ± 2.4 vs. 2.9 ± 2.1 mm Hg/L/min; $p < 0.0001$, Fig. 2). In addition, all patients with resting PH (n = 3, 7%) developed EIPH. Patients with EIPH were significantly older (62 ± 12 vs. 48 ± 11 years; p = 0.0001), more frequently female (90% vs. 62%, p = 0.03), had higher resting systolic blood pressure (139 ± 22 vs. 122 ± 18 mm Hg; p = 0.03) and resting pulse pressure (62 ± 16 vs. 50 ± 11 mm Hg; p = 0.02). There were no significant differences between the 2 groups regarding variables of lung function tests (Table 1).

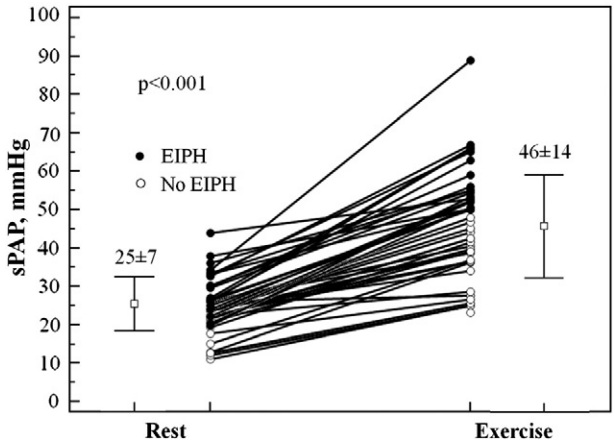

Fig. 1. Resting and exercise systolic pulmonary arterial pressure in the whole population. sPAP indicates systolic pulmonary arterial pressure; EIPH indicates exercise-induced pulmonary arterial hypertension.

3.2. Resting and exercise echocardiography

At rest (Table 2), patients of the EIPH group had significantly lower RV end-diastolic area (12.5 ± 3.1 vs. 14.9 ± 4.3 cm^2; p = 0.04) higher resting PVR (2.6 ± 0.8 vs. 1.4 ± 1.1 vs. Woods unit; p = 0.0004), higher LV E/e′ ratio (6.8 ± 1.8 versus 5.5 ± 1.8; p = 0.03), as a result of a lower e′ (11 ± 3 versus 13 ± 3 cm/s; p = 0.03), and higher LAP (10.3 ± 0.5 vs. 8.8 ± 2.3 mm Hg, p = 0.03), as compared to patients of the no EIPH group. During exercise, EIPH group exhibited (Table 3) higher LV E/e′ ratio resulting from lower value of e′ (respectively: 9.2 ± 1.8 vs. 5.7 ± 1.4; $p < 0.0001$ and 13 ± 1 vs. 17 ± 4 cm/s; p = 0.01), higher LAP (13.3 ± 2.3 vs. 9 ± 0.5 mm Hg; $p < 0.0001$). The LVCO significantly increased from rest to exercise in all patients (3.7 ± 0.9 vs. 7.2 ± 2.0 L/min; $p < 0.001$, Fig. 3), but in a lower extent in the EIPH group (4.2 ± 1.9 vs. 3.0 ± 1.3 L/min; p = 0.04) and patients of this group had a significantly lower resting LV end-systolic volume (25 ± 6 vs. 31 ± 11 mL; p = 0.04) and exercise-induced changes in LV end-diastolic diameter in the EIPH group (−8 ± 25 vs. 24 ± 46 mm; p = 0.002). Exercise PVR was significantly higher in patients with EIPH (3.6 ± 0.7 vs. 2.1 ± 0.9 Woods units; $p < 0.0001$).

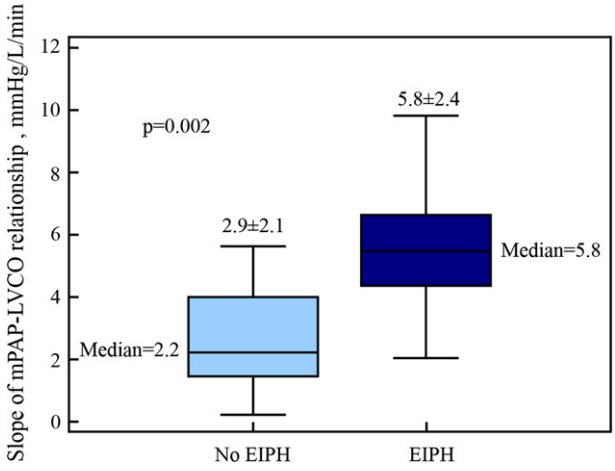

Fig. 2. Comparison of the slope of mean pulmonary arterial pressure and left ventricular relationships between the two groups. Slope of mPAP–LVCO indicates the ratio between change in mean pulmonary arterial pressure and change in left ventricular cardiac output; EIPH indicates exercise-induced pulmonary arterial hypertension.