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Cardiopulmonary exercise testing in a combined screening approach to individuate pulmonary arterial hypertension in systemic sclerosis

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Abstract

Objectives. The DETECT algorithm has been developed to identify SSc patients at risk for pulmonary arterial hypertension (PAH) yielding high sensitivity but low specificity, and positive predictive value. We tested whether cardiopulmonary exercise testing (CPET) could improve the performance of the DETECT screening strategy.

Methods. Consecutive SSc patients over a 30-month period were screened with the DETECT algorithm and positive subjects were referred for CPET before the execution of right-heart catheterization. The predictive performance of CPET on top of DETECT was evaluated and internally validated via bootstrap replicates.

Results. Out of 314 patients, 96 satisfied the DETECT application criteria and 54 were positive. PAH was ascertained in 17 (31.5%) and pre-capillary pulmonary hypertension in 23 (42.6%) patients. Within CPET variables, the slope of the minute ventilation to carbon dioxide production relationship (VE/VCO₂ slope) had the best performance to predict PAH at right-heart catheterization [median (interquartile range) of specificity 0.778 (0.714–0.846), positive predictive value 0.636 (0.556–0.750)]; exploratory analysis on pre-capillary yielded a specificity of 0.714 (0.636–0.8) and positive predictive value of 0.714 (0.636–0.8).

Conclusion. In association with the DETECT algorithm, CPET may be considered as a useful tool in the workup of SSc-related pulmonary hypertension. The sequential determination of the VE/VCO₂ slope in DETECT-positive subjects may reduce the number of unnecessary invasive procedures without any loss in the capability to capture PAH. This strategy had also a remarkable performance in highlighting the presence of pre-capillary pulmonary hypertension.

Key words: pulmonary arterial hypertension, systemic sclerosis, screening, cardiopulmonary exercise testing

Rheumatology key messages

- Early detection of pulmonary arterial hypertension in SSc positively influences prognosis.
- The screening strategy for pulmonary arterial hypertension or haemodynamic pulmonary hypertension with DETECT is suboptimal.
- Cardiopulmonary exercise testing improves DETECT's performance in the screening for pulmonary arterial hypertension.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease affecting the pre-capillary pulmonary vascular bed, leading to an increase in pulmonary vascular resistance, right ventricular failure and death [1]. SSc is one of the

main conditions associated with PAH, with a prevalence ranging from 5 to 12% [1]. Despite an optimized treatment, PAH is still a relevant cause of death in SSc, with an estimated 3-year survival rate no higher than 52% [2].

Recent evidence indicates that an early diagnosis and treatment are the most relevant factors to improve the

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prognosis and to reduce the mortality secondary to SSc-PAH [3, 4], thus a structured screening of PAH is highly recommended in SSc. However, an early diagnosis of SSc-PAH is difficult because of the absence of specific biomarkers and the presence of several non-specific symptoms confounding the clinical assessment [1, 5, 6]. In 2014 the first evidence-based screening algorithm for SSc-PAH (DETECT) was published [6], in which the false-negative rate was determined by performing right-heart catheterization (RHC) in all patients. The DETECT algorithm showed a remarkably high sensitivity (96%) and negative predictive value (NPV) (98%) in diagnosing SSc-PAH, outperforming the European Society of Cardiology/European Respiratory Society (ESC/ERS) screening approach, and thus reducing the rate of missed diagnoses [6, 7]. However, DETECT had a low specificity (48%) and positive predictive value (PPV) (35%), and resulted in a high proportion of unnecessary RHC procedures (65%).

Cardiopulmonary exercise testing (CPET) proved a useful tool in the diagnosis of cardiopulmonary diseases, including PAH. A recent study showed that abnormalities in gas exchange during exercise seem to be correlated to pulmonary vascular disease in SSc [8].

We thus hypothesize that CPET might improve PAH screening procedures, allowing a reduction of the number of unnecessary RHCs and better highlighting the occurrence of treatable forms of pulmonary hypertension (PH) [3, 4]. To test this hypothesis, we sequentially coupled CPET with the DETECT screening algorithm, looking for functional parameters that may help to increase its PPV while avoiding dampening its sensitivity.

Methods

Patients and procedures

Consecutive adult SSc patients referred to our institutions were screened between June 2017 and February 2019 according to the DETECT criteria: (i) diagnosis of SSc according to the ACR [9], (ii) predicted diffusing capacity for carbon monoxide <60% of predicted and (iii) disease duration >3 years from first non-Raynaud symptom.

Pulmonary function tests and blood samples were performed according to the DETECT approach [6]. Doppler echocardiography along with CPET were performed by experienced cardiologists (M.V., I.R.). All RHCs were performed by single operator. Echocardiography and CPET were separately analysed by two trained clinicians (R.C. and I.R.); discordant results were solved by convergence.

CPET was performed on a stationary cycle ergometer with an incremental work rate between 5 and 15 W/min up to the patients' maximum tolerance, followed by 3 min of recovery. The exercise protocol was selected according to the patient's exercise capacity to aim for 8–12 min in length. Gas exchange was measured breath-by-breath during the test, using calibrated COSMED Quark-B2 CPX equipment (COSMED, Rome, Italy). The first ventilatory threshold (fVT) was determined from gas exchange by the V-slope method, derived from a plot with VO_2 (x-axis)

and VCO_2 (y-axis) on equal axis scaling, and was recognized as the point where VCO_2 started increasing faster than VO_2 . The gradient of the relationship between minute ventilation (VE) and carbon dioxide production (VCO_2) (VE/ VCO_2 slope) was calculated by linear regression analysis using data acquired from the whole test [10].

Following DETECT indications, patients underwent RHC performed according to current recommendations [11]. Every single pressure curve was manually analysed at the end of RHC to avoid potential errors from automatic reading. PAH was defined as the presence of a mean pulmonary artery pressure ≥ 25 mmHg at rest with a pulmonary artery wedge pressure ≤ 15 mmHg and pulmonary vascular resistances ≥ 3 Wood units. These definitions were used in the original DETECT paper and to tune the screening algorithm [6]. Besides these definitions and according to the haemodynamic definition recently proposed by the 6th World Symposium on Pulmonary Hypertension task force, we also classified patients with pre-capillary PH as those with mean pulmonary artery pressure >20 mmHg, pulmonary vascular resistance ≥ 3 Wood units and pulmonary artery wedge pressure ≤ 15 mmHg [12].

All patients signed written consent for the study, which was approved by the local ethics committee (Comitato Etico Area 2) with number 265_2016bis and subsequent modification (21 June 2017).

Statistical analysis

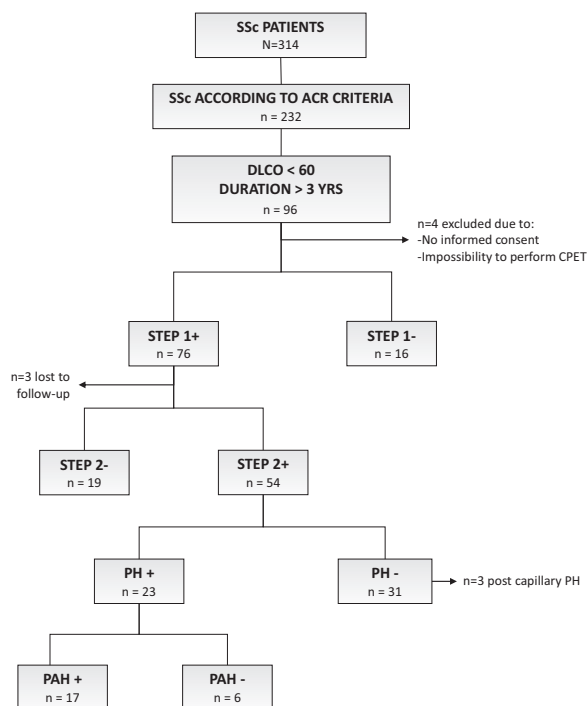
Continuous variables were compared either by the Student's *t* test or the Mann-Whitney *U* test if normally or non-normally distributed, respectively. Categorical variables were compared by means of Fisher's exact test.

A bootstrap aggregating (bagging) procedure was used to determine and validate the performance of CPET in DETECT-positive patients. To this end, 50 000 bootstrap samples with replacement were generated; for each CPET variable in each bootstrap sample, we chose the threshold that maximized the sensitivity to capture PAH; the chosen threshold was then tested in the out-of-bag samples. Median and interquartile ranges of out-of-bag results are presented. The optimal target of CPET as a screening tool should be a sensitivity equal to 1 (100%), that is the capability of not spoiling the NPV of DETECT; a count of models/variables with perfect sensitivity is then performed to provide an estimate of the goodness of the sequential use of CPET in DETECT-positive patients. Albeit the sensitivity and NPV of DETECT in the context of pre-capillary PH is undetermined, we used the same criterion to determine the performance of CPET in capturing pre-capillary PH.

Results

Overall, 314 SSc patients were screened. Ninety-six were considered at risk according to DETECT entry criteria; of these, 76 passed the DETECT step 1 and 54 the step 2, and were thus referred for CPET and RHC. Twenty-three patients (42.6%) had pre-capillary PH according to the new proposed haemodynamic criteria [12], including 17

Fig. 1 Flow chart of subject recruitment and main haemodynamic findings



with PAH (31.5%) according to the ESC/ERS 2015 guidelines (Fig. 1) [1]. Additionally we identified three post-capillary PH (5.5%). In our cohort, seven patients had signs of interstitial lung disease at high-resolution CT. Interstitial lung disease extension was mild in four cases (<10% of lung parenchyma) and intermediate in three (10–20% of lung parenchyma). In the absence of extensive interstitial lung disease, no patient could be assigned to group 3 PH [1]. Clinical, demographic, haemodynamic, CPET and echocardiographic characteristics of the patients are reported in Table 1.

We did not find significant differences in demographical and echocardiographic data between the PAH and non-PAH groups, or between those with or without pre-capillary PH (Table 1).

After bagging validation, two CPET variables had the best performance in assessing PAH. The VE/VCO_2 at the fVT ($VE/VCO_2@fVT$) had sensitivity equal to 1.0 in 63% of models, with a median sensitivity of 1.0 (0.857–1.0), specificity of 0.833 (0.769–0.882), PPV of 0.7 (0.6–0.8) and NPV of 1.0 (0.923–1.0). The VE/VCO_2 slope had a sensitivity equal to 1.0 in 87% of models, with a median sensitivity of 1.0 (1.0–1.0), specificity of 0.778 (0.714–0.846), PPV of 0.636 (0.556–0.750) and NPV of 1.0 (1.0–1.0). The bootstrapped thresholds to detect the presence of PAH were 41.2 and 39, respectively.

When pre-capillary PH was considered, we obtained the performance metrics reported hereafter. $VE/VCO_2@fVT$:

sensitivity 1.0 (0.889–1.0), specificity 0.455 (0.364–0.556), PPV 0.571 (0.5–0.643) and NPV 1.0 (0.857–1.0), with perfect sensitivity in 63.1% of models; VE/VCO_2 slope: sensitivity 1.0 (0.889–1.0), specificity 0.714 (0.636–0.8), PPV 0.714 (0.636–0.8) and NPV 1.0 (0.889–1.0), with maximum sensitivity in 63.7% of models. The bootstrapped thresholds to detect the presence of pre-capillary PH were 35.5 and 36, respectively.

None of the other CPET or ecocardiographic variables listed in Table 1 had a substantial effect on improving the DETECT performance in capturing PAH/pre-capillary PH.

Discussion

The main finding of our study is the potential capability of selected CPET parameters to reduce the number of referrals for RHC in patients at risk for PAH. Namely, we showed that when sequentially applied to the DETECT screening, the measure of $VE/VCO_2@fVT$ or VE/VCO_2 slope is predictive for the presence of SSc-PAH. Due to a better technical reproducibility and higher rates of perfect screening fit (i.e. models with sensitivity equal to 1), the VE/VCO_2 slope seems the parameter of choice to be used in combination with the DETECT screening algorithm. Indeed, in our population this strategy and a VE/VCO_2 slope cut-off value ≥ 39 would have yielded a theoretical reduction in the number of RHCs from 54 to 25 without any missed diagnoses. Due to the changing definition of PH we also exploratively evaluated the performance of CPET in the context of the newly proposed haemodynamic criteria for pre-capillary PH [12]. A slightly lower VE/VCO_2 threshold (≥ 36) was found to be of use in assessing the presence of pre-capillary PH. It is worth noting that the DETECT screening algorithm was optimized to capture SSc-PAH with a high sensitivity and that the 'true' performance of DETECT in pre-capillary PH is unknown. Theoretically, the feature selection and validation strategy that led to the development of DETECT [6] should be reworked altogether to tune the algorithm to optimize its performance in pre-capillary PH. Still, our data indicate that CPET may be useful in the context of pre-capillary PH.

Our data on ventilatory efficiency are in accordance with Dumitrescu *et al.* [8], while we could not confirm a role for peak VO_2 in screening for SSc-PAH. These differences could be due to the different selection criteria applied, as we indeed focused on a screened population, excluding cases with other forms of lung involvement that may increase peak VO_2 in the absence of pulmonary vasculopathy.

Several factors may link ventilatory efficiency to pulmonary vascular disorders. The functional assessment and the ventilatory adaptation to effort are able to individuate the presence of pulmonary vascular remodelling [13]. The excess in exercise-induced hyperventilation may be explained by several factors. Firstly, we can hypothesize a role for the ventilation/perfusion mismatch. The increase in the dead space impairs the mobilization of CO_2 from blood to the airspace, forcing ventilation to increase in the effort to eliminate metabolic CO_2 . In low perfusion

TABLE 1 Clinical, haemodynamic and functional characteristics of participants

	SSc (n = 54)	PAH+ (n = 17)	PAH- (n = 37)	PC-PH+ (n = 23)	PC-PH- (n = 31)
Demographic and clinical data					
Age, years	63.4 (12.1)	66.2 (7.6)	62.1 (13.6)	65.5 (8.3)	61.8 (14.2)
BMI, kg/m ²	22.6 (4.1)	21.5 (4.2)	23.1 (3.9)	22.5 (4.7)	22.7 (3.5)
Disease duration, years	14.1 (7.1)	15.9 (7.6)	13.3 (6.8)	15.9 (7.6)	13.3 (6.8)
FVC, %	99.7 (23.9)	94.9 (18.7)	101.8 (25.9)	96.1 (19.3)	102.4 (26.8)
DLCO, %	45.7 (9.0)	40.3 (9.5)**	48.1 (7.8)	42.5 (9.5)	48.1 (8.0)
NTproBNP, ng/dl	185.0 (87.2–290.0)	256 (111.6–813.8)	171 (77.5–268)	245.5 (124.7–460.5)	153.0 (75.0–259.0)
Uric acid, mg/dl	4.9 (1.3)	5.3 (1.7)	4.8 (1.1)	7.6 (3.7)	4.6 (1.1)
Females, n (%)	52 (96)	17 (100)	35 (95)	23 (100)	29 (93)
lcSSc, n (%)	44 (81)	13 (76)	31 (84)	17 (74)	27 (87)
ACA, n (%)	38 (70)	12 (71)	26 (70)	15 (65)	23 (74)
Teleangectasia, n (%)	51 (94)	15 (88)	36 (97)	21 (91)	30 (97)
Right axis deviation, n (%)	2 (4)	2 (1)	0	2 (1)	0
Haemodynamic parameters					
mPAP, mmHg	22.7 (5.5)	28.8 (2.4)***	19.9 (4.1)	27.2 (3.5)**	19.4 (4.3)
PCWP, mmHg	8.6 (3.6)	8.6 (2.9)	8.5 (3.9)	8.2 (2.8)	8.8 (4.1)
RAP, mmHg	4.6 (2.5)	4.6 (2.0)	4.6 (2.7)	4.4 (2.1)	4.7 (2.8)
PVR, WU	3.2 (1.6)	4.9 (1.6)***	2.3 (0.8)	4.5 (1.5)**	2.1 (0.6)
Cardiac index, l/min/m ²	3.1 (0.8)	2.9 (0.6)	3.2 (0.9)	2.9 (0.5)	3.2 (0.9)
CPET parameters					
VO ₂ /kg max, ml/min/kg	16.0 (4.0)	14.5 (4.3)	16.7 (3.9)	15.3 (4.5)	16.6 (3.9)
VO ₂ /HR max, ml/b.p.m.	6.7 (1.5)	6.2 (1.9)	6.9 (1.5)	6.7 (2)	6.6 (1.4)
VE/VCO ₂ @fVT	41.1 (7.4)	49.0 (5.5)***	37.4 (4.8)	46.8 (6.3)***	36.8 (4.8)
VE/VCO ₂ slope	38.7 (6.6)	45.3 (4.4)***	35.7 (5.1)	43.4 (5.1)***	35.2 (5.3)
PetCO ₂ @fVT, mmHg	29.9 (4.6)	25.6 (2.6)***	31.8 (3.9)	26.8 (3.3)***	32.1 (4.1)
Echocardiographic parameters					
LVEDV/BSA, ml/m ²	50.6 (10.5)	49.3 (13.4)	51.2 (9.0)	49.0 (11.8)	51.7 (9.5)
LVEF, %	62.7 (7.3)	62.6 (6.7)	62.8 (7.7)	62.6 (6.7)	62.8 (7.9)
LAEDV/BSA, ml/m ²	28.4 (10.6)	27.6 (12.1)	28.2 (9.9)	26.4 (12.5)	29.2 (10.2)
RA area, cm ²	15.3 (3.4)	14.5 (3.9)	15.7 (3.2)	15.0 (3.8)	15.6 (3.2)
RV basal diameter, mm	35.1 (4.9)	33.9 (5.4)	33.7 (4.6)	33.6 (4.9)	36.2 (4.7)
Trjet vel max, cm/s	2.6 (0.5)	2.8 (0.7)	2.6 (0.4)	2.8 (0.7)	2.6 (0.4)
PacT, cm/s ²	104.7 (27.8)	94.9 (31.4)	109.4 (25.0)	94.5 (29.5)*	112.5 (24.1)
TAPSE, mm	21.9 (3.5)	21.4 (3.4)	22.2 (3.5)	21.7 (2.9)	22.2 (3.9)
RV S', cm/s	12.8 (2.9)	13.0 (3.8)	12.7 (2.4)	13.0 (3.3)	12.6 (2.6)
RV FAC, %	40.3 (9.0)	36.7 (8.7)	41.8 (8.8)	36.9 (8.3)*	42.7 (8.8)
IVC size >2.1 cm or sniff variation <50%, n (%)	1 (2)	1 (6)	0	1 (6)	0

*Values expressed as mean (s.d.) except NTproBNP, expressed as median (interquartile range). $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. PAH+: SSc patients with pulmonary arterial hypertension; PAH-: SSc without PAH; PC-PH+: patients with pre-capillary pulmonary hypertension (PH); PC-PH-: patients without PC-PH; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressure; PVR: pulmonary vascular resistance; CPET: cardiopulmonary exercise testing; VE: minute ventilation (VE); VO₂: oxygen production; VCO₂: carbon dioxide production; HR: heart rate; VE/VCO₂@fVT: VE/VCO₂ at the fVT; PetCO₂@fVT: low end-tidal CO₂ pressure at fVT; LVEDV/BSA: left ventricular end-diastolic volume per body surface area; LVEF: left-ventricular ejection fraction; LAEDV/BSA: left atrium end-diastolic volume per BSA; RA: right atrium; RV: right ventricle; Trjet vel max: peak velocity of the trans-tricuspid jet; RV S': RV longitudinal myocardial velocity; PacT: pulmonary artery acceleration time; TAPSE: tricuspid anulus; FAC: fractional area change; IVC: inferior vena cava.

states, decreased blood passing by the alveoli and lower diffusion across the alveolar-arterial junction led to exhaled gas with less CO₂, that is, a low end-tidal CO₂ (PetCO₂@fVT) [13, 14], as we indeed observed in our SSc-PAH/pre-capillary PH subjects. Secondly the neural reflex pathways, influencing sympathetic activation and hyperventilation, might contribute to our results. As reported elsewhere, the degree of ventilatory inefficiency seems to be correlated to chemosensitivity and sympathetic

activation [15, 16]. Autonomic balance alterations may be present in SSc patients [17] and seem to be correlated to exercise tolerance and aerobic capacity [18]. Accordingly, our results showed that SSc-PAH patients had lower VO₂ peak as well as PetCO₂@fVT than those without PAH. Impaired aerobic capacity and dysregulated CO₂ control mechanisms should be considered as indirect signs of altered chemosensitivity and activated sympathetic nervous system [19]. Finally, we may suppose that

SSc-PAH patients with high pulmonary vascular resistance would increase the right ventricular afterload during exercise and then enhance the dysregulation of ventilatory control mechanisms via cardiac autonomic reflex (Bainbridge reflex), eliciting a high VE/VCO₂ slope [13, 14]. Thus, the CPET may represent a valid physiological assessment to stress the cardiopulmonary system in SSc and to exhibit a hidden pulmonary vascular involvement when right heart remodelling/overload is not appreciable at US. Accordingly, in our population, echocardiographic parameters did not differ between SSc patients with or without PAH (Table 1). Only 56% of our patients would have been referred to RHC according to the ESC/ERS criteria, missing four PAH (23.5%), confirming the rates of missed diagnoses reported in the DETECT population (29%) [6]; expectedly, the performance of ESC/ERS criteria were even worse when pre-capillary PH was considered, with 8/23 (35%) missed diagnoses.

Albeit the physiopathological mechanisms described above constitute a strong basis for the use of CPET in SSc patients at risk for PAH/pre-capillary PH and despite the robust and extensive internal validation method we used, the limited sample size and lack of an external population to test the generalizability of our approach are clear limitations of our study. Similarly, we cannot make any inference about the validity of CPET coupled with screening algorithms other than DETECT or in conjunction with algorithms specifically optimized for pre-capillary PH. Moreover, due to the influence of left-heart disease on CPET parameters, any strategy aimed at excluding left-heart impairment would help to overcome CPET limitations, further enhancing its significance in a structured screening strategy. Despite these shortcomings, CPET appears to be a promising, non-invasive tool in the screening workup for SSc-related PH.

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