Reduced ventilatory efficiency during exercise predicts major vascular complications and mortality for interstitial lung disease in systemic sclerosis

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ABSTRACT

Objective. *Major vascular complication, such as digital ulcers (DUs), pulmonary arterial hypertension (PAH) and scleroderma renal crisis (SRC) are hallmarks of systemic sclerosis (SSc). Interstitial lung disease (ILD) is the major cause of mortality in SSc. The aim of study is to identify cardiopulmonary exercise testing (CPET) variables that predict MVC and mortality for ILD in SSc patients.*

Methods. *In this cohort study, 45 SSc patients underwent clinical evaluation, echocardiography, pulmonary function tests (PFTs), high resolution computerised tomography (HRCT) and CPET. PFTs and echocardiography were performed annually for a 5-year follow-up.*

Results. *16 (35.6%) SSc patients had MVC: 14 new DUs (31.1%), 1 PAH (2.2%) and 1 SRC (2.2%). At univariate regression analysis, mRss [HR 1.099 (1.008–1.199), p<0.05], NVC patterns (active and late) [HR 0.032 (0.004–0.250), p<0.001], V'E/V'CO2 slope [HR 1.123 (1.052–1.198), p<0.001] were predictive of new onset of MVC. In multivariate analysis, NVC patterns (active and late) (HR 0.044 (0.004–0.486), p<0.05), V'E/V'CO2 (HR 1.094 (1.020–1.198), p<0.05) were predictive of new onset of MVC. The 5-year mortality for ILD is 8.9%. In univariate analysis, DLco [(HR 0.927(CI 0.874-0.983), p<0.05], V'E/V'CO2 slope and lung parenchymal with radiological patterns of ILD [(1.2.02 (CI 1.018-1.419), p<0.05], represent risk factors for 5-year mortality for ILD [HR 1.142 (1.030-1.267), p<0.05]. In multivariate analysis, only V'E/V'CO2 slope [1.268 (CI 1.003–1.602), p<0.05] represents a risk factor for 5-year mortality for ILD.*

Conclusion. *V'E/V'CO2 slope is a prognostic marker of MVC and five-year mortality for ILD.*

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by endothelial dysfunction, microvascular damage and fibrosis of skin and internal organs. Vascular damage is the hallmark of the disease. Endothelial dysfunction and microvascular damage occur early in the pathogenesis of SSc. Pathogenesis of major vascular complications (MVC) of SSc, such as digital ulcers (DUs), pulmonary arterial hypertension (PAH) and scleroderma renal crisis (SRC) is due to endothelial dysfunction and vascular damage (1).

Mortality in SSc patients is higher than in general population. In a recent meta-analysis, Rubio-Rivas *et al*. found an overall standardised mortality ratio of 2.72 (1.5–5.40). Interstitial lung disease (ILD) is the major determinant of morbidity and mortality in SSc (2). Poudel *et al*. reported that pulmonary involvement is the primary reason for hospitalisation in 20% of patients who died in hospital (3). Pulmonary Function Tests (PFTs) and High Resolution Computerised Tomography (HRCT) are commonly used to detect early occurrence of ILD in SSc. The most common finding at HRCT is non-specific interstitial pneumoniae (NSIP).

Cardiopulmonary exercise testing (CPET) is the gold standard for evaluating the causes of exercise intolerance in patients with pulmonary and cardiac diseases (4). CPET comprises the imposition of symptom-limited incremental exercise, commonly in combination with comprehensive breath-by-breath monitoring of cardiopulmonary variables, *e.g*. peak O2 uptake (V'O2 peak) and ventilatory equivalents for carbon dioxide production (V'E/V'CO2) (4). The slope of the relation V'E/V'CO2 (V'E/V'CO2 slope) reflects the efficiency of lung gas exchange during

exercise. In normal individuals V'E/V'CO2 slope is expected to be 25+2; values above 32 are considered to be pathological and usually associated to a worse prognosis in chronic heart failure (5). High values of V'E/V'CO2 slope are observed in patients with idiopathic PAH, chronic obstructive pulmonary diseases and adult cystic fibrosis (6).

CPET has been utilised in SSc for early detection of pulmonary arterial hypertension and pulmonary vasculopathy. SSc patients with DUs history showed V'E/V'CO2 slope values significantly higher than patients without DUs history. VE/VCO_2 slope increases with progression of capillaroscopic damage and it is a marker of pulmonary vasculopathy (7). In SSc patients without cardiopulmonary involvement, autonomic dysfunction is associated with better exercise tolerance and cardiac function during physical effort (8, 9). Although DETECT algorithm and echocardiography represent a screening test for pulmonary arterial hypertension, measurement of V'E/VCO2 slope in subject with risk factor may reduce the number of unnecessary invasive procedures (10). Recently, Ewert *et al*. suggested that low V'O2 peak and high V'E/V'CO2 slope may predict mortality in SSc patients (11).

The aim of study is to identify CPET variables that predict MVC and mortality for ILD in SSc patients. Secondary endpoint is to evaluate the role of V'E/V'CO2 slope as marker of worsening DLco, FVC and sPAP during follow-up.

Methods

Participants

Forty-five consecutive patients fulfilling the American College of Rheumatology/European League for classification and diagnosis of SSc meeting the inclusion criteria were enrolled in this prospective observational study (12).

At baseline, all SSc patients underwent clinical evaluation, echocardiography, PFTs, HRCT and CPET. During the five years of follow up, PFTs and echocardiography are repeated annually.

Patients with pulmonary disease not related to SSc, chronic heart failure, cardiac arrhythmias and conduction disorders, history of uncontrolled systemic hypertension, valvular heart diseases, cerebrovascular and peripheral vascular diseases, thrombophilia, anaemia, smokers and pregnant or breastfeeding women were excluded from the study.

This study was conducted in accordance with the Declaration of Helsinki. The ethics committee of Sapienza University (n. 427/19) approved the study and written informed consent was obtained from all patients.

Clinical assessments

We systematically collected age, disease duration, new DUs, modified Rodnan Skin Score (mRSS). Nailfold videocapillaroscopy (NVC) was performed with a videocapillaroscope (Pinnacle Studio v. 8) equipped with a 500 × optical probe. According to Cutolo *et al*., the patterns identified within the "SSc pattern" included early, active and late (13). New onset of PAH was confirmed by right heart catheterisation according to ESC guidelines (14). New onset of SRC was done according to UK Scleroderma Study Group guidelines (15). The interval of onset of major vascular complications (MVC) is calculated at time of first MVC.

Pulmonary function tests (PFTs)

Spirometric parameters of flows and volumes [FEV1 (forced expiratory volume in the 1st second), FVC (Forced vital capacity), FEV1/FVC)] and DLco, corrected for haemoglobin concentration, were recorded with a Quark PFT 2 spirometer (Cosmed, Rome, Italy) and expressed according to the standards recommended by the American/European Respiratory Society (16-17). All spirometric parameters are expressed as percentage of predicted.

High resolution computed tomography (HRCT)

HRCT was performed according to standard protocol using a CT 64GE light Speed VCT power scanner (Somatom Definition, Siemens AG, Forcheim, Germany) with a voltage of 120kV and modulating the tube current levels to the scanning volume to reduce the dose. CT images has been processed by know CALIPER (Computer Aided Lung Informatics for Pathology Evaluation and Rating), a quantitative CT algorithm provided by Imbio LLC (807 Broadway St. NE, Suite 350, Minneapolis, MN 55413) (18). The CT images has been loaded on a web server where they were processed, and an output was generated according to our previous study. The output was in form of a dictionary containing the percentage of lung volume corresponding to one of the following radiological parenchymal patterns: normal, decreased lung attenuation (grouped in three different grades: mild, moderate and marked), ground glass opacification, reticular pattern and honeycombing.

Echocardiography

Echocardiograms were performed with the General Electric Vivid S5 apparatus (GE Medical Systems, Israel Ltd.). Left ventricle (LV) diameter, wall thickness, LV ejection fraction, right ventricle (RV) diameter, tricuspidal annular plane systolic excursion (TAPSE) were assessed in the standard fashion. Systolic pulmonary arterial pressure (sPAP) was determined from peak tricuspidal jet velocity using the simplified Bernoulli equation and combining this value with an estimate of the right atrium pressure: sPAP = 4(V)2 + RA pressure, where V is the peak velocity (in metres per second) of the tricuspid valve regurgitant jet, and RA pressure is estimated from inferior vena cava diameter and respiratory changes (19-20).

Cardiopulmonary exercise test (CPET)

An incremental symptom-limited CPET was performed on an electronically braked cycloergometer (Ergoline-800, Mortara, Bologna, Italy), according to a standardised protocol and following international guidelines. The subject was connected to the breath-by-breath lung gas exchange system by the use of a mask and breathing through a bidirectional turbine mass flow sensor (Quark PFT, Cosmed, Rome, Italy). The exercise protocol consisted of 3 minutes of rest and 3 minutes of unloaded cycling, followed by an incremental work rate to induce voluntary exhaustion in about 10 minutes, followed by 3 minutes of recovery. ECG and pulse oximetry were continuously monitored, and blood pres-

sure was measured every two minutes. Calcium channel blockers, endotelin-1 receptor antagonist and phosphodiesterase type 5 inhibitors were interrupted 72 hours before CPET examination. CPET were performed 24 hours prior the next infusion of Iloprost. Tidal volume (VT), respiratory rate (RR), heart rate (HR) and lung gases exchange (O2, CO2) was measured breath-by-breath continuously during the whole test. V'O2, V'CO2, V'O2/HR, and the respiratory exchange ratio (V'CO2/V'O2, RER) were computed and averaged every 10 seconds. The lactic threshold (LT) was determined by the V-slope method. The relation between V'E and V'CO2 (V'E/V'CO2 slope) was calculated as the slope of the linear relationship between VE and VCO2 from one minute after the beginning of loaded exercise to the end of the isocapnic buffering period. A submaximal test is defined by RER ≤1.05 (4, 15).

Statistical analysis

The coefficient of skewness and kurtosis with Shapiro-Wilk test were used to evaluate normal distribution of data. All results are expressed as median and IQR. SPSS v. 25.0 software was used for the statistical analysis. Group comparisons were made by Mann-Whitney test. Spearman's rank correlation coefficient was used to test for an association between numerical variables. Multiple regression analysis was used to evaluate correlation between variables significant in bivariate analysis. All time-to-event end points were estimated with the Kaplan-Meier method and analysed with the log-rank test. Hazard ratios with 95% confidence intervals were calculated with the use of Cox regression models. A multivariate analysis was applied for the estimation of CPET variables in the worsening of delta of PTTs and echocardiography parameters. The chi-square test or Fisher's exact test, as appropriate, were used to compare categorical variables. *P*-values <0.05 were considered significant.

Results

Baseline findings

Forty-five SSc patients (39 females; mean age 49±12 years) were enrolled.

Table I. Systemic sclerosis patients' epidemiological and clinical features.

Female, n (%)	39 (86.7)
Age, years	49 (46-53)
Disease duration, years	10 (8-12)
mRss	8 (6-12)
BMI, kg/m^2	22.7 (21.5-23.1)
dcSSc/lcSSc, n (%)	28 (62.2)/17 (37.8)
Digital ulcers, n (%)	17 (37.8)
SSc-specific autoantibodies, n (%)	
Scl70	25 (55.6)
Anticentromere	15 (33.3)
None	5 (11.1)
Capillaroscopic pattern, n (%)	
Early	13 (28.9)
Active	15 (33.3)
Late	17 (37.8)
CCB	43 (95.6)
ILOPROST	44 (97.8)
ERA	16 (35.6)
PDE-5i	1 (2.2)

mRSS: modified Rodnan skin score; BMI: body mass index; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; Scl70: antitopoisomerase I antibodies; ACA: anticentromere antibodies; CCB: calcium channel blockers; ERA: endotelin-1 receptor antagonist; PDE-5i: phosphodiesterase type 5 inhibitors.

Table II. Findings of pulmonary function tests (PFTs), echocardiography, computer-aided lung informatics for pathology evaluation and rating (CALIPER) analysis and cardiopulmonary exercise testing (CPET).

Variables of PFTs	**Mean ± standard deviation**
FVC, % of predicted	101.6 (89.4-109)
FEV1, % of predicted	96.1 (90.4-101)
DLco, % of predicted	77.3 (70.5-80.7)
CALIPER analysis	**Mean ± standard deviation**
Normal lung, % parenchyma	90.2 (88.1-92.9)
Ground glass pattern, % parenchyma	0.51 (0.33-2.79)
Reticular pattern, % parenchyma	1.74 (0.9-3.4)
Honeycombing pattern, % parenchyma	0.87 (0.72-1.2)
Variables of echocardiography	**Mean ± standard deviation**
Left ventricular EF, %	60 (60-62)
LV end diastolic diameter, mm	44 (44-47)
LVM, g	104 (100-119)
RV diameter, mm	26 (26-28)
TAPSE, mm	22 (22-25)
sPAP, mmHg	27 (26-30)
Variables of CPET	**Mean ± standard deviation**
RR peak	36.2 (34.7-40.7)
RER	1.18 (1.16-1.22)
Watt peak, W	80 (75-90)
V'O2 peak, ml/min	1229 (1094-1321)
VO2, ml/min/kg	20.2 (18-25.2)
V'O2 peak, %	79 (73-89)
V'E/V'CO2 slope	29.4 (28-31.5)
HR rest, bpm	82 (78-94)
HR peak, bpm	155 (149-163)
Basal SBP, mmHg	118 (110-120)
Peak SBP, mmHg	160 (160-170)

FVC: forced vital capacity; FEV1: forced expiratory volume in the 1st second; DLco: single-breath carbon monoxide diffusing capacity; RV: right ventricle; LV: left ventricle; TAPSE: tricuspidal annular plane systolic excursion; sPAP: systolic pulmonary artery pressure; EF: ejection fraction; LVM: left ventricular mass; RR: respiratory rate; RER: respiratory exchange ratio; V'O2 peak: peak oxygen uptake; V'E/V'CO2: ventilatory equivalents for carbon dioxide production; HR: heart rate; SBP: systolic blood pressure.

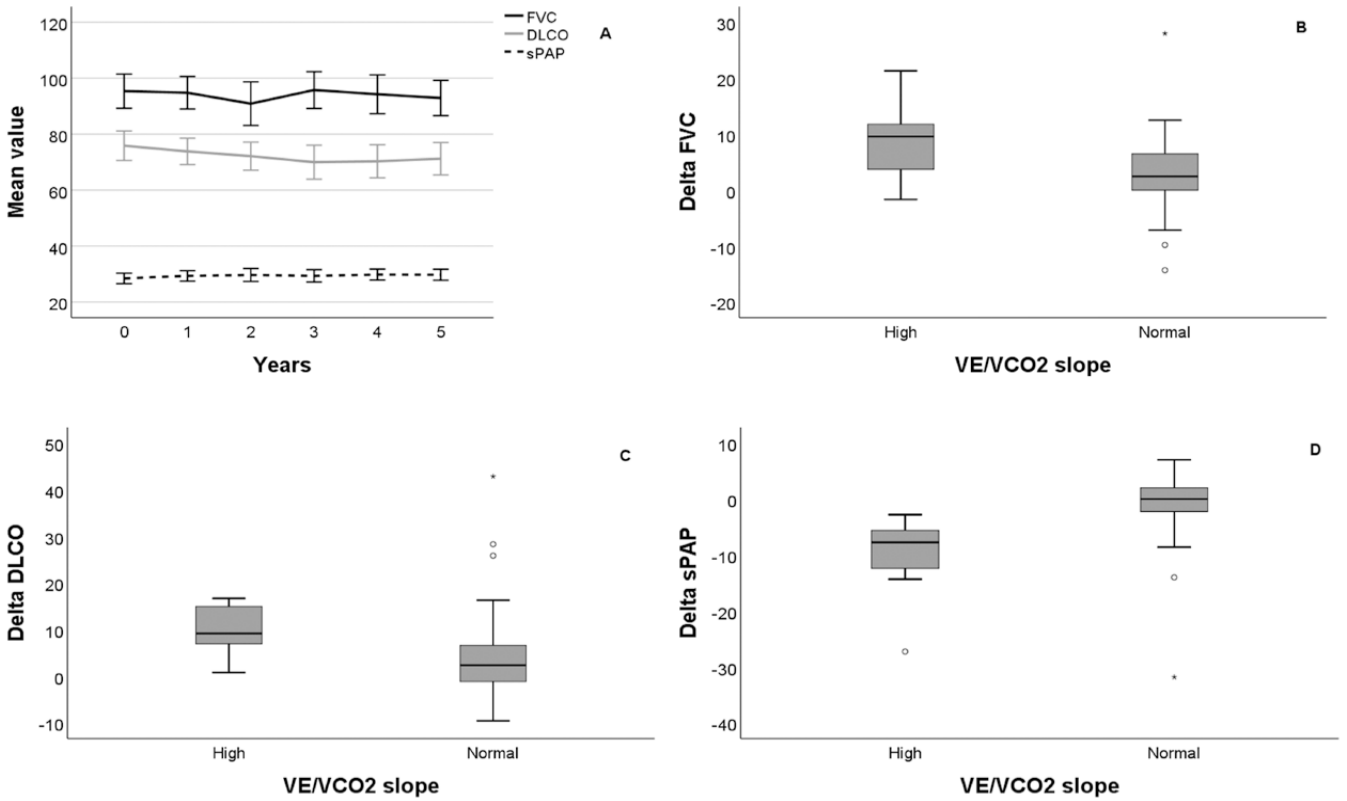

Fig. 1. A: Mean value and confidence interval of Forced vital capacity (FVC), Diffusion lung carbon monoxide (DLco) and systolic pulmonary arterial pressure (sPAP) during of follow-up; **B:** Delta of FVC in SSc patients with $V'_E/V'CO_2$ slope <35 and $V'_E/V'CO_2$ slope >35; **C:** Delta of DLco in SSc patients with $V'_E/V'CO_2$ slope <35 and $V'_E/V'CO_2$ slope >35; **D:** Delta of sPAP in SSc patients with $V'_E/V'CO_2$ slope <35 and $V'_E/V'CO_2$ slope >35.

Seventeen patients had limited cutaneous SSc (lcSSc) and 28 had diffuse cutaneous SSc (dcSSc). Table I shows the SSc patients' epidemiological and clinical features. The median values and IQR of FVC, DLco and sPAP are 101 (89.4–109) % of predicted, 77.3 (70.5–80.7) % of predicted and 27 (26-30) mmHg. All findings of PFTs and echocardiography are shown in Table II.

In CALIPER analysis, normal lung parenchyma is 90.2 (88.1–92.9) %, conversely lung parenchymal with radiological patterns of ILD is 9.83 (7.26–16.1): ground glass 0.51 (0.33–2.79) %, reticular 1.74 (0.9–3.4) %, honeycombing 0.87 (0.72–1.2) % and hyperlucent 3.05 (1.96–4.59).

All SSc patients performed a maximal CPET because RER is 1.18 (1.16–1.22). The median values and IQR of V'O2 peak and V'E/V'CO2 slope are 79 (73-89) and 29.4 (28–31.5) (Table II). Using a cut-off ≤70 for V'O2 peak and ≥35 for V'E/V'CO2 slope, 12 (26.7%) SSc patients had reduced V'O2 peak and eight (17.8%) had increased V'E/V'CO2 slope.

In bivariate analysis, a significant correlation is present between lung parenchymal with radiological patterns of ILD and mRss (r=0.41, p<0.05), FVC (r=-0.47, p<0.01), DLco (r=-0.73, p<0.0001). Instead, no correlation exists between lung parenchymal with radiological patterns of ILD and disease duration, age, V'O2 peak and V'E/V'CO2 slope. In multiple regression analysis, only DLco shows a correlation with lung parenchymal with radiological patterns of ILD [beta coefficient= -0.56 (CI -0.57–0.10, p<0.01].

Delta of FVC, DLco and sPAP during follow-up

The delta of FVC, DLco and sPAP was calculated as difference between mean values at enrolment and mean of five years. The mean value of delta was 3.8±7.5 for FVC, 5.3±9.8 for DLco and -2.9±7.5 for sPAP. Annual media values are reported in Figure 2A. Delta of FVC [9.6 (0.5–12.2) *vs*. 2.4 (0.4–5), p<0.05] and DLco [9.2 (6.4–16.6) *vs*. 2.3 (0.5–5.2), p<0.01] are higher in SSc patients with increased V'E/V'CO2, conversely delta sPAP is lower [-7.8 (-14.3 – -5.2) *vs*. 1 (1.5–3), p<0.0001]. There are no significant differences of delta FVC, DLco and sPAP between SSc patients with V'O2 peak <70% and V'O2 peak ≥70%.

Major vascular complications

In five-year follow-up, 16 (35.6%) SSc patients had MVC: 14 new DUs (31.1%), 1 PAH (2.2%) and 1 SRC (2.2%). At univariate regression analysis, mRss [HR 1.099 (1.008–1.199), p<0.05], NVC patterns (active and late) [HR 0.032 (0.004–0.250), p<0.001], V'E/V'CO2 slope [HR 1.123 (1.052–1.198), p<0.001] were predictive of new onset of MVC (Table III). Variables included in a multivariate model were based on those statistically significant in univariate analysis. The final multivariate model included NVC patterns (active and late) (HR 0.044 (0.004–0.486), p<0.05), V'E/V'CO2 (HR 1.094(1.020–1.198), p<0.05) (Table III).

Kaplan-Meier analysis comparing free survival from MVC in SSc patients with increased V'E/V'CO2 slope and

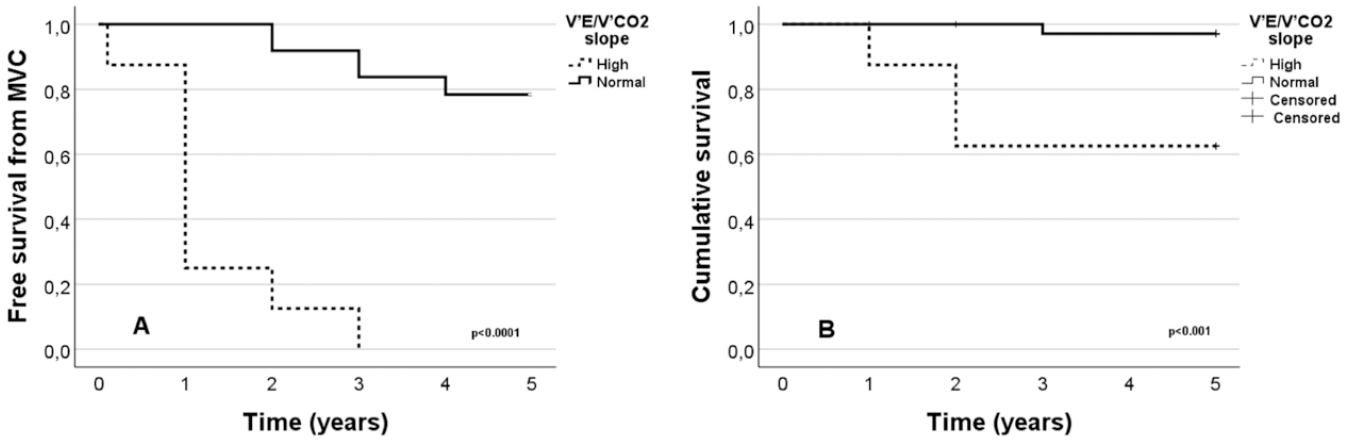

Fig. 2. **A:** Kaplan-Meier analysis comparing free survival from MVC in SSc patients with increased $V'_E/V'CO_2$ slope and SSc patients with normal $V'_E/V'CO_2$ slope; **B:** Kaplan-Meier analysis comparing survival in SSc patients with normal and increased $V'_E/V'CO_2$ slope.

Table III. Univariate and multivariate analysis with hazard ratio and confidence interval (CI) to evaluate the predictive variables of major vascular complications.

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (CI)	*p*	Hazard ratio	*p*
	Major vascular complications			
Age, years	1.066 (0.964-1.050)	>0.05	-	
mRss	1.099 (1.008-1.199)	<0.05	1.020 (0.886-1.179)	>0.05
Disease duration, years	1.061 (0.993-1.135)	>0.05	-	
Subset (lcSSc-dcSSc)	1.056 (0.393-2.837)	>0.05	-	
NVC (active and late)	0.032 (0.004-0.250)	<0.001	0.044 (0.004-0.486)	<0.05
ACA and Scl70	0.772 (0.100-5.943)	>0.05	-	
$V'_E/V'CO_2$	1.123 (1.052-1.198)	<0.001	1.094(1.020-1.198)	<0.05
$V'O_2$ peak	0.389 (0.164-0.924)	>0.05	-	

mRSS: modified Rodnan Skin Score; NVC: nailfold videocapillaroscopy; lcSSc: limited coutaneous SSc; dcSSc: diffuse cutaneous SSc; Scl70: antitopoisomerase I antibodies; ACA: anticentromere antibodies; FVC: forced vitality capacity; DLCO: lung diffusion for carbone oxyde; V'O2 peak: peak O2 uptake; V'E/V'CO2 slope: ventilatory equivalents for carbon dioxide production slope.

SSc patients with normal V'E/V'CO2 slope demonstrates that SSc patients with increased V'E/V'CO2 slope had significant increase of MVC (p<0.0001) (Fig. 2A).

Five-year mortality for ILD

All-cause mortality is 15.5% (n=7) and the 5-year mortality for ILD is 8.9% (n=4). V'E/V'CO2 slope was higher in SSc patients that died for all causes or ILD, instead FVC and DLco were significantly lower (Table IV). In univariate analysis, DLco [(HR 0.927(CI 0.874–0.983), p<0.05], V'E/V'CO2 slope and lung parenchymal with radiological patterns of ILD [(1.2.02 (CI 1.018–1.419), p<0.05], represent risk factors for 5-year mortality for ILD [HR 1.142 (1.030–1.267), p<0.05]. In multivariate analysis, only V'E/V'CO2 slope [1.268 (CI 1.003–1.602), p<0.05] represents a risk factor for 5-year mortality for ILD (Table IV). Kaplan-Meier analysis comparing survival in SSc patients with normal and increased V'E/V'CO2 slope shows that SSc patients with increased V'E/V'CO2 slope had high mortality for SSc (p<0.001) (Fig. 2 B).

Discussion

In this study, we demonstrate that V'E/V'CO2 slope predicts MVC and it is a reliable marker of worsening sPAP during five-years of follow-up. Several studies demonstrated that CPET is a safe and valuable method in the non-invasive detection of SSc-associated PAH. It may be particularly beneficial for reducing unnecessary right heart catheterisation procedures (10, 21). An estimated sPAP >36 mmHg was significantly and independently associated with reduced survival (22). Rosato *et al*. demonstrated that in SSc patients without evidence of pulmonary and cardiac involvement, CPET it useful to evaluate pulmonary vasculopathy (7). In addition, V'E/V'CO2 slope is high in SSc patients with digital ulcers and high capillaroscopic damage (7). Previous studies also demonstrated that V'E/V'CO2 slope is a marker of vascular kidney damage. V'E/V'CO2 slope is high in SSc patients with high intrarenal stiffness (23). Progression of NVC pattern is associated to increased risk of DUs. Capillaroscopic skin ulcer risk index that can predict the onset of new DUs (24). Since V'E/V'CO2 slope is a reliable marker of pulmonary vasculopathy and it has an association with digital and renal vascular damage, we

Table IV. Univariate and multivariate analysis with hazard ratio and confidence interval (CI) to evaluate the predictive variables of five-year mortality for interstitial lung disease.

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (CI)	*p*	Hazard ratio	*p*
	Five-year mortality for ILD			
Age, years	1.022(0.932-1.120)	>0.05	-	
mRss	1.096 (0.920-1.305)	>0.05	-	
Disease duration, years	0.979 (0.840-1.141)	>0.05	-	
Subset (lcSSc-dcSSc)	2.836 (0.295-27.282)	>0.05	-	
Digital ulcers history	0.293 (0.030-2.819)	>0.05	-	
ACA and Scl70	3.014 (0.313-29.026)	>0.05	-	
FVC, % of predicted	0.928 (0.860-1.000)	>0.05	-	
DLco, % of predicted	0.927(0.874-0.983)	<0.05	0.713 (0.454-1.118)	>0.05
$V'O_2$ peak	0.938 (0.867-1.015)	>0.05	-	
$V'_E/V'CO_2$	1.142 (1.030-1.267)	<0.05	1.268 (1.003-1.602)	<0.05
Radiological pattern of ILD	1.2.02 (1.018-1.419)	<0.05	-	
sPAP, mmHg	1.110 (0.979-1.260)	>0.05	-	

lcSSc: limited coutaneous SSc; dcSSc: diffuse cutaneous SSc; mRSS: modified Rodnan Skin Score; Scl70: antitopoisomerase I antibodies; ACA: anticentromere antibodies; FVC: forced vitality capacity; DLCO: lung diffusion for carbone oxyde; V'O2 peak: peak O2 uptake; V'E/V'CO2 slope: ventilatory equivalents for carbon dioxide production slope; ILD: interstitial lung disease; sPAP: systolic pulmonary arterial pressure.

can hypothesise that it can also be used as marker of MVC. In clinical practice, SSc patients with known risk indices of MVC (active/late pattern of NVC, anticentromere antibodies, anti RNA polymerase II antibodies) and high V'E/V'CO2 slope values should undergo a short follow-up. SSc-related vasculopathy might be mainly expressed in digital arteries in some patients and in pulmonary or kidney arteries in others. In SSc, there may be different vascular phenotypes that are responsible for the MVC (25). Although the majority of patients take vasoactive drugs, we have interrupted vasoactive therapy 72 hours before CPET examination to reduce influence in evaluation of V'E/V'CO2 slope.

In our study, V'E/V'CO2 slope is also a reliable marker of worsening FVC and DLco during follow-up. Kaplan- Meyer curves showed a reduced cumulative survival in SSc patients with high V'E/V'CO2 slope and cox regression analysis demonstrated that V'E/V'CO2 slope predicts five-year mortality for ILD. Although V'O2 peak is associated in the univariate analysis with an increased mortality risk, the data is not confirmed by the multivariate analysis. Ewert *et al*. demonstrated that V'O2 peak and V'E/V'CO2 slope had a significant association with worse survival. The authors found no differences of survival between subsets of disease (dcSSc *vs*. lcSSc). Unexpectedly, the authors found no differences of survival between patients without ILD and those with extensive ILD or limited ILD (11). Martis *et al*. demonstrated that CPET is useful for the characterisation of multifactorial exercise limitation in 27 patients with SSc and in identifying SSc-related complications such as ILD and pulmonary vasculopathy (26). V'O2 peak is lower and V'E/V'CO2 slope is higher in patients with idiopathic pulmonary fibrosis than in patients with idiopathic non-specific interstitial pneumonia. Although O2 pulse peak appears to be lower in idiopathic pulmonary fibrosis subjects, this difference was not significant. V'O2 peak and V'E/V'CO2 slope are useful discriminators between idiopathic non-specific interstitial pneumonia with good to moderate prognosis and idiopathic pulmonary fibrosis with poor prognosis (27). Our results suggest that V'E/V'CO2 slope is the most reliable parameter of five-year mortality in SSc-ILD.

In conclusion, this study shows that reduced ventilatory efficiency during exercise, demonstrated by high V'E/V'CO2 slope values, is not only a prognostic marker of ILD progression, but also of pulmonary vasculopathy that correlates with generalised SSc vasculopathy. High value of V'E/V'CO2 is a prognostic marker of MVC and five-year mortality for ILD. Future larges studies are needed to confirm our findings.

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