Effects of autonomic dysfunction on exercise tolerance in systemic sclerosis patients without clinical and instrumental evidence of cardiac and pulmonary involvement

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ABSTRACT

Objective. *Autonomic dysfunction (AD) in systemic sclerosis (SSc) was already confirmed through heart rate variability (HRV) analysis. Cardiopulmonary exercise testing (CPET) is a useful tool in early detection of exercise tolerance in SSc patients. Aim of the study was to assess the relationships existing between AD and exercise tolerance.*

Methods. *Thirty-two [4 M, 28 F; median age: 47.5 (20-65) years] consecutive SSc patients were enrolled. All patients underwent pulmonary function testing, incremental symptom-limited CPET and twenty-four hours ECG Holter recording with HRV analysis in time and frequency domain. Multiple regression analysis was performed in order to identify independent HRV predictors of exercise tolerance and cardiac efficiency during the effort.*

Results. *HRV analysis showed significant differences in power in low and high frequency (LF and HF, respectively) and their ratio (LF/HF) compared to healthy controls. Nocturnal ratio between power in low and high frequency at HRV (LF/HF_{night}) was shown to be the only independent positive predictor of maximal work load (R^2=18.6%, p=0.014) and maximal oxygen consumption ($V'O_2$ peak) expressed both as absolute value (R^2=24.2%, p=0.004) and as corrected for body weight (R_2=21.6%, p=0.007). A positive linear relationship was also found between nocturnal LF (LF_{night}) and the oxygen uptake/work rate ($V'O_2/W$) slope (R^2=15.8%, p=0.024).*

Conclusion. *In SSc patients without cardiopulmonary involvement AD is associated with better exercise tolerance and cardiac function during physical effort. Further studies are needed to confirm these results.*

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by endothelial dysfunction, microvascular damage and fibrosis of the skin and internal organs (1). Clinical and pathological evidences strongly support the concept that the primary insult in targeted organs of SSc patients is directed at blood vessels, resulting in tissue ischaemia, fibrosis and ultimately major organs malfunction, with heart and pulmonary vascular diseases being among the main causes of morbidity and mortality (2).

Cardiac manifestations of SSc can affect all structures of the heart, and may result in pericardial effusion, arrhythmias, conduction system defects, valvular impairment (in rare cases), myocardial ischaemia, myocardial hypertrophy and heart failure. Clinically evident cardiac involvement is recognised as a poor prognostic indicator (3). Increasing evidence strongly suggests that cardiac involvement is related to recurrent focal ischaemic injury causing irreversible myocardial fibrosis. The underlying mechanism appears to be micro-circulatory impairment with abnormal vaso-reactivity, which is caused by abnormal autonomic nervous control of the heart (4). Several studies measuring heart rate variability (HRV) confirmed autonomic dysfunction (AD) in SSc, particularly characterised by depression of the circadian rhythm of heart rate (5). Significant correlations were found between AD and microvascular damage, proving that the autonomic nervous system plays a key role in determining and maintaining the mechanisms responsible for the features of vasoactive system in SSc patients (6, 7).

The role of cardiopulmonary exercise

testing (CPET) in the identification and evaluation of the impairment in aerobic fitness, cardiac performance and pulmonary gas exchange was recently demonstrated even in SSc patients without clinical and instrumental evidence of heart and lung involvement at rest (8, 9). The aim of this study was therefore to assess the effects of AD on exercise tolerance in SSc patients with no evidence of cardiac and pulmonary dysfunction at rest.

Subjects and methods

Study population

Thirty-two [4 males, 28 females; median age: 47.5 (20-65) years] consecutive, non-smoker patients with SSc and 16 age-, sex- and BMI-matched healthy controls [2 males, 14 females; median age: 48.0 (42-65) years] were enrolled in this study. All patients met the American College of Rheumatology/European League Against Rheumatism Collaborative Initiative criteria for the classification of SSc (10). Every patient had already undergone high resolution computed tomography (HRCT) of the chest, Doppler echocardiography and right heart catheterisation (RHC) at the time of enrolment. Patients with pulmonary hypertension, heart failure with reduced and/or preserved ejection fraction, valvular heart diseases, cardiac arrhythmias and conduction disorders, pulmonary fibrosis, interstitial lung disease (ILD) and significant gas exchange abnormalities [defined as a diffusion lung capacity for CO (DL_{CO}) ≤60% of predicted value) were excluded. Subjects with relevant systemic comorbidities, such as an history of uncontrolled systemic hypertension, dyslipidaemia, diabetes mellitus, cerebrovascular and peripheral vascular diseases, haepatic or thyroid dysfunction, anaemia, coagulopathy and pregnant or breastfeeding women were not eligible as well.

Median duration of Raynaud's phenomenon (RP) and disease were 6 (3-34) and 5 (1-25) years, respectively. Twenty patients (62.5%) had diffuse cutaneous SSc (dcSSc), while twelve (37.5%) had limited cutaneous SSc (lcSSc), as defined by LeRoy *et al.* (11). Table I shows SSc patients' anthropometric and clinical features.

At the time of enrolment, all SSc patients were undergoing treatment with calcium channel blockers (nifedipine 30 mg/day). None of the patients was treated with immunosuppressive agents (*e.g.* cyclophosphamide or mycophenolate mofetil or corticosteroids therapy at an equivalent dose of prednisone ≥ 10 mg/day) or was taking β-blockers, antiarrhythmic drugs, ACE-inhibitors or angiotensin receptor antagonists.

Subjects' written consent was obtained according to the Declaration of Helsinki and the study was conducted in agreement with local ethics committee's directives.

Study procedures

Pulmonary function testing

Spirometry, nitrogen washout and single-breath determination of DL_{CO} were performed for every participant through an automated pulmonary function testing system (Quark PFT, COSMED, Rome, Italy), according to the standards recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS) (12-16). All pulmonary function data were standardised and expressed as percentage of predicted normal values (17, 18).

Cardiopulmonary exercise testing

An incremental symptom-limited CPET was performed on an electronically braked cyclo ergometer (Ergoline-800, Ergoline GmbH, Bitz, Germany), using an automated system (Quark CPET, COSMED, Rome, Italy), in accordance to international guidelines (19, 20). CPET consisted of standardised protocol for every participant, with a steady-state resting period, then one minute of unloaded pedaling warm-up followed by a stepwise protocol in which the work load was increased at one minute intervals by increments of 10 Watts. The test was continued until the point of symptom limitation (peak of exercise). Gas exchange [oxygen consumption ($V'O_2$) carbon dioxide output ($V'CO_2$)], tidal volume (V_T), respiratory frequency (Rf) and minute ventilation (V'E) were analysed breath-by-breath during the test. Heart rate (HR), ECG and haemoglobin saturation by pulse oximetry (SpO_2) were continuously monitored, and blood pressure was measured every two minutes from rest to peak of exercise. All measured and derived parameters [*e.g.* respiratory exchange ratio (RER), ventilatory equivalents for O_2 and CO_2 ($V'E/V'O_2$ and $V'E/V'CO_2$, respectively), end-tidal O_2 and CO_2 ($P_{ET}O_2$ and $P_{ET}CO_2$, respectively), oxygen pulse ($V'O_2/HR$), $V'O_2/W$ slope] were recorded and averaged every ten seconds. Anaerobic threshold (AT) was non-invasively determined by the use of the dual methods approach (V-slope method and ventilatory equivalents method). Subject's effort was considered to be maximal either if RER reached ≥1.10 or, otherwise, if heart rate (HR) achieved ≥85% of maximal predicted value at peak of exercise (21). CPET parameters were compared with the predicted normal values (22). All CPET were executed and analysed by two physicians blinded to patients' clinical features.

Heart rate variability

All subjects underwent twenty-four hours ambulatory three-channel ECG Holter recording (Lifecard CF, Spacelabs Healthcare, Snoqualmie, WA, USA). Autonomic nervous activity was assessed by heart rate variability (HRV) in time and frequency domain, according to the recommendation of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (23).

Subjects were analysed throughout the twenty-four hours ECG recording period, at 10 minutes intervals. Artefactual data and arrhythmic events were excluded. Recording time was then divided in two periods: day (7 am-12 pm) and night (12 pm-7 am). Individual data were finally averaged for total recording duration.

Spectral estimates of normal-to-normal RR intervals (NN)were obtained from stationary intervals free of ectopic beats and technical artifacts. The following parameters were computed in time domain analysis: the standard deviation of NN (SDNN), which captures total HRV and reflects circadian heart rhythm, and the square root of the mean of the sum of the squares

of differences between adjacent NN intervals (RMSSD), which correlates with the parasympathetic modulation of heart rate. In the frequency domain Fast Fourier Transform was used to obtain power spectral estimates of HRV. Power in the low frequency range (LF: 0.04–0.15 Hz, reflecting the combined modulation of efferent vagal and efferent sympathetic nervous system activity, controlled by baro reflex activity), in the high frequency range (HF: 0.15–0.40 Hz, reflecting modulation of efferent parasympathetic activity by ventilation) and their ratio (LF/HF, also referred to as sympatho-vagal balance) were analysed. The power of LF and HF components was evaluated in normalised units (nu). Data analyses were performed with Cardio-navigator plus software package (Spacelabs Healthcare, Snoqualmie, WA,USA). Given the lack of unequivocal reference values in scientific literature, HRV data were compared to data obtained from age, sex and BMI-matched healthy controls in order to evaluate the presence of significant abnormalities in SSc patients.

Statistical analysis

Numerical data are expressed as median value and range, while categorical data are presented as number and percentage. Comparisons between patients and healthy controls were performed, for numerical data, by the use of Student's *t*-test and Mann-Whitney U test (for values with normal and non-normal distribution, respectively) and Fisher's exact for categorical data. The assessment of statistical relations between HRV and CPET variables was carried out using two analytical steps. Firstly, bivariate correlations were identified with the use of Pearson's and Spearman's rank tests, for normally and non-normally distributed parameters, respectively. Resultant statistically significant correlations were then used for the creation of several forward stepwise linear regression models, each one designed defining the indexes of AD at HRV (*i.e.* LF, LF/HF) as the independent variables and the indexes of aerobic fitness and cardiac performance (*i.e.* V'O_2 peak, W peak, V'O_2/W slope) as the dependent ones. Multivariate analysis was used to evaluate the relationship between measures of AD and heart rate variability and SSc-specific serologic and clinical features. *P*-values <0.05 were considered as statistically significant. Analyses were performed using the SPSS Statistics version 22.0 software package (IBM, Armonk, New York, USA).

Table I. Anthropometric data of all participants and clinical features of SSc patients.

	Patients (n = 32)	Healthy Controls (n =16)	*p*-value
Sex (males/females)	4/28	2/14	ns
Age, years (median and range)	47.5 (20 – 65)	48.0 (42 – 65)	ns
BMI, kg/m^2 (median and range)	21.1 (17.6 – 27.1)	22.0 (20.0 – 26.0)	ns
Disease duration, years (median and range)	5.0 (1 – 25)		
RP duration, years (median and range)	6.0 (3 – 34)		
Disease phenotype (dcSSc/lcSSc)	20/12		
mRSS (median and range)	13.0 (4 – 24)		
DAI (median and range)	1.8 (0.5 – 5.0)		
DSS (median and range)	4.5 (2.0 – 11.0)		
SSc-specific autoantibodies			
Anti-topoisomerase I, n (%)	21 (65.6%)		
Anti-centromere, n (%)	9 (28.1%)		
None, n (%)	2 (6.3%)		
Digital ulcers positive history, n (%)	17 (53.1%)		
Nailfold videocapillaroscopic pattern			
Early, n(%)	11 (34.4%)		
Active, n (%)	9 (28.1%)		
Late, n (%)	12 (37.5%)		

BMI: body mass index; RP: Raynaud's phenomenon; dcSSC: diffuse cutaneous SSc; lcSSC: limited cutaneous SSc; mRSS: modified Rodnan skin score; DAI: disease activity index; DSS: disease severity scale; ns: not significant.

Table II. Comparisons of twenty-four hours ECG Holter recording and HRV analysis data.

	Patients (n=32)	Healthy Controls (n=16)	*p*-value
SDNN, ms	123.5 (84.0 – 222.0)	150.0 (103.0 – 191.0)	0.014
RMSSD, ms	36.5 (15.0 – 100.0)	38.0 (20.0 – 48.0)	0.983
LF_{24h}, nu	59.052 (39.763 – 74.591)	58.045 (45.015 – 67.090)	0.512
HF_{24h}, nu	30.282 (15.741 – 53.937)	36.799 (28.596 – 43.904)	0.001
LF/HF_{24h}	2.921 (1.225 – 5.966)	1.827 (1.120 – 2.883)	0.001
LF_{day}, nu	59.225 (30.767 – 74.232)	64.420 (47.044 – 77.770)	0.106
HF_{day}, nu	28.934 (15.059 – 64.814)	30.564 (14.784 – 40.062)	0.600
LF/HF_{day}	2.906 (0.684 – 6.133)	2.470 (1.360 – 5.250)	0.131
LF_{night}, nu	58.609 (37.490 – 75.061)	44.576 (31.057 – 55.011) §	<0.001
HF_{night}, nu	31.574 (16.826 – 43.810)	51.335 (40.461 – 65.059) §	<0.001
LF/HF_{night}	2.736 (1.508 – 5.700)	0.986 (0.498 – 1.537) §	<0.001

SDNN: standard deviation of normal-to-normal RR intervals; RMSSD: square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals; LF: low frequency; HF: high frequency; 24h: 24 hours registration; day: daily registration (7 am – 12 pm); night: nocturnal registration (12 pm – 7 am).
p-values referred to inter-group variables comparisons.
§*p*-value <0.05 for comparison of corresponding daily *vs*. nocturnal HRV data within the same group of participants.

Results

Pulmonary function testing (PFT) showed a forced vital capacity (FVC) median value equal to 99.2% of predicted (71.1-136.5%), while median forced expiratory volume in the 1st second (FEV_1) was 94.4% (71.4-127.3%) of predicted. Median FEV_1/FVC was 0.82 (0.71-0.99), with no subjects showing values <0.70 suggestive of respiratory obstructive disorders. Total lung capacity median value was 96.6% (72.5-114.7%) of predicted, with 6 subjects (18.8%) showing values <80% of predicted, indicative of mild respiratory restrictive disorder. DL_{CO} median value resulted to be above the chosen threshold of normality (>60%), although 11 out of 32 patients (34.4%)

showed values 60 <DL_{CO}<80% of predicted, suggestive of mild impairment in gas exchange (16).

All patients performed maximal CPET. Dyspnea, leg discomfort or both equally were reported as the exercise limiting symptom in 12.5%, 62.5% and 25% of cases, respectively. Patients reached a median work rate of 80 Watts. Median oxygen uptake at peak of exercise ($V'O_2$ peak) was 1172.5 ml·min^{-1} (809.0–2640.0 ml·min^{-1}), corresponding to 20.39 ml·min^{-1}·kg^{-1} (15.46–34.29 ml·min^{-1}·kg^{-1}) when normalised for weight. When expressed as percentage of predicted value, median $V'O_2$ peak was 76.5% (52.8–100.2%). A reduced exercise tolerance (defined as $V'O_2$ peak <80% of predicted) (24) was documented in 18 (56.3%) patients. Median oxygen pulse at peak exercise and $V'O_2$/W slope were 87.5% of predicted (60.8–113.8%) and 9.4 ml·W^{-1}, respectively. AT was detected at a median value of 46.0% of predicted maximal $V'O_2$, both suggesting the absence of significant metabolic abnormalities. No ventilatory limitations to exercise (*i.e.* V'E at peak exercise >15% of estimated maximal voluntary ventilation) were detected. $V'E/V'CO_2$ at AT and $V'E/V'CO_2$ slope median values were 30.2 (23.5-39.8) and 25.6 (19.9-37.8), respectively. Impaired ventilatory efficiency (defined as $V'E/V'CO_2$at AT >34 and/or $V'E/V'CO_2$ slope >30) (19, 25) was found in 10 out of 32 patients (31.3%).

HRV analysis revealed significantly lower values of SDNN and HF with a higher LF/HF ratio in SSc patients (p<0.05). Sub-analysis of daily and nocturnal recordings detected significant differences between the two groups in LF_{night}, HF_{night} and LF/HF_{night} ratio (p<0.001), whereas daily data seemed to be substantially comparable (Table II).

Significant bivariate correlations were found between LF_{night} and LF/HF_{night} and W peak, $V'O_2$ peak (expressed both as absolute value and as normalised for weight) and $V'O_2$/W slope. No significant correlations were identified involving HF (Table III).

Multiple regression analysis revealed that LF/HF_{night} was the only independent predictor of maximal work load and maximal oxygen consumption during CPET, however explaining only a relatively small percentage of their variance (R^2=18.6% and 24.2%, p=0.014 and 0.004, respectively). LF_{night}, instead, was shown to be the only independent predictor of the $V'O_2$/W slope (R^2=15.8%, p=0.024; Table IV and Fig. 1).

In the multivariate analysis we did not observe a relationship between continuous variables of disease (disease duration, mRSS, DAI, DSS) and AD and heart rate variability. In the multiple regression analysis we observed an association between SDNN and disease phenotype (dcSSc/lcSSc) and SSc-specific antibodies. The SDNN median value is lower (p=0.02) in dcSSc than in lcSSc [119 (108-127) *vs.* 139 (119-164)]. The SDNN median value is lower (p=0,02) in SSc patients with Scl-70 antibodies than in SSc patients with ACA [119 (107-127) *vs.* 138 (118-174)].

Table III. Statistically significant correlations between CPET and HRV variables.

		LF_{24h}	HF_{24h}	LF/HF_{24h}	LF_{night}	HF_{night}	LF/HF_{night}
W peak	*p*-value	ns	ns	ns	0.020	ns	0.032
	correlation coefficient	-	-	-	0.410	-	0.380
$V'O_2$ peak	*p*-value	ns	ns	0.042	0.029	ns	0.021
	correlation coefficient	-	-	0.361	0.387	-	0.405
$V'O_2$/kg peak	*p*-value	0.037	ns	0.026	0.009	ns	0.007
	correlation coefficient	0.371	-	0.392	0.453	-	0.464
$V'O_2$/W slope	*p*-value	ns	ns	ns	0.024	ns	0.031
	correlation coefficient	-	-	-	0.398	-	0.381

LF: low frequency; HF: high frequency; 24h: 24 hours registration; night: nocturnal registration (12 pm – 7 am); W peak: maximal work load; $V'O_2$ peak: maximal oxygen consumption; $V'O_2$/W slope: oxygen consumption/work load slope; ns: non-statistically significant (*i.e.* $p \geq 0.05$).

Table IV. Linear regression analysis models of correlations between CPET and HRV variables.

Model	Dependent	Predictors	Unstandardised coefficients T	Unstandardised coefficients SE	Standardised coefficients β	95% CI	*p*-value	R^2
1	W peak	(Constant)	52.057	15.181		21.052 – 83.061	0.002	
		LF/HF_{night}	13.452	5.132	0.432	2.971 – 23.933	0.014	
Excluded variables: LF_{night}								**18.6%**
2	$V'O_2$ peak	(Constant)	746.343	183.878		370.815 – 1121.872	<0.001	
		LF/HF_{night}	192.189	62.159	0.492	65.244 – 319.133	0.004	
Excluded variables: LF/HF_{24h}, LF_{night}								**24.2%**
3	$V'O_2$/kg peak	(Constant)	15.867	2.087		11.604 – 20.130	<0.001	
		LF/HF_{night}	2.026	0.706	0.464	0.585 – 3.467	0.007	
Excluded variables: LF_{24h}, LF/HF_{24h}, LF_{night}								**21.6%**
4	$V'O_2$/W slope	(Constant)	4.983	1.887		1.129 – 8.837	0.013	
		LF_{night}	0.076	0.032	0.398	0.011 – 0.142	0.024	
Excluded variables: LF/HF_{night}								**15.8%**

SE: standard error; CI: confidence interval; W peak: maximal work load; $V'O_2$ peak: maximal oxygen consumption; $V'O_2$/W slope: oxygen consumption/work load slope; LF: low frequency; HF: high frequency; 24h: 24 hours registration; night: nocturnal registration.

Discussion

In the present study high percentages of reduced exercise tolerance were found in SSc patients, despite the absence of both echocardiographic signs of cardiac and pulmonary circulation involvement and radiologic evidence

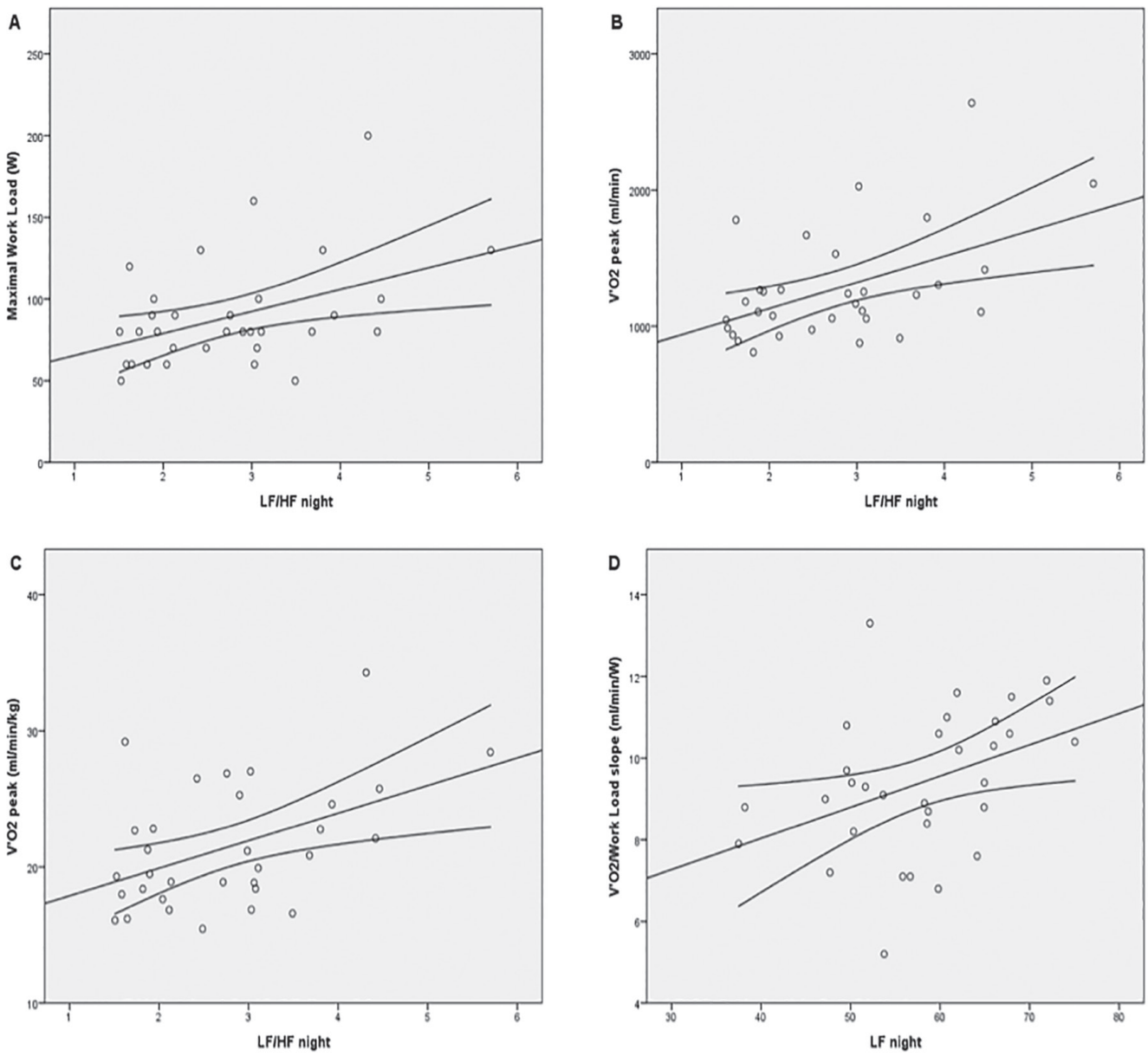

Fig. 1. Correlations between sympathovagal imbalance and exercise tolerance.

of ILD. Frequency and magnitude of CPET abnormalities cannot be entirely explained by the mild pulmonary impairment resulting from PFT in some patients: indeed, up to 50% of patients with V'O_2 peak <80% of predicted had completely normal PFT results.

The results of HRV analysis in this study agree with those of previously published ones; particularly, the loss of normal circadian rhythm, denoted by a significantly reduced SDNN, the evidence of a sympatho-vagal imbalance mainly due to a reduced parasympathetic tone (*i.e.* HF) and the presence of remarkable differences respect to healthy controls especially throughout nocturnal rather than daily HRV recordings, strengthen the hypothesis that in SSc patients AD is primarily related to an impairment in vagal regulatory efferences, with consequent relative sympathetic hypertone and blunted baroreflex activity.

Moreover, we found that SSc patients with Scl-70 antibodies and diffuse form have a greater autonomic dysfunction. In several studies, the presence of dcSSc and Scl-70 antibodies were associated with major organ dysfunction (28).

To our knowledge, this is the first study performed in order to assess the presence of direct effects of AD on exercise performance in SSc patients without clinical evidence of cardiopulmonary function impairment.

Among HRV frequency domain variables LF_{night} and LF/HF_{night} were recognised as significant, even if weak, independent predictors of exercise testing results, with the evidence of positive linear relationships with several CPET parameters concerning exercise tolerance, aerobic fitness and cardiac pump efficiency during the effort. Even in this case, the fact that only nocturnal abnormalities were related to the indexes of exercise performance seems

to support the hypothesis that in SSc patients with early stage disease AD might stem from an initial impairment in parasympathetic activity, which is well known to be the main regulator of heart rate throughout night hours.

This study proves that, unlike healthy subjects and especially endurance athletes, where aerobic capacity and ventilatory efficiency seem to be strongly related to an enhanced vagal modulation of the heart (26, 27), SSc patients with higher sympathetic activity and impaired sympatho-vagal balance seem to have better exercise tolerance, aerobic performance and cardiac function, as if AD could positively affect pulmonary gas exchange during physical effort. Although surprising, these results are consistent with those described by few previously published studies concerning populations of patients suffering from chronic cardiovascular and respiratory diseases (29, 30). Particularly, Ponikowsky *et al*. showed the presence of significant positive correlations between SDNN, RMSSD, LF and $V'O_2$ peak, as well as significant negative correlations between SDNN, RMSSD, LF, HF and $V'E/V'CO_2$ slope in a cohort of seventy-two chronic heart failure patients with impaired left ventricle systolic function. Multiple regression analysis then revealed that only the ventilatory response to exercise was independently correlated with HRV variables (29).

We can hypothesise that SSc patients without clinical evidence of cardiac and pulmonary impairment can better tolerate exercise because of compensatory sympathetic autonomic system activation, through an increase in coronary vasodilation, myocardial contractility, heart rate and, finally, cardiac output. Early beta-adrenergic system hyperactivity is well known in chronic heart failure. This phenomenon originates from an initial attempt to compensate the haemodynamic changes secondary to the reduction in cardiac output. This persisting stimulation elicits adrenergic responses in excess of the homeostatic demands, leading to a gradual cardiac remodelling and progressive continuous deterioration of left ventricle function, together with a higher risk of fatal arrhythmias (31). These elements provide the rationale to the use of beta-blockers as standard treatment for chronic heart failure (32). Though with not yet known pathophysiological mechanisms, sympathetic hyper activation in SSc patients might partially derive from a compensatory response to cardiopulmonary microvascular changes already present in the earliest stages of disease. However, if not modulated, the same mechanisms may themselves be determining factors in the progression of microvascular damage and irreversible organ complications. In this reading key, therapeutic interventions aimed to discontinue this process (such as, for example, beta-blockers) would be accompanied by an interesting question, whether it is worth trying to avoid long-term complications at the price of prematurely worsening exercise tolerance and cardiac function, which are important prognostic factors in PV.

We can conclude that in SSc patients without signs of cardiopulmonary involvement AD is associated with better exercise tolerance and cardiac function during the effort. Parasympathetic withdrawal together with sympathetic hypertone and blunted baroreflex activity could represent a compensatory mechanism secondary to pre-clinical cardiac and pulmonary microvascular damages. Nevertheless, further studies are needed in order to confirm these results.

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