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[Original article]

Cardiovascular outcome in systemic sclerosis

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Objectives Cardiovascular involvement is recognized as a poor prognostic factor in systemic sclerosis (SSc). The aim of this study was to evaluate the usefulness of nailfold video-capillaroscopy (NVC), brain natriuretic peptide (BNP) blood level and exercise echocardiography to predict the occurrence of cardiovascular events in SSc.

Methods We prospectively enrolled 65 patients with SSc (age 54 ± 14 years, 30% female) followed in CHU Sart-Tilman, Liège, Belgium. All patients underwent graded semi-supine exercise echocardiography. Both baseline resting pulmonary hypertension (PH) and PH during follow-up (FUPH) were defined as systolic pulmonary arterial pressure (sPAP) > 35 mmHg, and exercise-induced PH (EIPH) as sPAP > 50 mmHg during exercise.

Results EIPH was present in 21 patients. During FU (27 ± 18 months), 13 patients developed FUPH and 9 presented cardiovascular complications. Patients with cardiovascular events were significantly older (63 ± 14 vs 52 ± 13 years; $P = 0.03$), presented more frequently NVC grade > 2 (89 vs 43%; $P = 0.009$), had higher resting and exercise sPAP (30 ± 6 vs 24 ± 6; $P = 0.007$ and 57 ± 13 vs 44 ± 13 vs mmHg; $P = 0.01$, respectively), and higher BNP blood level (112 ± 106 vs 26 ± 19 pg/ml; $P = 0.0001$). After adjustment for age and gender, NVC grade > 2 ($ß = 2.4 \pm 1.1$; $P = 0.03$), EIPH ($ß = 2.30 \pm 1.13$; $P = 0.04$), FUPH ($ß = 0.24 \pm 0.09$; $P = 0.01$ and $ß = 3.52 \pm 1.16$; $P = 0.002$, respectively;) and BNP ($ß = 0.08 \pm 0.04$; $P = 0.02$) were independent predictors of CV events. Beyond age, an incremental value of EIPH, BNP and NVC grade > 2 was predictive of cardiovascular events ($P < 0.001$).

Conclusion Cardiovascular complications are not rare in SSc (18%). NVC, BNP blood level assessment and exercise echocardiography could be useful tools to identify patients at risk of SSc.

Keywords *Systemic sclerosis – echocardiography – pulmonary hypertension – exercise – nailfold videocapillaroscopy – cardio-vascular diseases – brain natriuretic peptide.*

ABBREVIATIONS

BNP: brain natriuretic peptide; CO: cardiac output; LAP: left atrial pressure; EIPH: exercise-induced pulmonary arterial hypertension; FUPH: occurrence of resting pulmonary arterial hypertension during follow-up; LV: left ventricular; NVC: nailfold videocapillaroscopy; PH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; sPAP: systolic pulmonary arterial pressure; SSc: systemic sclerosis; SV: stroke volume.

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INTRODUCTION

Systemic sclerosis (SSc) is a rare and complex autoimmune disease. The main lesion is characterized by a micro-vascular impairment leading to systemic fibrosis and in some severe cases to vital organs impairment[1]. Nailfold videocapillaroscopy (NVC) has emerged as an interesting tool to predict severe organ involvement such as lung fibrosis and skin ulcer[2,3]. However, NVC remains a poorly explored tool for the cardiovascular risk stratification in this population. Similarly, the usefulness of exercise echocardiography has been demonstrated in various cardiac diseases[4–7] and assessment of systolic

pulmonary arterial pressure (sPAP) has been suggested as a potential tool for the prediction of resting PH development[8,9]. Also, brain natriuretic peptide (BNP) level assessment has become a strong and well-recognized indicator of the cardiovascular risk in SSc[10]. Whether all these parameters have an additive risk value in the individual patient is unknown. In the present study, we hypothesized that combining NVC, BNP, and the exercise echocardiography results would improve the risk stratification of patients with SSc.

METHODS

Population

We prospectively studied 65 consecutive patients with a diagnosis of SSc, followed in the rheumatology centre of CHU Sart-Tilman in Liège. Exclusion criteria were: (1) inability to provide informed consent, (2) previous ischaemic heart or valvular heart diseases, and (3) inability to perform an exercise test. The relevant institutional review boards approved the present protocol and all patients gave written informed consent.

Echocardiography protocol

Comprehensive resting echocardiography was performed in all patietns 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 (SV) was calculated as the difference between LV end-diastolic and systolic volumes assessed by the biapical Simpson disc method and LV ejection fraction was derived from the ratio SV/LV end-diastolic volume. Cardiac output (CO) was obtained by multiplying LVSV and heart rate. Peak E- and peak A-wave velocities of the mitral inflow were measured with pulsed-wave Doppler. Doppler tissue imaging (DTI) was applied for measurement of the e' wave at the lateral mitral annulus. Classical right ventricular (RV) function echocardiographic parameters were assessed: RV fractional area change, tricuspid annular plane systolic excursion (TAPSE) and maximal systolic velocity of the tricuspid annulus (s').

The sPAP was derived from the maximal velocity of tricuspid regurgitant (TR) jet according to the simplified Bernoulli equation and adding right atrial (RA) pressure, estimated from the dimension and collapsibility of the inferior vena cava, according to the American guidelines[8]. All patients had estimated RA pressure equal to 5 mmHg. A peak value > 35 mmHg was considered to define resting PH[9] at baselineand during follow-up (FUPH). At peak exercise, sPAP was derived from TR jet velocity, adding 10 mmHg for the estimation of the RA pressure, as previously validated[11]. EIPH was defined as a sPAP > 50 mmHg [11]. sPAP was indexed to CO (indexed sPAP). The mPAP was estimated by the Chemla formula: $mPAP = 0.61 \times sPAP + 2$. 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[12,13]. The slope of the mPAP/LVCO relationship was estimated as the ratio between changes (peak-rest values) in mPAP and changes in LVCO. All measurements were performed according to the current guidelines[14].

Exercise test

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 minutes, the workload was gradually increased by 25 W every 2 minutes. 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.

NVC protocol

Using an optical probe videocapillaroscope, the nailfold of the second, third, fourth and fifth fingers was examined bilaterally in each patient as previously described[3]. NVC grades were qualitatively assessed as normal (grade 1: normal capillaries morphology, regular distribution and no capillary loss), early (grade 2: few capillary micro-haemorrhages and giant capillaries, no loss of capillaries and preserved distribution), active (grade 3: frequent capillary micro-haemorrhages and giant capillaries, moderate loss of capillaries, mild disorganization of the microvascular architecture and absent or mild ramified capillaries) and late (grade 4: irregular enlargement of capillaries, few or absent giant capillaries and micro-haemorrhages, severe loss of capillaries and large avascular areas, disorganization of capillary and ramified capillary).

Lung function assessment

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

BNP blood level assessment

BNP blood level was assessed at rest in 40 patients. Venous blood samples were drawn before echocardiography, after 10 min of supine rest. Chilled ethylenediaminetetraacetic acid tubes were centrifuged immediately at 4,000 rpm (4-8 °C) for 15 min.

Study end points

The patient outcome was defined as the occurrence during the FU of combined cardiovascular events and/or symptoms of resting PH[15]. Pre-specified events were defined as cardiovascular-related death or hospitalization including left or right heart failure, atrial or ventricular arrhythmia, symptomatic resting PH confirmed by right heart catheterization (mPAP > 25 mmHg) and peripheral vascular complications as defined by cerebral vascular attack, peripheral ulcer requiring hospitalization for management.

Statistical analysis

Continuous variables are expressed as means ± SD; categorical variables are presented as numbers and percentages. Data comparisons were performed according to the presence or absence of cardiovascular events during FU, using the Student unpaired and paired *t* test, χ^2 test or Fischer exact test when appropriate. The relationships between BNP blood level and other continuous variables (i.e. demographic data, resting and exercise echocardiographic data) were evaluated by simple linear regressions. Independent predictors of cardiovascular events at FU were obtained with the use of multiple logistic regressions. Values of $P < 0.05$ were considered statistically significant. All statistical analyses were performed with JMP Software version 10.0.2.

RESULTS

Population characteristics at baseline and during follow-up

Fifteen patients were excluded from the whole population (n = 65) due to unquantifiable sPAP, 1 for ≥ moderate mitral regurgitation and 2 for coronary artery diseases. None of patients presented an abnormal exercise test (chest pain and/or abnormal electrocardiogram). Mean age of the whole population was 54 ± 14 years and the incidence of female gender was 30%. Fifteen patients presented diffuse form. After a mean FU of 27 ± 18 months, 9 patients presented CV events. There were 2 transient ischaemic cerebrovascular events without significant carotid stenosis, 2 hospitalizations for dyspnoea with resting PH confirmed by right heart catheterization, 1 hospitalization for paroxysmal atrial fibrillation associated with heart failure and 4 severe peripheral vascular ischaemic events (finger and toe) leading to amputations without macrovascular arterial stenosis. One of these patients died after peripheral vascular surgery. There were no significant differences between the groups of patients presenting with or without cardiovascular events at FU regarding medication, variables of lung function tests and chronic renal failure (defined as creatinine clearance < 60 ml/min, table 1).

NVC grades

NVC grade 1 was found in 9%, grade 2 in 39%, whereas grade 3 and 4 were present in 26% (figure 1). There was a significant relationship between different NVC grades and the occurrence of cardiovascular events during FU ($P = 0.01$). Patients with cardiovascular events presented more frequently a NVC grade 4 (67% vs 16%; $P = 0.003$) and less frequently a NVC grade 2 (11% vs 46%; $P = 0.04$). There was a significantly higher incidence of NVC > grade 2 in the cardiovascular event group (89 vs 43%; $P = 0.009$, figure 1). After adjustment for age and gender, NVC > grade 2 remained significantly associated with the occurrence of cardiovascular events during FU ($ß = 2.4 \pm 1.1$; $P = 0.03$).

Resting and exercise echocardiography

None of the patients presented wall motion abnormalities during exercise echocardiography. The sPAP increased significantly during exercise (from 25 ± 7 to 46 ± 14 mmHg; $P < 0.0001$). 47% of the whole population developed EIPH (n = 21). Patients with CV events had higher resting sPAP (30 ± 6 vs 24 ± 6 mmHg; $P = 0.007$), mPAP (20 ± 4 vs 16 ± 4 mmHg; $P = 0.007$), exercise sPAP (57 ± 13 vs 44 ± 13 mmHg; $P = 0.01$), exercise mPAP (37 ± vs 29 ± 8 mmHg; $P = 0.01$) but there was no significant difference in exercise-induced change in sPAP (27 ± 12 vs 21 ± 9 mmHg; $P = 0.14$) and exercise-induced change in mPAP (16 ± 7 vs 13 ± 6 mmHg; $P = 0.14$). However, when indexed to CO, exercise sPAP and exercise-induced change in sPAP were significantly higher in the cardiovascular event group (8.9 ± 3.6 vs 6.3 ± 2.3 mmHg/L/min; $P = 0.04$ and 11.6 ± 5.9 vs 6.8 ± 3.9 mmHg/L/min; $P = 0.03$, respectively). The slope of the mPAP-LVCO relationship was higher in patients with CV during FU (7.1 ± 3.6 vs 4.2 ± 2.4 mmHg/L/min; $P = 0.03$). After exclusion of patients with resting baseline sPAP > 35 mmHg, EIPH was more frequent in the CV event group (86 vs 37%; $P = 0.02$).

There was also a significant difference between the 2 groups regarding resting LA area (18 ± 6 vs 14 ± 3 cm^2;

Table 1 Demographic, clinical, and exercise data

Variables	Whole cohort (n = 50)	No CV events (n = 41, 82%)	CV events (n = 9, 18%)	*P*
Demographic and clinical data				
Age, years	54 ± 14	52 ± 13	62 ± 13	0.03
Female gender, n (%)	15 (30)	12 (29)	3 (33)	0.81
Body mass index, kg/m²	25 ± 8	24 ± 5	25 ± 8	0.76
Heart rate, bpm	81 ± 17	71 ± 2	81 ± 4	0.06
Systolic arterial pressure, mmHg	141 ± 33	128 ± 4	141 ± 9	0.20
Diastolic arterial pressure, mmHg	74 ± 18	74 ± 9	74 ± 19	0.90
Diffuse form, n (%)	15 (30)	10 (24)	5 (55)	0.06
Duration of diseases, months	62 ± 71	54 ± 62	73 ± 84	0.34
Raynaud's phenomenon, n (%)	37 (74)	30 (73)	7 (77)	0.77
Biological data				
BNP, pg/ml	112 ± 106	26 ± 19	112 ± 106	0.0001
Creatinine clearance < 60 mL/min, n (%)	6 (12)	6 (15)	0 (0)	0.22
Risk factors				
Systemic hypertension, n (%)	5 (10)	3 (8)	2 (22)	0.23
Hypercholesterolaemia, n (%)	10 (20)	9 (23)	1 (11)	0.42
Smoker, n (%)	13 (26)	12 (29)	1 (11)	
Family history of CV disease, n (%)	3 (6)	3 (8)	0 (0)	0.26
Pulmonary function				
Total lung capacity, % predicted	95 ± 26	93 ± 3	95 ± 9	0.83
Vital capacity, % predicted	98 ± 28	100 ± 4	98 ± 11	0.68
Force vital capacity, % predicted	95 ± 29	100 ± 3	95 ± 10	0.60
FEV1, % predicted	88 ± 32	93 ± 4	88 ± 10	0.62
FEV1/vital capacity, % predicted	94 ± 15	98 ± 2	94 ± 6	0.51
DLCO, % predicted	58 ± 13	65 ± 2	58 ± 7	0.94
Medication				
ACE inhibitors, n (%)	4 (8)	2 (6)	2 (30)	0.09
Beta blockers, n (%)	4 (8)	3 (8)	1 (14)	0.63
Diuretic, n (%)	2 (4)	1 (3)	1 (14)	0.13
Calcium inhibitors, n (%)	25 (50)	21 (58)	4 (57)	0.95
Corticoid, n (%)	17 (34)	12 (29)	5 (55)	0.13
Immunosuppressors, n (%)	7 (14)	5 (14)	2 (29)	0.37
Exercise data				
Workload, W	56 ± 31	78 ± 5	56 ± 11	0.09
Duration of exercise, min	4.7 ± 1.4	4.5 ± 1.4	4.5 ± 1.8	0.98
Heart rate, bpm	116 ± 27	119 ± 17	116 ± 26	0.69
Systolic arterial pressure, mmHg	167 ± 15	167 ± 23	167 ± 15	0.98
Diastolic arterial pressure, mmHg	79 ± 8	82 ± 12	79 ± 8	0.98

CV: indicates cardiovascular, EIPH: exercise-induced pulmonary arterial hypertension, FEV1: forced expiratory volume in 1 second, DLCO: diffusing capacity of the lung for carbon monoxide, ACE: angiotensin-converting enzyme.

P = 0.01, table 2). Patients developing CV complications had a higher exercise LA (20 ± 8 vs 13 ± 3 cm²; *P* = 0.002) and a higher exercise LV E/e' ratio resulting from lower e' wave velocity (9.2 ± 2.2 vs 6.2 ± 2.2; *P* = 0.002 and 0.1 ± 0.1 vs 0.2 ± 0.5 cm/s; *P* = 0.03, respectively; table 3) and exercise LAP (13 ± 3 vs 10 ± 2 mmHg; *P* = 0.002). Exercise-induced change in LAP (3.1 ± 1.6 vs 0.9 ± 2.1; *P* = 0.03) and LA area (3.1 ± 2.1 vs – – 0.2 ± 2.5; *P* = 0.005) were significantly different between the 2 groups (table 4). There were no significant differences between

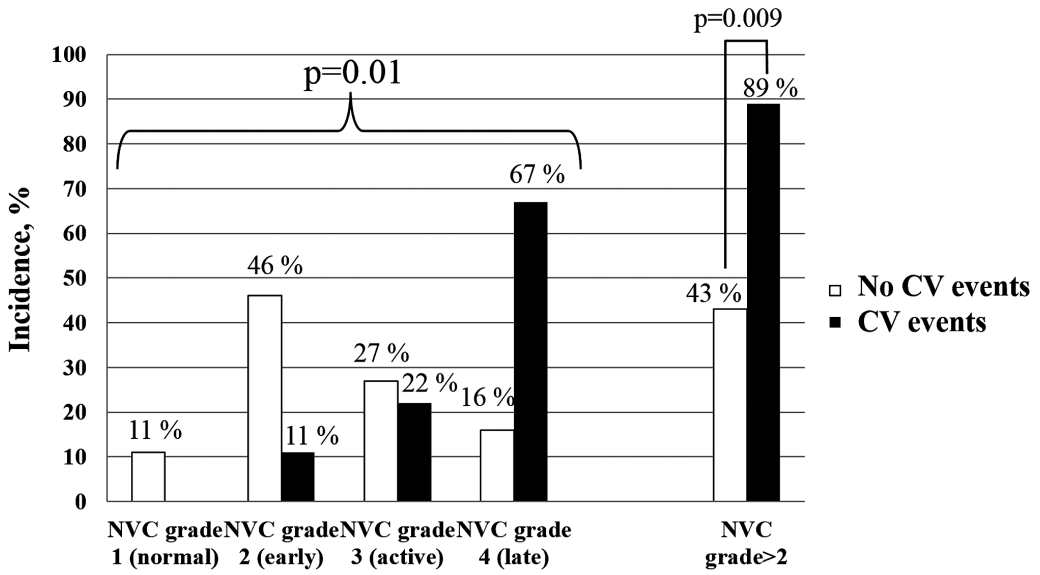

Fig. 1 Comparison of the incidence of nailfold videocapillaroscopy grades according to the 2 groups. CV: cardiovascular, NVC: nailfold videocapillaroscopy.

Table 2 Resting echocardiographic data

Variables	Whole cohort (n = 50)	No CV events (n = 41, 82%)	CV events (n = 9, 18%)	*P*
Resting LV echocardiographic data				
LV end-diastolic volume, mL	83 ± 23	83 ± 25	79 ± 15	0.63
LV end-systolic volume, mL	29 ± 10	30 ± 11	26 ± 3	0.37
LV stroke volume, mL	54 ± 16	54 ± 16	53 ± 16	0.85
LVEF Simspon, %	65 ± 6	65 ± 6	65 ± 7	0.87
CO, L/min	3.9 ± 1.1	3.8 ± 1.1	4.2 ± 1.1	0.35
E, cm/s	0.7 ± 0.1	0.70 ± 0.14	0.71 ± 0.13	0.88
E deceleration time, ms	179 ± 39	182 ± 40	162 ± 28	0.22
A, cm/s	0.67 ± 0.18	0.65 ± 0.18	0.74 ± 0.18	0.24
E/A ratio	1.2 ± 0.5	1.2 ± 0.6	1 ± 0.29	0.42
e', cm/s	0.1 ± 0.1	0.12 ± 0.04	0.12 ± 0.03	0.63
E/e'ratio	6.1 ± 1.9	6.1 ± 1.9	6.8 ± 1.7	0.40
LAP, mmHg	10 ± 2	9 ± 2	10 ± 2	0.40
Pericardial effusion, n (%)	2 (4)	1 (2)	1 (11)	0.23
Resting RV echocardiographic data				
RV end-diastolic area, cm^2	14 ± 4	14 ± 4	15 ± 6	0.77
RV end-systolic area, cm^2	8 ± 3	7 ± 3	8 ± 3	0.53
RVFAC, %	47 ± 9	49 ± 8	45 ± 10	0.33
TAPSE, mm	23 ± 5	30 ± 4	23 ± 6	0.83
s', cm/s	12 ± 3	12 ± 3	13 ± 3	0.76
Pulmonary acceleration time, ms	298 ± 45	139 ± 35	127 ± 25	0.34
Resting PVR, Woods	2 ± 1.1	2 ± 1.1	2.4 ± 0.6	0.43
sPAP, mmHg	25 ± 7	24 ± 6	30 ± 6	0.007
Indexed sPAP, mmHg/L/min	6.8 ± 2.4	6.7 ± 2.5	7.2 ± 1.8	0.65
mPAP, mmHg	17 ± 4	17 ± 4	20 ± 4	0.007
Resting atrial area				
LA area, cm^2	14.2 ± 4	14 ± 3	18 ± 6	0.01
RA area, cm^2	12.7 ± 4.4	12.2 ± 4	15.4 ± 6.2	0.08

CV: indicates cardiovascular, SV: stroke volume, LVEF: left ventricular ejection fraction, CO: cardiac output, LAP: left atrial pressure, RVFAC: right ventricular fractional area change, TAPSE: tricuspid annular plane systolic excursion, PVR: pulmonary vascular resistance, sPAP: systolic pulmonary arterial pressure, mPAP: indexed sPAP: ratio between sPAP and CO: mean pulmonary arterial pressure, RA: right atrial, LA: left atrial.

Table 3 Exercise echocardiographic data

Variables	Whole cohort (n = 50)	No CV events (n = 41, 82%)	CV events (n = 9, 18%)	*P*
Exercise LV echocardiographic data				
LV end-diastolic volume, mL	90 ± 25	90 ± 24	88 ± 30	0.85
LV end-systolic volume, mL	27 ± 9	28 ± 9	26 ± 8	0.61
LV stroke volume, mL	63 ± 18	63 ± 18	62 ± 24	0.98
LVEF Simspon, %	70 ± 6	70 ± 6	70 ± 4	0.98
CO, L/min	7.2 ± 2.1	7.2 ± 2	7 ± 3	0.81
E, cm/s	1 ± 0.2	1 ± 0.9	1 ± 0.2	0.57
E deceleration time, ms	121 ± 36	116 ± 38	143 ± 27	0.10
A, cm/s	0.9 ± 0.2	0.9 ± 0.2	1 ± 0.2	0.65
E/A ratio	1.1 ± 0.3	1.1 ± 0.3	1 ± 0.1	0.60
e', cm/s	0.2 ± 0.1	0.2 ± 0.5	0.1 ± 0.1	0.03
E/e'ratio	6.9 ± 2.1	6.2 ± 1.6	9.2 ± 2.2	0.002
LAP, mmHg	10 ± 3	10 ± 2	13 ± 3	0.002
Exercise RV echocardiographic data				
RV end-diastolic area, cm^2	13 ± 4	13 ± 4	13 ± 2	0.99
RV end-systolic area, cm^2	6 ± 2	6 ± 2	6 ± 2	0.65
RVFAC, %	52 ± 9	53 ± 10	50 ± 8	0.60
TAPSE, mm	27 ± 5	28 ± 5	25 ± 8	0.24
s', cm/s	17 ± 4	17 ± 3	17 ± 6	0.97
sPAP, mmHg	46 ± 14	44 ± 13	57 ± 13	0.01
Indexed sPAP, mmHg/L/min	6.6 ± 2.6	6.3 ± 2.3	8.9 ± 3.6	0.04
mPAP, mmHg	30 ± 8	29 ± 8	37 ± 8	0.01
Slope of mPAP-LVCO, mmHg/L/min	4.6 ± 2.7	4.2 ± 2.4	7.1 ± 3.6	
EIPH, n (%)	21 (42)	15 (37)	6 (86)	0.02
PVR, Woods units	2.7 ± 1.2	2.4 ± 1	3.6 ± 1.6	0.06
Exercise atrial area				
LA area, cm^2	14.5 ± 5	13 ± 3	20 ± 8	0.002
RA area, cm^2	12.9 ± 4.5	12.2 ± 3.3	17.5 ± 8.6	0.02

CV: indicates cardiovascular, SV: stroke volume, LVEF: left ventricular ejection fraction, CO: cardiac output, LAP: left atrial pressure, RVFAC: right ventricular fractional area change, TAPSE: tricuspid annular plane systolic excursion, PVR: pulmonary vascular resistance, sPAP: systolic pulmonary arterial pressure, mPAP: indexed sPAP: ratio between sPAP and CO: mean pulmonary arterial pressure, RA: right atrial, LA: left atrial.
Slope of mPAP-LVCO indicates ratio between changes in mPAP and changes in LVCO.

Table 4 Exercise-induces changes echocardiographic data

Variables	Whole cohort (n = 50)	No CV events (n = 41, 82%)	CV events (n = 9, 18%)	*P*
LV echocardiographic data				
LV stroke volume, mL	8 ± 9	7.8 ± 9.1	5.9 ± 11.3	0.67
LVEF Simspon, %	5 ± 7	5.6 ± 7.3	3.8 ± 8.8	0.63
CO, L/mn	3.3 ± 1.6	3.4 ± 1.6	2.9 ± 2	0.51
E/e'ratio	1 ± 1.7	0.7 ± 1.7	2.5 ± 1.3	0.03
LAP, mmHg	1.3 ± 2.2	3.1 ± 1.6	0.87 ± 2.1	0.03
RV echocardiographic data				
RVFAC, %	5 ± 11	4 ± 10	6 ± 16	0.78
TAPSE, mm	4 ± 5	5 ± 5	2 ± 5	0.15
s', cm/s	4 ± 3	4 ± 3	4 ± 6	0.94
sPAP, mmHg	27 ± 12	21 ± 9	27 ± 12	0.14
Atrial area				
LA area, cm^2	0.4 ± 2.7	-0.2 ± 2.5	3.1 ± 2.1	0.005
RA area, cm^2	0.4 ± 2.4	0.2 ± 2.4	1.5 ± 2.1	0.28

CV: indicates cardiovascular, SV: stroke volume, LVEF: left ventricular ejection fraction, CO: cardiac output, LAP: left atrial pressure, RVFAC: right ventricular fractional area change, TAPSE: tricuspid annular plane systolic excursion, PVR: pulmonary vascular resistance, sPAP: systolic pulmonary arterial pressure, mPAP: indexed sPAP: ratio between sPAP and CO: mean pulmonary arterial pressure, RA: right atrial, LA: left atrial.

the 2 groups for resting PVR and a trend for higher exercise PVR in the cardiovascular events group (2.4 ± 0.6 vs 2 ± 1.2 Woods units; $P = 0.42$ and 3.6 ± 1.6 vs 24 ± 1 Woods units; $P = 0.06$, respectively). After adjustment for age and gender, exercise sPAP ($\beta = 0.08 \pm 0.04$; $P = 0.02$, exercise-indexed sPAP ($\beta = 0.39 \pm 0.21$; $P = 0.06$), exercise-induced change in indexed sPAP ($\beta = 0.25 \pm 0.12$; $P = 0.04$), EIPH ($\beta = 2.30 \pm 1.13$; $P = 0.04$), exercise LA area and exercise LAP remained independent predictors of CV events ($\beta = 0.24 \pm 0.12$; $P = 0.04$ and $\beta = 0.93 \pm 0.45$; $P = 0.04$, respectively).

Relationship between maximal resting sPAP during FU and outcome

Mean maximal resting sPAP during FU was (33 ± 11 mmHg) and 30% of the population developed FUPH. There was higher maximal resting sPAP during FU in the cardiovascular event group (47 ± 12 vs 30 ± 7 mmHg; $P < 0.0001$) and FUPH occurred significantly more frequently in patients developing CV complications (88% vs 17%; $P = 0.0001$). After adjustment for age and gender, maximal resting sPAP during FU and FUPH were independent predictors of cardiovascular events ($\beta = 0.24 \pm 0.09$; $P = 0.007$ and $\beta = 3.52 \pm 1.16$; $P = 0.002$, respectively).

BNP blood level

BNP blood level was significantly higher in the CV event group (112 ± 106 vs 26 ± 19 pg/ml; $P = 0.0001$, table 1). Log BNP blood level correlated with exercise sPAP ($r^2 = 0.12$; $P = 0.03$), resting LA area ($r^2 = 0.14$; $P = 0.02$), exercise RA area ($r^2 = 0.19$; $P = 0.01$), resting sPAP ($r^2 = 0.20$; $P = 0.004$), age ($r^2 = 0.32$; $P = 0.0002$). Better correlations were found with exercise LA area ($r^2 = 0.31$; $P = 0.002$), exercise LAP ($r^2 = 0.38$; $P = 0.002$) and also with maximal resting sPAP during FU ($r^2 = 0.38$; $P = 0.0002$). After adjustment for age and gender, the BNP blood level remained significantly associated with the occurrence of CV events ($\beta = 0.08 \pm 0.04$; $P = 0.02$).

Of note, there was an incremental value for BNP ($\chi^2 = 14.7$; $P = 0.001$), EIPH ($\chi^2 = 16.4$; $P = 0.001$) and NVC > grade 2 ($\chi^2 = 20.2$; $P = 0.001$) to predict the occurrence of cardiovascular events in SSc (figure 2).

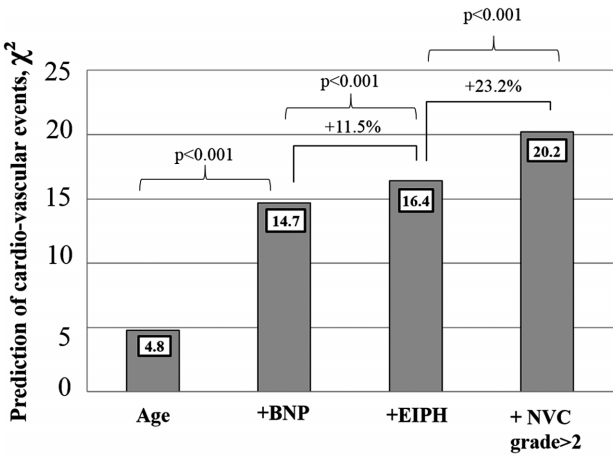

Fig. 2 Incremental value of brain natriuretic peptide, exercise-induced pulmonary arterial hypertension and nailfold videocapillaroscopy grade to predict the occurrence of cardio-vascular complications during follow-up.
BNP: brain natriuretic peptide, EIPH: exercise-induced pulmonary arterial hypertension, NVC: nailfold videocapillaroscopy.

DISCUSSION

The main findings of the present study are: (1) one-fifth (18%) of our patients with SSc developed CV events during follow-up; (2) NVC grade, BNP level, and exercise echocardiographic parameters (i.e. EIPH) emerged as independent predictors of the outcome; (3) combining NVC > grade 2, high BNP level, and EIPH (sPAP > 60 mmHg) resulted in incremental risk stratification.

Cardiovascular disease in SSc

CV complications in SSc include peripheral vascular disease, cerebrovascular disease, coronary disease and primary myocardial disease[16]. The incidence of CV disease varies widely (15% to 30%) in the literature, depending on its definition[17,18]. When present, CV diseases dramatically affect the prognosis[18], representing the main cause of death in SSc since the improvement in renal outcome[19]. In our study, we confirmed the high rate of CV events. The main cause of CV events was peripheral vascular disease secondary to microvascular impairment (n = 6, 66%). Of note, right heart catheterization confirmed the presence of symptomatic pre-capillary resting PH in 2 patients. Finally, 1 patient presented atrial arrhythmia associated with heart failure preserved LV ejection fraction and diastolic dysfunction.

NVC grade and CV events

NVC investigates the substratum of the disease (microvascular impairment). Its importance to predict systemic organ involvement and peripheral vascular disease[2,20] was recently studied. Smith al.[20] showed its potential clinical significance in 66 SSc patients. NVC was graded qualitatively into 4 stages. After a clinical

follow-up of 18-24 months, the authors found a close relationship between worsening NVC grade, severe lung disease and peripheral vascular involvements. The same group confirmed these results in a larger and independent cohort[2]. In our study, we found a close relationship between NVC >grade 2 and the occurrence of CV events, strengthening the potential clinical value of NVC in CV risk stratification of SSc patients. Our results suggest that local microvascular status (finger) probably represents global microvascular impairment reaching peripheral arterial circulation (peripheral arterial members ulcers), coronary microcirculation (increased exercise estimated LV filling pressure) and pulmonary circulation (pre-capillary PH).

BNP level in SSc

BNP or NT-proBNP evaluation is extensively used to stratify the risk of patients with CV diseases[21–25]. In the last few years, the assessment of this marker has emerged in the research field of SSc. Allanore et al.[25] showed, in a relative small population (40 patients), a moderate but significant correlation with resting sPAP ($r = 0.44$; $P = 0.006$). This result was confirmed in a larger cohort of patients by Williams et al.[26]. NT-proBNP was also a predictive factor of the occurrence of resting PH during follow-up[27]. In a population of 69 patients, these authors demonstrated that NT-proBNP could predict overall cardiac involvement[28]. Interestingly, we confirmed the relationship between log BNP and resting sPAP with a similar level of correlation ($r^2 = 0.20$; $P = 0.004$). In addition, we demonstrated strong correlations with LV exercise echocardiographic parameters such as LV E/e' ratio ($r^2 = 0.38$; $P = 0.002$) and LA area ($r^2 = 0.31$; $P = 0.002$). These results revealed the negative impact of increased LV filling pressure during exercise in SSc. We also found a good correlation with the evolution of sPAP during FU ($r^2 = 0.38$; $P = 0.0002$). Finally, patients developing CV events exhibited higher BNP level (112 ± 106 vs 26 ± 19 pg/ml; $P = 0.0001$). Our results highlighted the usefulness of this marker to increase CV risk stratification strategy in SSc.

Exercise sPAP and CV complications

In SSc, exercise echocardiography has been specifically applied to predict the development of resting PH. In 65 patients with SSc, Alkotob et al.[8] reported an inverse weak but significant relationship between exercise sPAP and maximal workload achieved ($r = -0.34$; $P = 0.006$) or exercise duration ($r = -0.31$; $P = 0.01$). Another recent exercise echocardiography study showed a significant relationship between exercise sPAP and FUPH in SSc[14]. Codullo et al.[14] found, in a cohort of 170 patients with SSc, that patients with FUPH (3.5 ± 0.2 years) had significantly higher exercise sPAP, exercise-induced changes in sPAP and in PAP when indexed to changes in CO. With multivariable analysis, exercise sPAP predicted the occurrence of FUPH (defined as mPAP ≥ 25 mmHg in right heart catheterization). However, to the best of our knowledge, EIPH has never been linked to CV events in SSc. Our results showed that exercise sPAP was higher and EIPH occurred more frequently in patients with CV events. This suggests that the assessment of sPAP during exercise could be useful to predict CV complications in SSc. Moreover, patients developing CV disease during FU, exhibited higher exercise LA area, higher exercise LAP suggesting increased exercise LV filling pressure. These results could be explained by a myocardial microvascular impairment, leading to subclinical ischaemia and consequently to increased exercise LV filling pressure. Our main hypothesis is supported by previous myocardial scintigraphy studies[29]. Evidence of reversible ischaemia and inducibility of coronary vasospasm by cold pressor provocation was shown, without any coronary lesion, suggesting microvascular myocardial ischaemia[29,30]. Our results also suggest the potential value of exercise echocardiography as a screening tool to identify patients at high risk of developing CV events.

Limitations of the study

The main limitation of our study is the relatively small size of the population. However, it reflects the low incidence of SSc. Secondary to this small sample size, some differences were not statistically significant between patients with CV events during follow-up and patients without CV complications. Therefore, there was a trend for a higher percentage of diffuse form and corticoid treatment in patients who developed CV during follow-up. Diffuse form and more severe clinical presentation of SSc may be predictive of CV complications during follow-up even if we cannot conclude formally on this point in our study. Finally, this probably suggests that NVC grade and exercise echocardiographic parameters, may be more sensitive than clinical presentation to predict the occurrence of CV events.

Second, the small LV volumes reported could be related to foreshortening views and may also explain the low CO reported. However, this underestimation affects the whole population. Consequently, this limitation does not influence the reliability of the main results of the study.

Third, patients who presented CV events during follow-up had a higher LV E/e' ratio and a greater LA area without LV systolic dysfunction. This may suggest that myocardial fibrosis may be related to CV

complications. However, magnetic resonance imaging with late gadolinium enhancement sequences was not systematically performed in our patients, therefore we cannot conclude on this point in the present study.

CONCLUSION

In patients with SSc, CV complications, which are common, can be incrementally predicted by the association of NVC > grade 2, high BNP level, and EIPH. When present in a single patient, the risk of developing CV disease is very high (63% vs 9%, $P = 0.002$). Although these data need to be confirmed in larger studies, they may already contribute to better stratify the risk of these patients. Whether these high-risk patients require a more aggressive treatment remains to be evaluated.

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