Detection of pulmonary vasculopathy by novel analysis of oxygen uptake in patients with systemic sclerosis: association with pulmonary arterial pressures

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ABSTRACT

Objective. *During cardiopulmonary exercise testing (CPET) compromised pulmonary vasculature in patients with systemic sclerosis (SSc) may lead to increases in pulmonary arterial pressures (PAP) and decreased oxygen uptake. We hypothesised that this may lead into a disproportional heart rate (HR) increase with a corresponding $V'O_2$/HR breakpoint and relates to systolic PAP at rest.*

Methods. *In a prospective design we evaluated $V'O_2$/HR slopes for breakpoints. To understand its physiological meaning, we evaluated $V'O_2$/HR and $V'O_2$/mPAP slopes for breakpoints in a historic data set of SSc patients, in which CPET and right heart catheterisation was performed simultaneously. $V'O_2$/HR slopes with a peak oxygen uptake outside the normal range were defined as pathologic.*

Results. *A breakpoint occurred in both $V'O_2$/mPAP and $V'O_2$/HR slope in 16/34 patients in the historic dataset and occurred in the $V'O_2$/mPAP slope at a lower V'O2 in 15 patients. In the prospective dataset, 73/121 patients showed a $V'O_2$/HR breakpoint and achieved a significantly lower peak oxygen uptake compared to 48/121 patients without a $V'O_2$/HR breakpoint (p=0.036). Mean systolic PAP in 41/121 patients with a pathologic $V'O_2$/HR slope differed significantly from patients without a pathologic $V'O_2$/HR slope (p=0.027). In 27/121 patients with a systolic PAP < 35 mmHg a pathologic $V'O_2$/HR slope was observed.*

Conclusion. *SSc patients with a $V'O_2$/HR breakpoint are characterised by a decreased oxygen uptake, likely caused by sudden PAP increases during exercise. Importantly, in patients with normal resting SPAP pathologic V'O2/HR slopes were observed. This suggests that these patients are at risk for developing pulmonary hypertension.*

Introduction

Patients with SSc are at risk for developing pulmonary hypertension (PH) with an estimated prevalence of 8-12% (1-4). In SSc, Doppler echocardiography (DE) is used for screening of PH and a SPAP threshold of 35 mmHg is used to define elevated pulmonary pressures which may suggest the presence of PH (3, 4). CPET is another important tool in the evaluation of patients with suspected PH which reveals impaired gas exchange and might therefore be useful as an early detection tool (2, 5, 6). The oxygen pulse, which normalises oxygen consumption for heart rate, is widely used as an indirect measurement for cardiac stroke volume (SV) (8) and is correlated with invasively measured SV (9). Usually reported against load or time during exercise (6), it may also be described as the oxygen uptake against heart rate ($V'O_2$/HR) (10). Peak oxygen uptake serves as a marker for cardiac performance during exercise in patients with PH (10-12). In SSc, elevated systolic pulmonary arterial pressures, SPAP ≥35 mmHg, are inversely correlated with peak oxygen uptake (7). However, the relation between the $V'O_2$/HR slope and the occurrence of cardiovascular dysfunction due to SSc related pulmonary vasculopathy (PV) is unknown. Therefore, this slope may contain additional information on the cardiovascular response to exercise in SSc.

In our clinical experience, a significant number of SSc patients show a $V'O_2$/HR slope with a breakpoint during exercise testing while pulmonary pressures measured by DE at rest are normal (10). In these patients, the heart rate

suddenly increases disproportionally to an increase in $V'O_2$ before reaching the predicted peak oxygen uptake. This response may reflect acute increased pulmonary arterial pressures to indicate a change in cardiac response (8, 10). We therefore hypothesised that the onset of a breakpoint in the $V'O_2$/HR slope is a result of a sudden increase in pulmonary arterial pressures. In these patients the exercise capacity and oxygen uptake may be decreased and may be related to SPAP at rest.

Methods

Ethics Statement

The local Medical Ethics Committee of the Leiden University Medical Center approved the protocol. A written informed consent was obtained from each patient prior to enrolment.

The $V'O_2$/HR breakpoint principle and analysis

Both oxygen uptake (on a breath-by-breath basis) as well as heart rate are recorded continuously during CPET. Both variables are related to each other and therefore may be presented in a single graph, resulting into a $V'O_2$/HR slope. In general, several hypothetical $V'O_2$/HR slopes (tracks) during CPET may be obtained (Fig. 1). Patients may either show a monophasic or a biphasic $V'O_2$/HR slope (10) characterised by one or two angles, respectively. In patients showing a biphasic $V'O_2$/HR slope, the heart rate is increasing disproportionally against an increase in oxygen uptake when exercise is in progress, and is reflected by a breakpoint. This breakpoint represents a change in cardiovascular response to exercise by an abrupt increase in heart rate since cardiac output cannot effectively increase by stroke volume alone.

Patients may show a biphasic $V'O_2$/HR slope and a peak $V'O_2$/HR located outside the normal range as indicated in Figure 1, track 2 and 3. On the other hand, patients may show no breakpoint but only a steep $V'O_2$/HR slope completely located outside the normal range (Fig. 1, track 1). Both responses are defined by us as pathologic.

The analytical problem was to mathematically identify the breakpoint in a biphasic $V'O_2$/HR slope. Regression lines were calculated between subsequent increases in $V'O_2$ and HR to define a breakpoint by applying freely available software for these calculations (*e.g.* Fig. 2) (13). In this program, a joinpoint (*i.e.* breakpoint) regression model is applied to describe such continuous changes. We used the grid-search method to fit the regression function with a predefined number of jointpoints and assumed constant variance and uncorrelated errors. As a result, this predefined joinpoint is found by performing several permutation tests. Other possible approaches, such as a polynomial fit to the data, could be considered, however, these do not produce a single value for a breakpoint. Therefore we adopted the joinpoint method in our analysis.

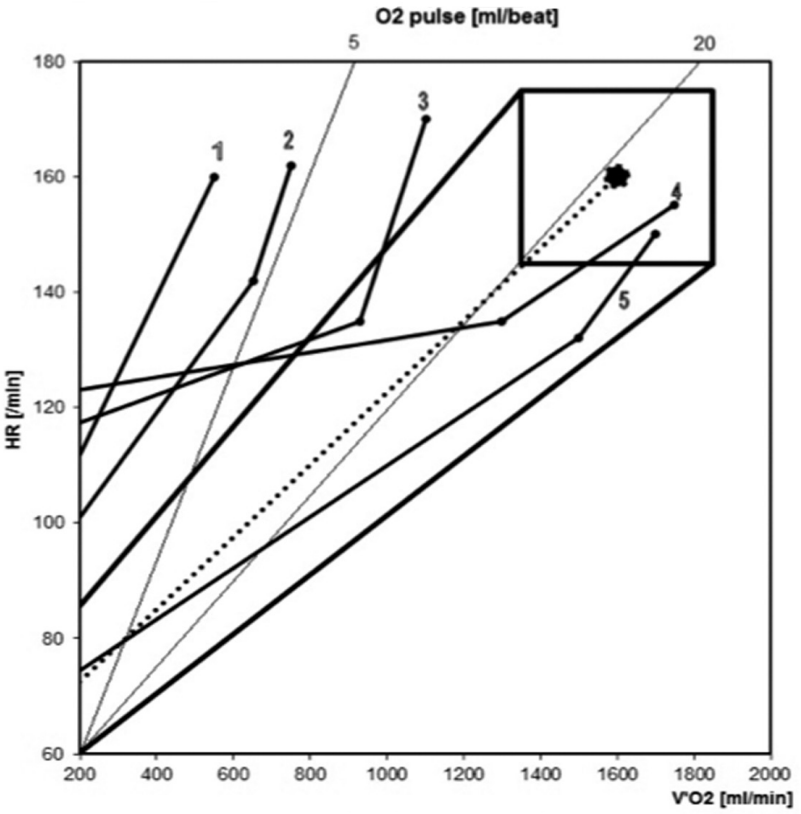

Fig. 1. Hypothetical $V'O_2$/HR slopes, in which corrected HR values are used. Normal $V'O_2$/HR slopes are located in the area defined by highly weighted black tracks: the heart rate has an upper and lower limit of 220-age (yr) ±15 beats/minute, whereas the peak $V'O_2$ has and upper and lower limit of predicted $V'O_2$ ± 15%[22]. The oxygen pulse isopleths are provided at 5 and 20 ml per beat.
The dotted track in the middle of this area represents the ideal $V'O_2$/HR, whereas the black dot in the square box represents the predicted peak oxygen pulse.
Track 1 represents a steep $V'O_2$/HR slope reflecting low stroke volumes from the start of exercise.
Track 2 represents a $V'O_2$/HR with a breakpoint and a peak oxygen pulse located outside the normal range (*i.e.* pathological oxygen pulse slope).
Track 3 represents an abnormal $V'O_2$/HR from the start, including a breakpoint and a peak oxygen pulse outside the normal range.
Track 4 represents initially an abnormal $V'O_2$/HR, including a breakpoint, which normalises as exercise progresses (*i.e.* "nervous anticipation").
Track 5 represents a $V'O_2$/HR with a breakpoint and a normal peak oxygen pulse (*i.e.* $V'O_2$peak = $V'O_2$max)

Patients

First, we explored the kinetics of $V'O_2$/HR slopes in a historic Austrian dataset of SSc patients. Data of some of these patients were described previously (5) and contained SSc patients in whom pulmonary artery pressures measured by right heart catheterisation (RHC) were obtained during CPET. An increase in the pulmonary pressures reflects a decreased pulmonary vessel wall compliance resulting in a sudden increase in heart rate or right ventricular stroke volume. Therefore, we were not

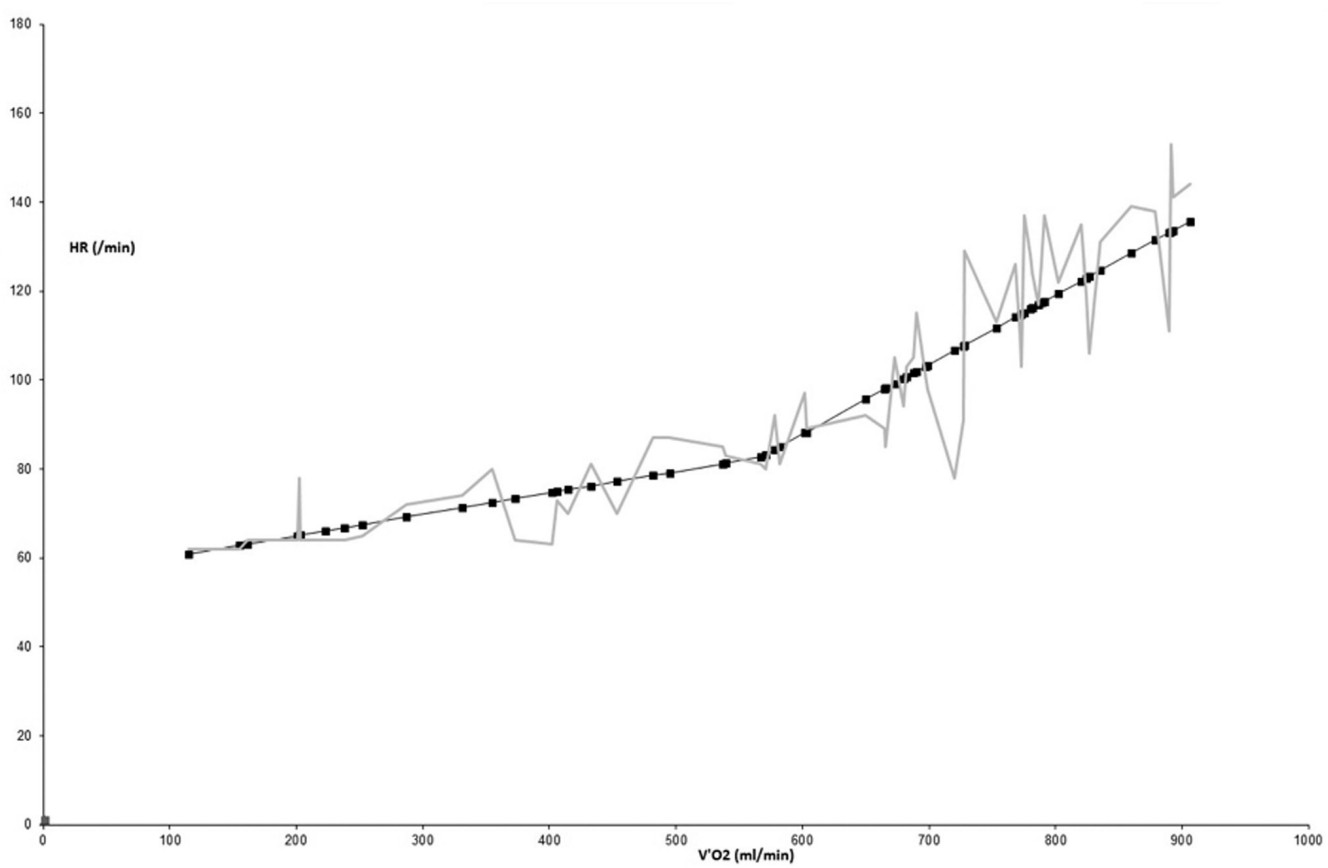

Fig. 2. Example of a mathematically defined breakpoint in a V'O2/HR slope in a single patient (track with square dots). The grey track represents the actual derived heart rate and $V'O_2$.

only able to evaluate whether a breakpoint in the $V'O_2$/HR slope was present but also if it was related to a change in mPAP (*i.e.* a $V'O_2$/mPAP breakpoint). In these patients, 40 out of 45 patients completed both CPET and RHC tests which proved eligible for our analysis. We applied our software for regression analysis to calculate a $V'O_2$/HR and $V'O_2$/mPAP breakpoint, respectively (13). Figure 3 shows the disposition of patients.

Secondly, in the Leiden University Medical Center (LUMC) we screened 131 SSc patients consecutively referred to an outpatient targeted health care program in a prospective design. Patients were classified as limited cutaneous systemic sclerosis (lcSSc) or diffuse cutaneous systemic sclerosis (dcSSc) according to the LeRoy criteria (14). All SSc patients underwent Doppler echocardiography using a commercially available system (Vingmed Vivid 7 and E9, General Electric Vingmed Ultrasound, Horten, Norway). Images were obtained using a 3.5-Mhz transducer and digitally stored in cine-loop format. Subsequent offline analysis was performed using EchoPAC version 110.0.0 (General Electric-Vingmed Ultrasound, Horten, Norway). In all patients Doppler envelopes were well developed. SPAP could therefore be estimated from the tricuspid regurgitation peak gradient using the Bernoulli equation, adding the right atrial pressure estimated by the dimension and the degree of the inferior vena cava respiratory collapse (15, 16). Patients were considered to have elevated pulmonary systolic pressures if SPAP was ≥35 mmHg (17). Furthermore, all patients had laboratory testing, pulmonary function testing (PFTs) (18, 19), symptom limiting non-invasive CPET (6, 20, 21), six minute walk test (6MWT) and high-resolution CT scan (HRCT). CT scans were scored as less or more than 20% involvement of interstitial lung disease (ILD) (22). All tests were done in one or two consecutive days.

Statistical analysis

Statistical analysis was performed with the SPSS 20.0 package (SPSS, Inc., Chicago, IL, USA). All data were checked for normal distribution. Continuous variables are expressed as mean value ± standard deviations. Two-sided *p*-values <0.05 were considered significant. Categorical data are presented as frequencies and percentages. Statistical comparisons were performed by using Student's *t*-test for continuous variables, and chi square test for binary variables.

Results

Evaluation of the $V'O_2$/HR breakpoint principle in a historic dataset

In 40 out of 45 patients of the historic dataset CPET and RHC data were available and suitable for analysis (Fig. 3). Six patients showed a mixed response in the occurrence of breakpoints. In total, 16 out of 34 of these SSc patients (47%) had a breakpoint in *both* $V'O_2$/HR and $V'O_2$/mPAP slopes. The re-

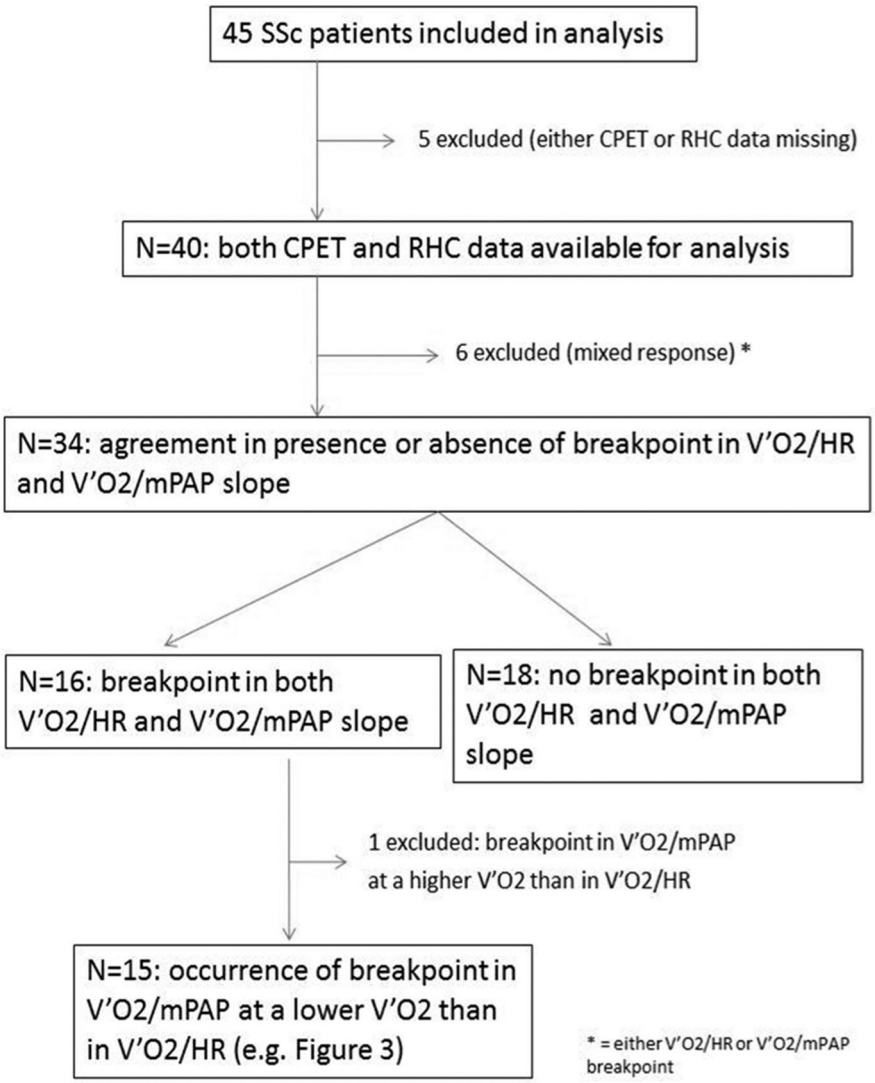

Fig. 3. Flowchart of SSc patient selection from Graz, Austria.

maining 18 patients had no breakpoint in either slope. As an example, Figure 4 shows the breakpoint in a $V'O_2$/HR slope and in a $V'O_2$/mPAP slope during exercise. For each patient we calculated the difference in $V'O_2$ between these two breakpoints. Mean difference in $V'O_2$ was 127 ml ± 63 ml. In 15/16 (94%) of these patients, the breakpoint in the $V'O_2$/mPAP slope preceded the breakpoint in the $V'O_2$/HR slope (*i.e.* earlier during exercise) (Fig. 4). Taken together, these data suggest that a sudden increase in pulmonary arterial pressures results into a disproportional heart rate response to exercise.

Patient characteristics

Patient characteristics of the prospectively collected data are shown in Table I. Patients with left ventricular dysfunction or heart valve disease (n=4), use of beta-receptor blocking agents (n=3) or endothelin receptor antagonists (n=3) were excluded from analysis.

Based on the SPAP measured by DE, SSc patients were stratified into a SPAP below and above 35 mmHg (98 and 23 patients respectively, Table I). Both groups did not differ in terms of gender, age or BMI. However patients with a SPAP ≥35 mmHg had significantly higher NT-proBNP, FVC and transfer factor for carbon monoxide were lower (Table I). Also, more ILD was present in patients with a SPAP ≥35 mmHg (p=0.04). During exercise testing, patients with SPAP ≥35 mmHg showed a significant decrease in peak $V'O_2$ and peak $V'O_2$/HR, an increase in $V'E/V'CO_2$ and a significant difference in $\Delta P_{et}CO_2 AT - P_{et}CO_2$start (Table II).

The $V'O_2$/HR breakpoint principle and analysis

In the prospectively designed study in LUMC SSc patients with a breakpoint in the $V'O_2$/HR slope had a significant lower peak $V'O_2$% predicted compared to patients without a breakpoint (Table III, p=0.036). Disease duration did not differ between these groups. Pathologic slopes classified 41/121 patients (34%, Table III). Classified by a $V'O_2$/HR breakpoint, patients with and without a pathologic $V'O_2$/HR slope differed significantly in 6MWD (p=0.015 and p=0.005).

Of 23 LUMC patients with a SPAP ≥35 mmHg, 14 had a pathologic $V'O_2$/HR slope (61%). Furthermore, mean SPAP differed significantly between patients with and without a pathologic $V'O_2$/HR (31.8 *vs*. 28.2 mmHg, respectively, p=0.027). Importantly, of 98 LUMC SSc patients 27 (28%) had a pathologic $V'O_2$/HR slope not expected by SPAP at rest (resting SPAP <35 mmHg).

Discussion

We report a novel analysis of the $V'O_2$/HR slope to exercise in the clinical evaluation of systemic sclerosis patients which showed that a breakpoint in the $V'O_2$/HR slope is preceded by a breakpoint in the slope of pulmonary arterial pressures against oxygen uptake. This suggests that the increase in pulmonary pressures results in a change in heart rate response to maintain sufficient cardiac output. In patients with a breakpoint in the $V'O_2$/HR slope, peak oxygen uptake was limited and differed significantly compared to patients without a breakpoint. Importantly, in patients with normal SPAP at rest, non-invasive CPET identified patients with a $V'O_2$/HR slope not fitting in the normal range (*i.e.* pathologic V'O2/HR slope). In the evaluation of SSc patients, analysis of the V'O2/HR slope may therefore reveal important information extending that of resting Doppler echocardiography. Taken together, these patients may be at risk for developing pulmonary vasculopathy and ultimately pulmonary hypertension.

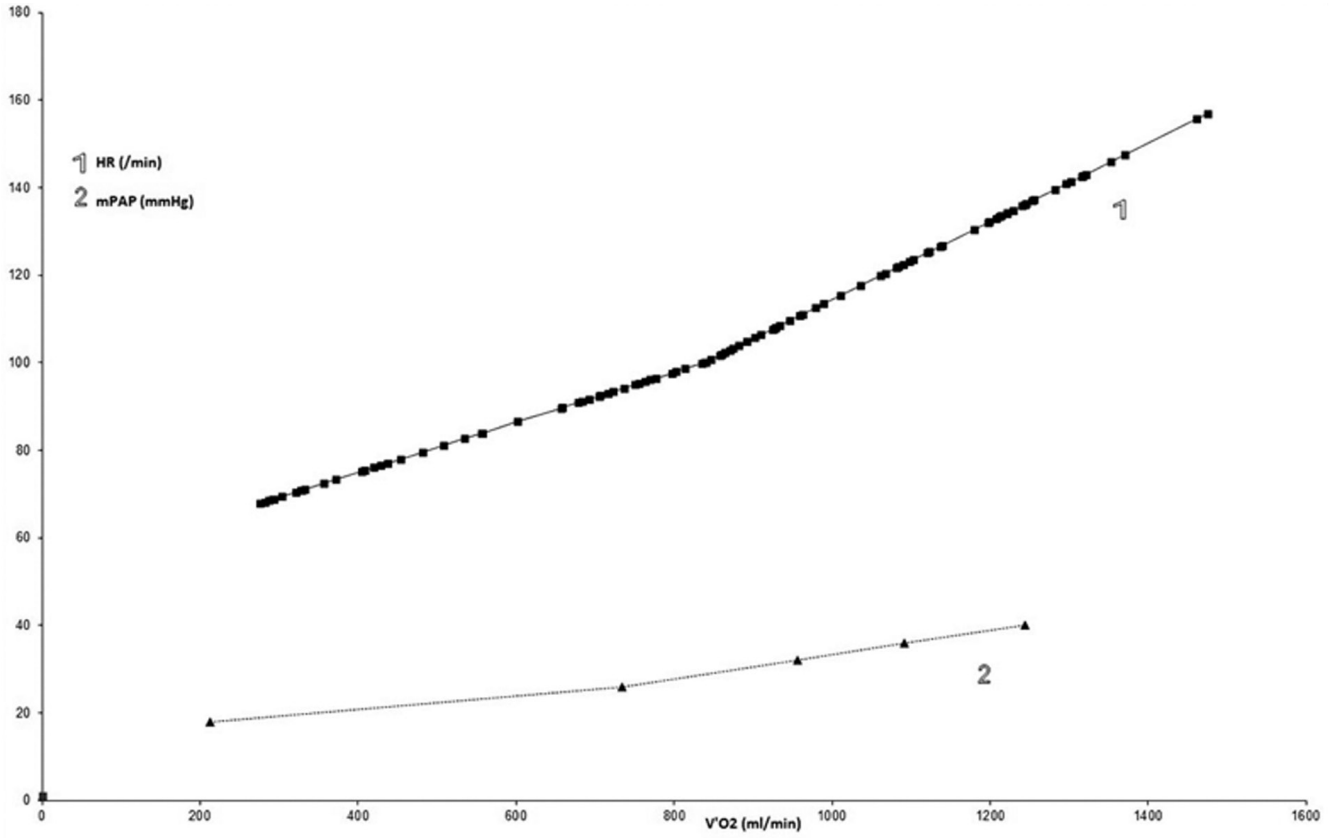

Fig. 4. Example of a breakpoint in the $V'O_2$/HR slope (track 1) and in the $V'O_2$/mPAP slope (track 2) during exercise from a SSc patient. Breakpoint in the $V'O_2$/HR slope occurred at a $V'O_2$ of 840ml. In the $V'O_2$/mPAP slope the breakpoint occurred at a $V'O_2$ of 734ml.

Since SSc patients may develop PH in their course of the disease, early detection and careful monitoring are warranted (23). Previously, Doppler echocardiography and right heart catheterisation have been evaluated to estimate or measure elevated pulmonary arterial pressures at rest (3, 9, 15-17).

Table I. Demographic characteristics of 121 SSc patients prospectively screened at LUMC.

	SPAP <35 mmHg (n=98)	SPAP ≥35 mmHg (n=23)	*p*-value
Gender (female) n, (%)	78 (79)	18 (78)	0.89
Age, years	55 ± 14.2	60 ± 15.4	0.097
BMI (kg/m^2)	22.8 ± 3.4	21.4 ± 3.1	0.68
lcSSc, n (%)	52 (53)	11 (48)	0.79
Laboratory results			
Hb, mmol L-1	8.1 ± 0.7	7.8 ± 0.6	0.09
Pro-BNP	186 ± 345	944 ± 961	<0.001
Doppler echocardiography			
SPAP	26.8 ± 4.4	42.4 ± 7.7	<0.001
Pulmonary function test			
FVC %pred	96.8 ± 20.9	78.0 ± 21.8	<0.001
DLCOc SB % pred	66.5 ± 16.5	49.3 ± 10.4	<0.001
FVC / DLCO	1.49 ± 0.39	1.59 ± 0.37	0.26
TLC-He % pred	88.9 ± 17.1	73.9 ± 17.5	<0.001
HRCT thorax			
>20% extent of disease, n (%)	24 (24)	9 (39)	0.04

BMI: Body mass index; lcSSc: limited systemic sclerosis; Hb: Haemoglobin; pro-BNP: pro-brain natriuretic peptide; SPAP: systolic pulmonary arterial pressure; FVC: forced vital capacity; DLCOc SB: diffusion capacity for carbon monoxide single breath; TLC-He: total lung capacity; Helium dilution method; HRCT: high-resolution computed tomography.

Stress Doppler echocardiography has been recently studied longitudinally and an increase of 18 mmHg during exercise was found to correspond with a sensitivity of 50% and a specificity of 90% of developing PH during follow-up (24). However, disadvantages of this technique include patient and operator dependent issues, such as evaluating exercise echocardiography images. Non-invasive CPET is another important tool in the evaluation of PH. Analysis of various gas exchange and cardiocirculatory parameters such as oxygen uptake is feasible and can be easily interpreted. Therefore we focused on additional analysis of these cardiocirculatory parameters during exercise.

In our clinical experience, SSc patients may display a breakpoint in the $V'O_2$/HR slope during exercise. In these patients, cardiac output cannot effectively increase by stroke volume alone. In general, in patients with increasing pulmonary pressures during exercise, heart rate increase is the main mechanism for increasing cardiac output.

Table II. CPET variables of 121 SSc patients prospectively studied.

		SPAP <35 mmHg (n=98)	SPAP >35 mmHg (n=23)	*p*-value
Aerobic capacity				
	Peak $V'O_2$ (% pred)	88 ± 22	70 ± 19	0.001
	AT (% peak $V'O_2$)	43 ± 14	38 ± 7	0.14
	RER	1.18 ± 0.12	1.18 ± 0.11	0.95
Cardiac function				
	Peak O_2-pulse (% pred)	97 ± 25	72 ± 21	0.006
	$\Delta V'O_2/\ \Delta WR$ (ml/min/W)	9.1 ± 1.9	8.6 ± 2.0	0.56
	HRR	14.6 ± 20.6	10.7 ± 14.6	0.29
Ventilatory efficiency				
	$V'E/V'CO_2AT$	31.5 ± 4.4	35.7 ± 4.5	<0.001
	$P_{et}CO_2AT$ (mmHg)	35.9 ± 3.79	33.7 ± 5.0	0.025
	$\Delta P_{et}CO_2AT$- $P_{et}CO_2$ start (mmHg)	4.17 ± 2.2	1.4 ± 1.9	0.002

Peak $V'O_2$: peak oxygen uptake; AT: anaerobic threshold; RER: respiratory exchange ratio; peak O_2-pulse: peak oxygen pulse; $\Delta V'O_2/\ \Delta WR$: oxygen uptake against work rate; HRR: heart rate reserve; $V'E/V'CO_2AT$: ventilatory equivalent for carbon dioxide at anaerobic threshold; $P_{et}CO_2AT$: end-tidal carbon dioxide tension.

Table III. V'O2/HR breakpoint and pathologic slope of LUMC SSc patients.

LUMC population n=121	Breakpoint in $V'O_2$/HR n=73			No breakpoint in $V'O_2$/HR n=48		*p*-value
Peak $V'O_2$ (% pred)	81			90		0.036
SPAP (mmHg)	30			29		0.52
6MWD (m)	482			527		0.074
	Pathologic $V'O_2$/HR n=23	No pathologic $V'O_2$/HR n=50	*p* value	Pathologic $V'O_2$/HR n=18	No pathologic $V'O_2$/HR n=30	*p*-value
Peak $V'O_2$ (% pred)	57	92	<0.001	79	108	<0.001
SPAP (mmHg)	32	28	0.10	31	28	0.12
6MWD (m)	413	515	0.015	489	587	0.005

Peak $V'O_2$: peak oxygen uptake (ml/min); SPAP: systolic pulmonary artery pressure; 6MWD: 6-minute walking distance.

This results in a significantly steeper slope of $V'O_2$/HR (25-27), which may contain a breakpoint at which the heart rate "takes off" (*e.g.* Fig. 1, track 2) (10, 28). To confirm that these responses are also present in SSc patients, we applied our slope analysis to a historic dataset in which exercise testing and right heart catheterisation were done simultaneously. We found that a sudden increase in the pulmonary pressures results in a disproportional sudden increase in HR during exercise.

Since the occurrence of a breakpoint in a $V'O_2$/HR slope may vary during exercise and reflects a sudden change in the pulmonary vasculature, it may be the result of a reduced compliance of the pulmonary vasculature. Indeed, the pulmonary vasculature in SSc may be affected by progressive obliteration of microvascular structures resulting into a reduced compliance (1, 4). When the pulmonary vascular resistance (PVR) is abnormally increased during exercise, or does not decrease appropriately, right ventricular function can become compromised (29). In patients with exercise induced pulmonary hypertension (EIPAH), two different groups were defined by the nature of their mPAP response to exercise (2, 29). Data during exercise were analysed using best-fit two-segment plots of mPAP versus oxygen uptake. Patients with severe EIPAH and resting PAH showed a "plateau" physiology (2). In these patients mPAP will increase as well as PVR during exercise until the cardiac output is compromised and starts to fall. Eventually, with a decline in cardiac output as a result of right ventricular dysfunction, PAP will not further increase or even fall resulting in a compensatory tachycardia. In contrast, patients with mild to moderate EIPAH showed a "take-off" physiology, suggesting pulmonary vasoconstriction during incremental exercise (2, 29). In these patients, mPAP further increases in which the cardiac output does not decrease. Therefore, it seems plausible that patients with PAH of varying duration and severity will exhibit different mPAP responses to exercise. Likewise, different comparable $V'O_2$/HR slopes may be expected in these patients.

In SSc pulmonary vascular remodeling occurs and may progress into pulmonary vasculopathy and pulmonary hypertension (30). Intimal proliferation, decreased compliance and increased elastance of the pulmonary vasculature may cause a "take-off" physiology. Indeed, 15 Austrian patients showed a "take-off" pattern and none a "plateau" pattern. Mean PAP in these patients measured at 50 Watts and at maximum exercise corresponded well to reported values in other patients with a "take-off" physiology (2, 29). Therefore, these pressures may represent an intermediate stage between a physiologic response and manifest PAH (30). Furthermore, in these patients sudden increases in pulmonary pressures during exercise were followed by sudden increases in heart rate against oxygen uptake. Since different mPAP responses in patients with varying PAH or EIPAH are present, different $V'O_2$/HR responses are likely to occur. In other words, pulmonary vasculopathy, as reflected by a sudden increase in pulmonary pressures, may result into a breakpoint in the $V'O_2$/HR slope during non-invasive CPET. Consequently, the pulmonary vasculature may be more affected in patients showing a pathologic V'O2/HR slope compared to patients without a pathologic $V'O_2$/HR slope. Mean SPAP was significantly different between these groups (Table III). Likewise, in patients showing a breakpoint in the V'O2/HR slope, predicted peak oxygen uptake ($V'O_2$% predicted) was significantly lower than in patients

without a V'O_2/HR breakpoint (Table III) indicating the importance of the V'O_2/HR slope analysis.

Concerning the occurrence of a breakpoint in the V'O_2/HR slope, some clarifications are important. First, in the absence of anaemia, carboxyhaemoglobinaemia, poor blood oxygenation in the lung, right-to-left shunt or low peripheral oxygen extraction, a breakpoint in the V'O_2/HR slope may reflect an impaired cardiovascular response (8, 10). However, in all these responses, a normal peak V'O_2 may still be achieved. Furthermore, in some subjects, a breakpoint due to "nervous anticipation" to exercise is observed (Fig. 1, track 4) or when V'O_2peak is approaching V'O_2max (Fig. 1, track 5). These latter responses to exercise are considered by us the only physiological exceptions when a V'O_2/HR slope contains a breakpoint (10). Secondly, in patients displaying a pathologic V'O_2/HR slope, a V'O_2/HR breakpoint may not always be present. Moreover, their V'O_2 slope may be steep from start of exercise (*e.g.* Fig. 1, track 1). Nevertheless, pulmonary hypertension at rest may develop in the course of their disease. In contrast, patients may display a pathologic V'O_2/HR slope *with* a breakpoint (*e.g.* Fig. 1, track 2). The latter response, however, is considered by us less pathologic since the slope starts less steep and peak V'O_2 approaches the predicted value more closely. Thirdly, in the LUMC dataset a decrease or a less than normal increase in end-tidal pCO_2 (Δ $P_{et}CO_2$AT- $P_{et}CO_2$start, Table II) was present in some of these patients, which may reflect hypoperfusion in well-ventilated acini (6). Fourthly, none of our patients showed an oxygen desaturation during CPET as measured by pulse oximetry. Therefore, reduced peripheral oxygen extraction as a cause of the pathological V'O_2/HR slope was not likely in the LUMC patients. Finally, in the present study, 9 patients with a SPAP ≥35 mmHg and 24 patients with a SPAP <35 mmHg had ≥20% involvement of ILD on their HRCT according to the classification of Goh *et al*. (22). However, in both groups breakpoints in the V'O_2/HR slopes did not influence peak oxygen uptake nor pathologic V'O_2/HR slopes were observed (data not shown). Therefore, the reduced peak oxygen uptake and pathologic V'O_2/HR slopes were considered to reflect changes in the pulmonary vasculature during exercise.

We conclude that our novel analysis of the V'O_2/HR slope showed that SSc patients with a breakpoint in this slope are characterised by a decreased oxygen uptake and exercise capacity. This breakpoint is preceded by a sudden increase in pulmonary arterial pressures and may therefore reflect an inadequate increase or even decrease in stroke volumes. Importantly, non-invasive CPET identified patients with a pathologic V'O_2/HR slope despite normal echocardiographic pulmonary pressures at rest. These patients may have a compromised pulmonary vasculature and are at risk for developing pulmonary vasculopathy and ultimately pulmonary hypertension. To assess the predictive value of the V'O_2/HR breakpoint analysis, we currently perform serial CPET and echocardiography in patients with normal SPAP and a pathologic V'O_2/HR slope or with a V'O_2/HR breakpoint. Our results imply that analysis of the V'O_2/HR slope is warranted in every newly diagnosed SSc patient. In addition, since a compromised pulmonary vasculature is not restricted to systemic sclerosis, our novel analysis may also be applicable to other types of lung disease coinciding with cardiovascular malfunction.

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