



# Right ventricular contractility in systemic sclerosis-associated and idiopathic pulmonary arterial hypertension

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**ABSTRACT:** Since systemic sclerosis (SSc) also involves the heart, the aim of the present study was to evaluate possible differences in right ventricular (RV) pump function between SSc-associated pulmonary arterial hypertension (PAH; SS CPAH) and idiopathic PAH (IPAH).

In 13 limited cutaneous SS CPAH and 17 IPAH patients, RV pump function was described using the pump function graph, which relates mean RV pressure ( $\bar{P}_{RV}$ ) and stroke volume index (SVI). Differences in pump function result in shift or rotation of the pump function graph.  $\bar{P}_{RV}$  and SVI were measured using standard catheterisation. The hypothetical isovolumic  $\bar{P}_{RV}$  ( $\bar{P}_{RV,iso}$ ) was estimated using a single-beat method. The pump function graph was approximated by a parabola:  $\bar{P}_{RV} = \bar{P}_{RV,iso} [1 - (SVI/SVI_{max})^2]$ , where  $SVI_{max}$  is the hypothetical maximal SVI at zero  $\bar{P}_{RV}$ , enabling calculation of  $SVI_{max}$ .

There were no differences in SVI and  $SVI_{max}$ . Both  $\bar{P}_{RV}$  and  $\bar{P}_{RV,iso}$  were significantly lower in SS CPAH than in IPAH ( $\bar{P}_{RV}$   $30.7 \pm 8.5$  versus  $41.2 \pm 9.4$  mmHg;  $\bar{P}_{RV,iso}$   $43.1 \pm 12.4$  versus  $53.5 \pm 10.0$  mmHg). Since higher pressures were found at similar SVI, the difference in the pump function graph results from lower contractility in SS CPAH than in IPAH.

Right ventricular contractility is lower in systemic sclerosis-associated pulmonary arterial hypertension than in idiopathic pulmonary arterial hypertension.

**KEYWORDS:** Myocardial contraction, pump function graph, right ventricular function, right ventricular pressure, stroke volume

Patients with systemic sclerosis (SSc) are at high risk of developing pulmonary arterial hypertension (PAH), with estimated prevalences ranging 7.9–12% [1, 2]. SSc-associated PAH (SS CPAH) patients exhibit a higher risk of death than those with idiopathic PAH (IPAH), as demonstrated by KAWUT *et al.* [3] and FISHER *et al.* [4]. These differences have not been explained satisfactorily to date but comorbidity due to the systemic character of SSc, age-related factors due to the later disease onset of PAH in SSc and differences in pulmonary vasculopathy [5] may all play a role. In addition, the SS CPAH patients described by KAWUT *et al.* [3] and FISHER *et al.* [4] showed a higher mortality despite a similar or lower pulmonary vascular resistance (PVR) at baseline. This suggests an inferior ability of the SS CPAH right ventricle (RV) to adapt to the arterial load compared with the IPAH RV. It was, therefore, hypothesised that RV contractility is impaired in SS CPAH compared with IPAH.

In order to test this hypothesis, possible differences in cardiac output (CO), RV pressure (PRV) and arterial load, in terms of PVR and pulmonary arterial compliance, were first characterised between the two groups. Following this, the RV pump function of both groups was characterised using the pump function graph [6], describing the cardiac pumping ability in terms of the relationship between mean PRV ( $\bar{P}_{RV}$ ) and CO.

## MATERIAL AND METHODS

### Study design

Patients diagnosed with SS CPAH (n=13) or IPAH (n=17) at the VU University Medical Centre (Amsterdam, the Netherlands) between July 2000 and July 2006 were included, and their PRV and pulmonary artery pressure ( $P_{pa}$ ) waveforms recorded and digitally stored during standard right heart catheterisation. The present study was approved by the Institutional Review Board on Research Involving Human Subjects of the VU University Medical Centre.

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## STATEMENT OF INTEREST

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## Methods

Pulmonary hypertension was confirmed by a mean  $P_{pa}$  ( $\bar{P}_{pa}$ ) of  $>25$  mmHg at rest and a pulmonary capillary wedge pressure ( $P_{pcw}$ ) of  $<15$  mmHg. All catheterisations were baseline measurements. Additional clinical diagnostic work-up was performed according to a standard diagnostic protocol [7] in order to exclude other causes of pulmonary hypertension. The diagnosis of SSc was based on the classification criteria proposed by LEROY *et al.* [8].

Pulmonary function testing (Vmax 229 and 6200; Sensor-Medics, Yorba Linda, CA, USA) and high-resolution computed tomography (HRCT; CT Somatom Plus 4; Siemens, Erlangen, Germany) were used to exclude underlying fibrotic lung disease as a cause of pulmonary hypertension.

## Analysis

Haemodynamic parameters

CO was calculated using the Fick method and PVR from  $(\bar{P}_{pa} - P_{pcw})/CO$ . The PRV waveform was averaged to obtain  $\bar{P}_{RV}$ . Stroke volume index (SVI) was calculated from cardiac index (CI) divided by cardiac frequency. Total pulmonary arterial compliance was calculated from stroke volume divided by pulse pressure [9, 10]. Pulse pressure was calculated from systolic minus diastolic  $P_{pa}$ . Pressure measurements were recorded digitally at a sampling frequency of 250 Hz using a customised LabVIEW data acquisition system (National Instruments Netherlands, Woerden, the Netherlands).

## Pump function graph

For the characterisation of RV pump function, a pump function graph was constructed. The pump function graph describes pump function quantitatively by the relationship between  $\bar{P}_{RV}$  and CO. Experimentally, this relationship has been determined by making the heart beat against a series of different arterial loads. Here SVI was used instead of CO in order to avoid

possible confounding effects of differences in cardiac frequency and normalise for body size. A pump function graph demonstrating the effects of alterations in diastolic filling and contractility is shown schematically in figure 1.

From the digitally recorded PRV waveform and SVI, it was possible to obtain individual pump function graphs, which were approximated by a parabola [11]:

$$\bar{P}_{RV} = \bar{P}_{RV,iso}[1 - (SVI/SVI_{max})^2] \quad (1)$$

where  $\bar{P}_{RV}$  is the (time) average of the PRV waveform,  $\bar{P}_{RV,iso}$  the average of the PRV waveform of an isovolumic beat and  $SVI_{max}$  the intercept with the SVI axis, *i.e.* the hypothetical maximal SVI at zero  $\bar{P}_{RV}$ . The  $\bar{P}_{RV}$  and SVI were measured at catheterisation to give the working point (fig. 1).

Subsequently, an estimate of the isovolumic PRV waveform,  $\bar{P}_{RV,iso}$ , was obtained using the single-beat method originally proposed by SUNAGAWA *et al.* [12], and validated for the RV by BRIMIOULLE *et al.* [13]. Its mean value is  $\bar{P}_{RV,iso}$ , and, since SVI is zero by definition for an isovolumic beat, this yielded the second point of the pump function graph. Finally,  $SVI_{max}$  was obtained by reorganising the previous equation:

$$SVI_{max} = SVI / \sqrt{1 - \bar{P}_{RV}/\bar{P}_{RV,iso}} \quad (2)$$

and inserting the measured SVI and  $\bar{P}_{RV}$ , and the calculated  $\bar{P}_{RV,iso}$ . Since  $SVI_{max}$  represents the intercept on the SVI axis, this yielded the third point of the graph. The three points are indicated in figure 1.

The single-beat method assumes that the pressure waveform of an isovolumic beat can be described by a sinusoidal function and that it can be obtained by a least-squares fit to the isovolumic phases of the PRV waveform of the ejecting beat. Isovolumic contraction was assumed to start at the minimum PRV before the steep rise in pressure (R-wave of ECG), and to end when PRV reached diastolic  $P_{pa}$ . The isovolumic relaxation period was defined as lasting from pulmonary artery valve closure, identified by overlaying the  $P_{pa}$  waveform over the PRV waveform, until the PRV reached the diastolic pressure from which the isovolumic contraction calculations were started. A schematic example is shown in figure 2. Before the analysis, underdamping catheter artefacts were removed from the pressure waveforms using a Butterworth filter (cut-off frequency of 10 Hz), and several cardiac cycles were averaged to obtain an average pressure waveform.

## Statistics

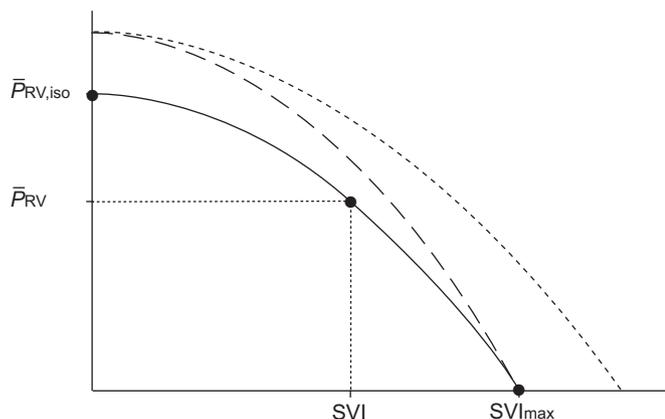
Group-averaged pump function graphs were obtained by averaging isovolumic PRV and  $SVI_{max}$ . Unpaired t-tests and Mann-Whitney U-tests were performed to compare data from both groups.

All data are presented as mean  $\pm$  SD in tables and as mean  $\pm$  SEM or median (interquartile range) in figures. A p-value of  $<0.05$  was considered significant.

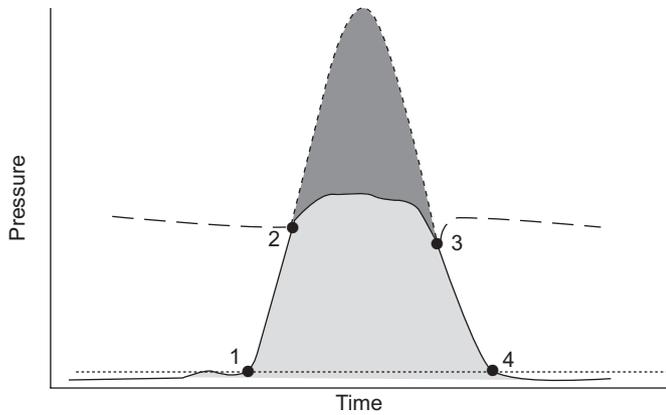
## RESULTS

### General patient characteristics

General patient characteristics are given in table 1. Patients with SScPAH were significantly older, with a mean age difference of 27 yrs. The SScPAH group comprised 100% female patients, whereas 77% of the patients in the IPAH



**FIGURE 1.** Schematically drawn ventricular pump function graph (also applicable to the left ventricle), relating mean ventricular output (stroke volume index (SVI)) and mean right ventricular pressure ( $\bar{P}_{RV}$ ), and characterising the heart as a pump. —: reference; ----: increased filling; - - - -: increased contractility. Alteration in contractility results in a rotation around the intercept on the output axis (hypothetical maximal SVI at zero  $\bar{P}_{RV}$  ( $SVI_{max}$ )), whereas increased filling increases both isovolumic  $\bar{P}_{RV}$  ( $\bar{P}_{RV,iso}$ ) and  $SVI_{max}$ . The three data points shown are the  $\bar{P}_{RV,iso}$ , at zero SVI, constructed using a single-beat method, the measured  $\bar{P}_{RV}$  and mean SVI (working point), and the (derived) maximum output,  $SVI_{max}$ .



**FIGURE 2.** Schematic example of the derivation of an isovolumic beat. Isovolumic contraction is assumed to start at the minimum right ventricular pressure ( $P_{RV}$ ; —), before the steep rise in pressure (1), and to end when it reaches diastolic pulmonary arterial pressure ( $P_{pa}$ ; - - -; 2). The isovolumic relaxation period is defined as lasting from pulmonary artery valve closure (3), identified from deviation of  $P_{RV}$  and  $P_{pa}$ , until the  $P_{RV}$  reaches the diastolic pressure (4). The area under the  $P_{RV}$  curve is used to calculate mean  $P_{RV}$  ( $\bar{P}_{RV}$ ; ■). -----: derivation of isovolumic  $P_{RV}$ ; the total area under this line is used to calculate isovolumic  $\bar{P}_{RV}$  ( $\bar{P}_{RV,iso}$ ; ■).

group were female. All of the SScPAH patients included suffered from the limited cutaneous form of SSc (lcSSc).

The 6-min walking distance did not differ significantly between the groups, and neither did mixed venous oxygen saturation or N-terminal-pro-B-type natriuretic peptide (NT-proBNP) levels. Evaluation of pulmonary function showed that pulmonary gas exchange in SScPAH patients, quantified by the transfer factor of the lung for carbon monoxide, was significantly lower than in IPAH patients, in agreement with previously reported values [14, 15]. Mean total lung capacity and evaluation by HRCT in the SScPAH group indicated that the pulmonary hypertension cannot be explained by severe pulmonary fibrosis. HRCT showed a typical pattern of pulmonary fibrosis in the dorsobasal lung fields in seven of the 13 SScPAH patients; these patients had a total lung capacity of >70% of the predicted value and arterial oxygen saturations of  $\geq 92\%$ .

**Haemodynamic invasive parameters and pump function graphs**

Haemodynamic parameters are listed in table 2. All patients had PVRs of  $>240 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ . A significantly lower  $\bar{P}_{pa}$  was found in the SScPAH group than in the IPAH group. The  $\bar{P}_{RV}$  was significantly lower in the SScPAH group than in the IPAH group, whereas the SVI was not significantly different (fig. 3). There was no significant difference in total arterial load, since neither PVR nor total arterial compliance differed between the groups (fig. 4).

In order to evaluate cardiac pump function, pump function graphs were constructed as described above. Examples of individual pump function graphs of an SScPAH patient and an IPAH patient are depicted in figure 5. The averaged pump function graphs are shown in figure 6.  $\bar{P}_{RV,iso}$  was found to be significantly lower in SScPAH patients than in IPAH patients.

**TABLE 1** General patient characteristics

	SScPAH	IPAH	p-value
<b>Subjects n</b>	13	17	
<b>Age yrs</b>	68.6 ± 12.4	41.9 ± 16.0	<0.001
<b>Females</b>	13 (100)	13 (77)	<0.001 <sup>+</sup>
<b>Cutaneous SSc</b>			
Limited <sup>#</sup>	13 (100)		
Diffuse <sup>#</sup>	0 (0)		
<b>Duration yrs</b>			
SSc disease <sup>†</sup>	9.6 ± 6.8 <sup>§</sup>		
Raynaud phenomenon	18 ± 15		
<b>ACA/anti-Scl-70/anti-U1-RNP</b>	7/1/1 (50/7/7)		
<b>Body surface area m<sup>2</sup></b>	1.7 ± 0.2	1.9 ± 0.3	0.005
<b>ABP mmHg</b>			
Systolic	129 ± 22	119 ± 23	0.49
Diastolic	74 ± 13	73 ± 11	0.78
<b>6-min walking distance m</b>	277 ± 116	358 ± 110	0.08
<b>Sv<sub>v</sub>O<sub>2</sub> %</b>	62.0 ± 6.5	63.5 ± 6.0	0.68
<b>NT-proBNP pg·mL<sup>-1</sup></b>	3546 ± 3035 <sup>f</sup>	1384 ± 1160 <sup>##</sup>	0.24
<b>TLC % pred</b>	89.9 ± 16.6	99.9 ± 11.8	0.26
<b>TL<sub>CO</sub> %</b>	42.8 ± 12.6	65.7 ± 16.1	0.002

Data are presented as mean ± sd or n (%), unless otherwise indicated. SScPAH: systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH); IPAH: idiopathic PAH; ACA: anticentromere antibody; Scl: scleroderma; RNP: ribonucleoprotein; ABP: arterial blood pressure; Sv<sub>v</sub>O<sub>2</sub>: mixed venous oxygen saturation; NT-proBNP: N-terminal-pro-B-type natriuretic peptide; TLC: total lung capacity; % pred: % predicted; TL<sub>CO</sub>: transfer factor of the lung for carbon monoxide. <sup>#</sup>: as defined in [8]; <sup>†</sup>: since first non-Raynaud symptom; <sup>+</sup>: Chi-squared statistic; <sup>§</sup>: n=12; <sup>f</sup>: n=10; <sup>##</sup>: n=9. 1 mmHg=0.133 kPa.

SVI<sub>max</sub> did not differ between the two groups. Thus, compared with the SScPAH patients, the IPAH patients demonstrated a higher pump function graph, rotated around the same point of the horizontal axis intercept, i.e. SVI<sub>max</sub>.

**DISCUSSION**

In the present study, cardiac pump function was compared between SScPAH and IPAH patients using the relationship between  $\bar{P}_{RV}$  and SVI. These variables were obtained using standard right heart catheterisation and Fick CO measurements. Lower values were found for  $\bar{P}_{RV}$  in the SScPAH group than in the IPAH group, whereas SVIs were not significantly different. Analysis of the arterial system in terms of PVR and total arterial compliance showed no difference in arterial load between the two groups. On the basis of these data, it is concluded that right heart pump function differs between the SScPAH and IPAH groups.

These haemodynamic differences between SScPAH and IPAH patients are in agreement with those described by FISHER *et al.* [4]. Although they did not evaluate cardiac function, their haemodynamic data showed a similar pattern to the present one, consisting of a similar CI at lower  $\bar{P}_{pa}$ . In their study, PVR was significantly lower in SScPAH than in IPAH, in contrast to the comparable PVRs between the groups in the present study cohort. This supports the present data; despite lower afterload, SScPAH patients were unable to generate a

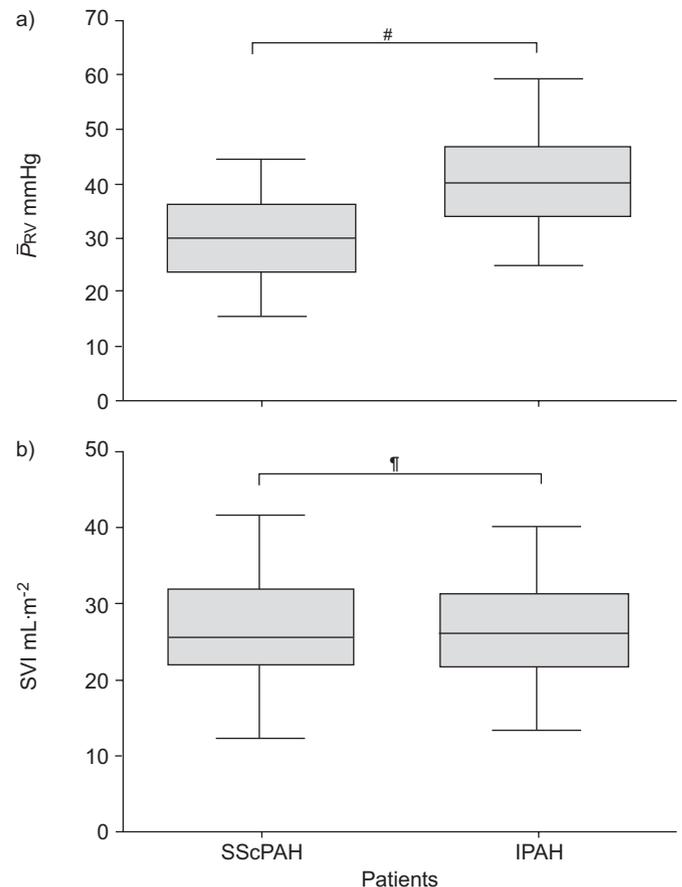
**TABLE 2** Haemodynamics and pump function graph data

	SsCPAH	IPAH	p-value
<b>Subjects n</b>	13	17	
<b>Cardiac frequency beats·min<sup>-1</sup></b>	82.4 ± 13.0	86.7 ± 13.8	0.43
<b><math>\bar{P}_{RA}</math> mmHg</b>	6 ± 4	8 ± 5	0.56
<b><math>\bar{P}_{RV}</math> mmHg</b>	31 ± 9	41 ± 9	0.006
<b><math>\bar{P}_{RV,iso}</math> mmHg</b>	43 ± 12	54 ± 10	0.043
<b><math>PRV_{sys}</math> mmHg</b>	43 ± 12	60 ± 10	<0.0001
<b><math>PRV_{dias}</math> mmHg</b>	11 ± 5	14 ± 7	0.48
<b><math>\bar{P}_{pa}</math> mmHg</b>	44 ± 10	60 ± 10	<0.0001
<b><math>P_{pa,sys}</math> mmHg</b>	70 ± 14	97 ± 19	<0.0001
<b><math>P_{pa,dias}</math> mmHg</b>	26 ± 6	37 ± 8	<0.0001
<b><math>P_{pcw}</math> mmHg</b>	9 ± 3	8 ± 4	0.62
<b>PVR dyn·s·cm<sup>-5</sup></b>	848 ± 397	1079 ± 433	0.13
<b>Compliance mL·mmHg<sup>-1</sup></b>	1.1 ± 0.42	0.9 ± 0.43	0.30
<b>SVI mL·m<sup>-2</sup></b>	27.1 ± 7.3	26.7 ± 7.6	0.84
<b>SVI<sub>max</sub> mL·m<sup>-2</sup></b>	53.5 ± 20.6	57.5 ± 15.9	0.23
<b>CI L·min<sup>-1</sup>·m<sup>-2</sup></b>	2.2 ± 0.6	2.3 ± 0.6	0.71

Data are presented as mean ± sd. SsCPAH: systemic sclerosis-associated pulmonary arterial hypertension (PAH); IPAH: idiopathic PAH;  $\bar{P}_{RA}$ : mean right atrial pressure;  $\bar{P}_{RV}$ : mean right ventricular pressure (PRV);  $\bar{P}_{RV,iso}$ : isovolumic PRV;  $PRV_{sys}$ : systolic PRV;  $PRV_{dias}$ : diastolic PRV;  $\bar{P}_{pa}$ : mean pulmonary arterial pressure ( $P_{pa}$ );  $P_{pa,sys}$ : systolic  $P_{pa}$ ;  $P_{pa,dias}$ : diastolic  $P_{pa}$ ;  $P_{pcw}$ : pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; Compliance: total pulmonary arterial compliance; SVI: stroke volume index; SVI<sub>max</sub>: maximal SVI at zero  $\bar{P}_{RV}$ ; CI: cardiac index. 1 mmHg=0.133 kPa.

higher CI than IPAH patients. In addition, they observed a significantly higher mortality in the SsCPAH group compared with the IPAH group, despite the fact that IPAH patients had higher PVRs, supporting the idea that cardiac involvement contributes to the early death in SsCPAH.

In order to characterise differences in cardiac function, a pump function graph was constructed for each patient. A pump function graph presents the pumping ability of the RV. ELZINGA and WESTERHOF [16, 17] have shown, in isolated cat hearts, that the pump function of the left and right heart can be described quantitatively by such a graph, which relates mean ventricular pressure with mean ventricular output. This relationship, which characterises the heart, was determined by making the heart eject against a series of different arterial loads. Changing the afterload of an individual heart moves the pressures and flows on this graph, *i.e.* increased load decreases CO and increases PRV. The pump function graph was shown to depend on cardiac frequency, ventricular filling and cardiac muscle contractility, *i.e.* muscle properties [6]. By using SVI instead of CI, the effects of differences in cardiac frequency were avoided in the present study. As schematically shown in figure 1, an increase in end-diastolic volume causes a parallel outward shift of the pump function graph, whereas increased contractility results in a rotation about the intercept on the SVI axis. Thus the present data, by showing this rotation of the pump function graph to lower pressures but with a comparable intercept on the abscissa in SsCPAH compared with IPAH, indicate lower contractility in the SsCPAH group.

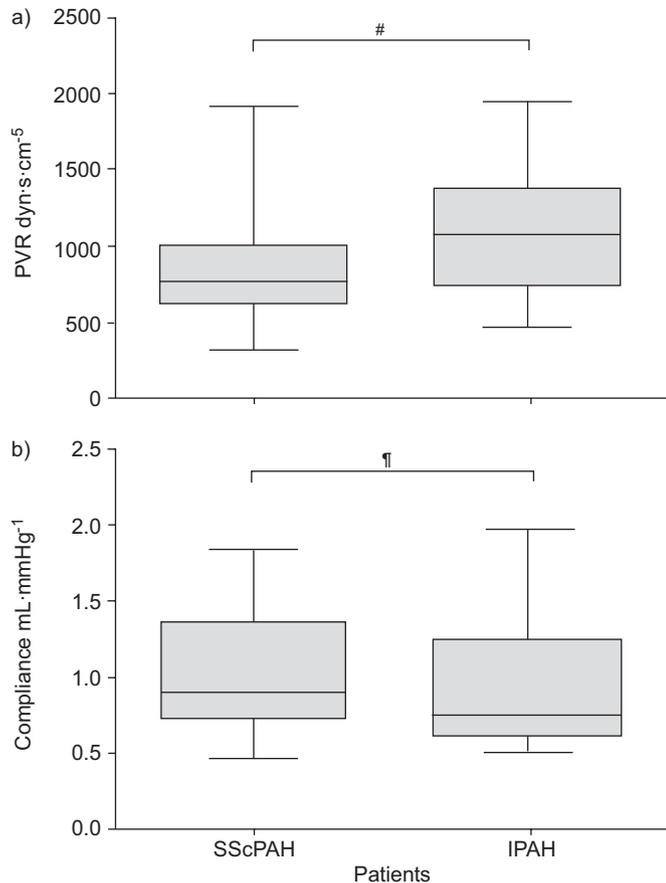


**FIGURE 3.** Boxplot showing a) mean right ventricular pressure ( $\bar{P}_{RV}$ ), and b) stroke volume index (SVI) in systemic-sclerosis-associated pulmonary arterial hypertension (SsCPAH; n=13) and idiopathic pulmonary arterial hypertension (IPAH; n=17). Boxes represent median and interquartile range; vertical bars represent range. #: p=0.006; ¶: p=0.84. 1 mmHg=0.133 kPa.

The single-beat method was used to derive isovolumic PRV from a measured PRV of an ejecting beat. SUNAGAWA *et al.* [12] found that, for the left ventricle, there is a correlation between the isovolumic pressure observed during an isovolumic beat and the isovolumic pressure that is predicted by sine wave extrapolation from the isovolumic parts of an ejecting beat. BRIMIOULLE *et al.* [13] showed that this single-beat method can also be used for the RV. In the present study, this method was used to predict the  $\bar{P}_{RV,iso}$  in individual patients in order to be able to describe a full pump function graph.

Since PVR and compliance did not differ, it was concluded that the difference in PRV between SsCPAH and IPAH hearts is based on differences in the performance of the heart itself.

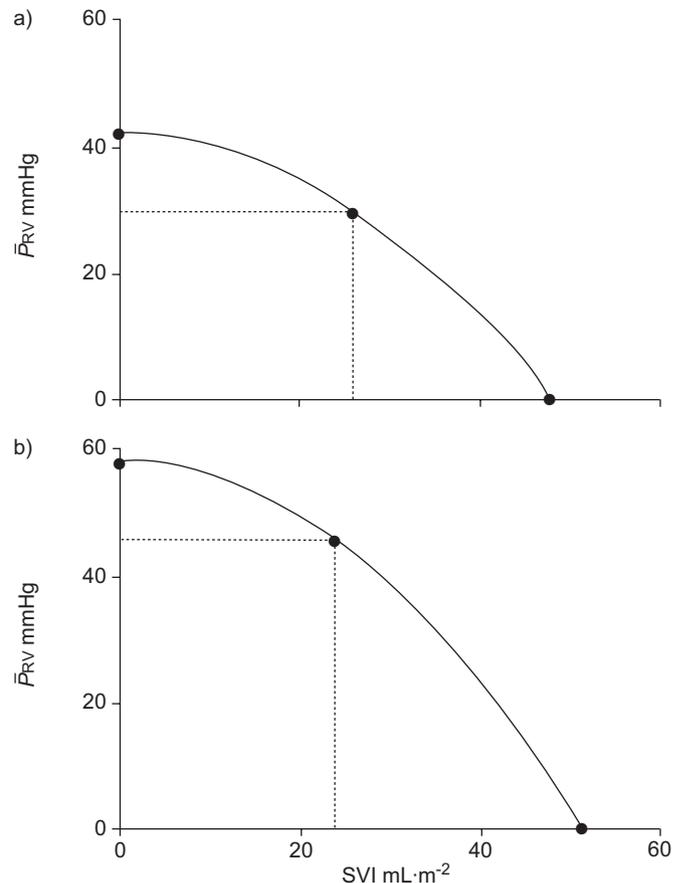
The advantage of the use of the ventricular pump function graph is that it is based on standard catheterisation measurements, Fick CO and PRV. However, this method still requires further validation in humans. Validation of the pump function graph method could be performed by the evaluation of difference in contractility between the SsCPAH and IPAH groups by construction of a series of RV pressure–volume loops during the temporary occlusion of the inferior vena cava, measured by means of a conductance catheter [18]. However,



**FIGURE 4.** Boxplot showing the arterial load. a) Pulmonary vascular resistance (PVR), and b) pulmonary arterial compliance in systemic-sclerosis-associated pulmonary arterial hypertension (SScPAH; n=13) and idiopathic pulmonary arterial hypertension (IPAH; n=17). Boxes represent median and interquartile range; vertical bars represent range. #:  $p=0.12$ ; †:  $p=0.30$ . 1 mmHg=0.133 kPa.

this is an intervention with substantial patient burden. Moreover, volume measurement using the conductance catheter in the RV is a possibility [19], but still not sufficiently evaluated. Another method would be to simultaneously measure  $PRV$  by right heart catheterisation and RV volume by magnetic resonance imaging analysis; this method also requires further validation [20].

The lower contractility in SScPAH might be explained in several ways. Myocardial fibrosis, as well as intramyocardial coronary vessel involvement, is known to affect the ventricles in SSc [21, 22]. FERNANDES *et al.* [23] analysed endomyocardial biopsy specimens from SSc patients with both the lcSSc and diffuse cutaneous SSc (dcSSc) forms, without signs or symptoms of heart failure, and excluded patients with pulmonary or arterial hypertension, left ventricular hypertrophy and left ventricular diastolic dysfunction. They demonstrated abnormal collagen deposition in 94% of cases. Impaired contractility of hearts of patients with SScPAH might then be explained by increased levels of extracellular matrix, which might affect normal contraction of the cardiac myocytes it surrounds [24, 25]. Remodelling of the heart due to persistent elevations of ventricular developed pressure leads

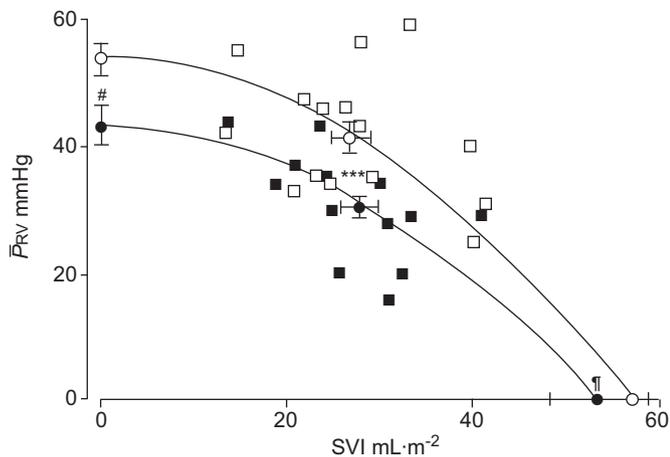


**FIGURE 5.** Examples of pump function graphs. a) A patient with systemic-sclerosis-associated pulmonary arterial hypertension (PAH); and b) a patient with idiopathic PAH.  $\bar{P}_{RV}$ : mean right ventricular pressure; SVI: stroke volume index. 1 mmHg=0.133 kPa.

to changes in the amount of collagen, collagen phenotype and collagen cross-linking [26]. Cross-linking has not been investigated in the hearts of SSc patients, but is increased in skin with SSc [27, 28]. It may be speculated that SSc myocardial tissue expresses an increased degree of collagen cross-linking that contributes to an impaired cardiac contractility.

An impaired contractility in SScPAH could also be explained by ischaemia due to vascular alterations. It has been shown that structural abnormalities of small coronary arteries or arterioles explain a reduced coronary reserve in SSc [29, 30].

Other underlying pathophysiological mechanisms may be found at the level of cardiac muscle *per se*. One of the mechanisms by which the cardiac muscle adapts to ventricular pressure overload under normal conditions is hypertrophy. However, impaired contractility of SScPAH hearts might not be explained by an inability of the SScPAH heart to undergo hypertrophy, since the RV mass of SScPAH hearts has been shown to be comparable to that of IPAH hearts ( $41.6 \pm 12.3$  (n=11) versus  $45.8 \pm 14.8$  g·m<sup>-2</sup> (n=14);  $p=0.51$ ) [31]. This does not exclude the possibility that other intrinsic myocyte pathology may be responsible for impaired cardiac contractility in the SScPAH group, although information on this topic, for example regarding intrinsic myocyte abnormalities that



**FIGURE 6.** Averaged ventricular pump function graph for systemic-sclerosis-associated pulmonary arterial hypertension (SScPAH; ● and ■; n=13) and idiopathic pulmonary arterial hypertension (IPAH; ○ and □; n=17). Data are presented as mean  $\pm$  SEM for: isovolumic mean right ventricular pressure ( $\bar{P}_{RV,iso}$ ) at zero stroke volume index (SVI); the measured  $\bar{P}_{RV}$  and SVI (working point); and the (derived) maximum output, maximal SVI at zero  $\bar{P}_{RV}$  ( $SVI_{max}$ ). The IPAH pump function graph is located above the SScPAH pump function graph, with a rotation around the  $SVI_{max}$ . #:  $p=0.04$ ; \*:  $p=0.23$  versus IPAH group. 1 mmHg=0.133 kPa.

may be responsible for impaired contractility in the SScPAH group, is not available. The present hypothesis of intrinsic myocardial involvement in SScPAH patients is supported by the findings of MEUNE *et al.* [32], who found a decreased RV ejection fraction in patients with early SSc (both lcSSc and dcSSc), without relation to  $\bar{P}_{pa}$ .

In the present study group, the SScPAH patients were significantly older than the IPAH patients, reflecting the normal epidemiological features [15, 33]. Age differences might affect RV diastolic function, but have not been demonstrated to affect RV systolic function [34, 35]. However, in order to exclude age-related factors as the underlying explanation of the differences found in the present study, a study with age-matched SScPAH and IPAH patients may elucidate the influence of age on RV contractility in PAH. Other limitations are the weak power of the present study due to low patient numbers. Moreover, there is heterogeneity of patients, as shown by the ranges of NT-proBNP levels, PVR and compliance.

The SScPAH population consisted of patients with the lcSSc form of SSc [8], which may lead to a bias since no dcSSc patients were studied. First, patients with the dcSSc form of SSc are more likely to suffer from pulmonary fibrosis as a contributor or cause of pulmonary hypertension, and, since the present patient group consisted of lcSSc patients with no or mild fibrosis on HRCT, fibrosis was not considered as a potential cause of pulmonary hypertension. It was thus assumed that the SSc patients in the present study suffered from pulmonary hypertension caused by pre-capillary vasculopathy and, as such, are comparable with the IPAH patients. Secondly, it might be that cardiac involvement in SSc differs between dcSSc and lcSSc. As differences in this respect have not been elucidated, it is difficult to extrapolate the present

findings to dcSSc, since no knowledge exists regarding differences in heart involvement and adaptation in response to elevated PVR between lcSSc and dcSSc.

In conclusion, using standard catheterisation data, it has been demonstrated that systemic sclerosis-associated pulmonary arterial hypertension patients exhibit lower cardiac contractility than idiopathic pulmonary arterial hypertension patients. Further study of right ventricular function in systemic sclerosis-associated pulmonary arterial hypertension should elucidate the underlying mechanisms.

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