

Pulmonary vasospasm in systemic sclerosis: noninvasive techniques for detection

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Abstract: In a subgroup of patients with systemic sclerosis (SSc), vasospasm affecting the pulmonary circulation may contribute to worsening respiratory symptoms, including dyspnea. Noninvasive assessment of pulmonary blood flow (PBF), utilizing inert-gas rebreathing (IGR) and dual-energy computed-tomography pulmonary angiography (DE-CTPA), may be useful for identifying pulmonary vasospasm. Thirty-one participants (22 SSc patients and 9 healthy volunteers) underwent PBF assessment with IGR and DE-CTPA at baseline and after provocation with a cold-air inhalation challenge (CACH). Before the study investigations, participants were assigned to subgroups: group A included SSc patients who reported increased breathlessness after exposure to cold air ($n = 11$), group B included SSc patients without cold-air sensitivity ($n = 11$), and group C patients included the healthy volunteers. Median change in PBF from baseline was compared between groups A, B, and C after CACH. Compared with groups B and C, in group A there was a significant decline in median PBF from baseline at 10 minutes (-10% ; range: -52.2% to 4.0% ; $P < 0.01$), 20 minutes (-17.4% ; -27.9% to 0.0% ; $P < 0.01$), and 30 minutes (-8.5% ; -34.4% to 2.0% ; $P < 0.01$) after CACH. There was no significant difference in median PBF change between groups B or C at any time point and no change in pulmonary perfusion on DE-CTPA. Reduction in pulmonary blood flow following CACH suggests that pulmonary vasospasm may be present in a subgroup of patients with SSc and may contribute to worsening dyspnea on exposure to cold.

Keywords: scleroderma, pulmonary vasospasm, noninvasive.

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Raynaud's phenomenon (RP), characterized by triphasic color changes secondary to digital artery vasospasm and subsequent reperfusion, is present in more than 90% of patients with systemic sclerosis (SSc) and is a cardinal feature of the disease.¹ Debate continues as to the presence and clinical significance of a more widespread visceral vasospastic process in SSc, with evidence of cold-induced ischemia affecting the myocardium,²⁻⁵ brain,⁶⁻⁹ and kidneys.¹⁰ Vasospasm affecting the pulmonary circulation remains controversial but may be of particular importance, given the high prevalence of pulmonary hypertension in SSc.¹¹ Similar histological changes have been reported in the digital arteries and pulmonary arteries,¹² and it is possible that repetitive pulmonary vasospasm may be one mechanism contributing to eventual fixed pulmonary hypertension in SSc.¹³

Various measurement techniques (including right heart catheterization [RHC], radioisotope lung perfusion scans, and diffusing capacity of the lung for carbon monoxide [DLCO]) have been evaluated for the detection of pulmonary vasospasm, with varying results.¹⁴⁻²² Technological advances now allow for the assessment of pulmonary blood flow (PBF) with several noninvasive techniques, including inert-gas rebreathing (IGR) and dual-energy computed-tomography pulmonary angiography (DE-CTPA).

Measurement of PBF with IGR is well established and has been validated against cardiac catheterization and cardiac magnetic resonance imaging (MRI).²³⁻²⁵ Gas concentration analysis performed with photoacoustic spectroanalysis enables rapid, accurate, and reproducible PBF measurements²⁶ and provides a measure of whole-lung, or "global," pulmonary perfusion. DE-CTPA, an evolving imaging modality, allows simultaneous image acquisition at the same phase of contrast enhancement, enabling the creation of an "iodine map" of pulmonary perfusion.²⁷ In contrast with IGR-measured global PBF, postprocessing DE-CTPA techniques allow the analysis of regional lung perfusion differences. We hypothesized that pulmonary vasospasm in SSc patients could be provoked with an inhalational cold-air challenge and may be detectable as a change in global or regional pulmonary perfusion from baseline measurements, as measured by IGR and DE-CTPA.

METHODS

Patient selection

Twenty-two patients with SSc attending the Royal Brompton Hospital Interstitial Lung Disease Clinic were evaluated prospectively by

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tween January 2011 and October 2012. Nine healthy volunteers were recruited as control subjects. All patients met the American College of Rheumatology criteria for SSc,²⁸ and only patients with limited interstitial lung involvement (defined as interstitial lung disease [ILD] extent of <20% on high-resolution computed tomography [CT] and/or forced vital capacity [FVC] of >70%)²⁹ were recruited to the study (to minimize the risk of interstitial change confounding DE-CTPA interpretation). No patient had pulmonary hypertension, and all patients had undergone screening echocardiography in the previous 12 months. No patients were receiving pulmonary vasodilator therapy (endothelin receptor antagonists, phosphodiesterase 5 inhibitors, or prostacyclins) or calcium channel antagonists.

Before undertaking the study protocol, patients were classified into three groups. Group A consisted of SSc patients who reported new or worsening dyspnea during cold exposure (suggestive of pulmonary vasospasm), group B of patients with SSc in whom dyspnea did not change on exposure to cold, and group C of healthy volunteers. Local ethics committee approval was given for the study, and informed consent was obtained from all participants.

Statistical analysis

All analyses were performed with STATA statistical software (ver. 12.0; Stata, College Station, TX). Data were expressed as mean and standard deviation (SD) or as median and range, as appropriate. Comparisons of PBF measurements (percent change from baseline) were made with the Wilcoxon signed-rank test. Spearman's rank correlation was calculated, comparing change in DE-CTPA parameters (including mean lung attenuation [MLA] and pixel intensity, as described in "DE-CTPA image analysis" below) with changes in PBF.

Study protocol

The sequence of study investigations is outlined in Figure 1, and all participants completed the study investigations in a single visit. Baseline spirometry and PBF measurements were performed, followed by a modified 3-minute isocapnic hyperventilation cold-air challenge (CACH; described below). After completion of the CACH, repeat spirometry was performed, followed by serial PBF measurements every 5–10 minutes for 30 minutes. After completion of respiratory maneuvers, a minimum 2-hour "rest break" was enforced. Following the break, baseline DE-CTPA was performed, followed by a second

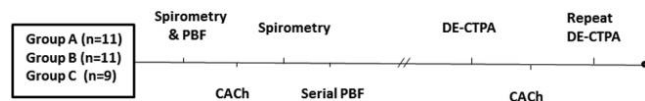


Figure 1. Sequence of study investigations. Group A included systemic sclerosis (SSc) patients who reported increased dyspnea on exposure to cold air, group B included SSc patients without cold-air sensitivity, and group C included healthy volunteers. After a cold-air inhalation challenge (CACH), pulmonary blood flow (PBF) measurements were performed every 5–10 minutes for 30 minutes. A minimum "rest break" of 2 hours was then enforced, before dual-energy computed-tomography pulmonary angiography (DE-CTPA).

CACH. Repeat DE-CTPA was performed, timed to coincide with the maximum observed post-CACH change in PBF. If no post-CACH change in PBF was observed, the DE-CTPA was performed 10–20 minutes after CACH. The exact timing of the DE-CTPA was recorded, and all parameters between examinations for each patient were kept constant. Individual study investigations are described in detail below.

Spirometry. Forced expiratory volume in 1 second (FEV₁) and FVC were measured (Jaeger Masterscreen; Cardinal Health UK 240, Warwick, UK) at baseline and after cold-air inhalation, to assess for cold-induced bronchoconstriction.

CACH. A modified isocapnic hyperventilation CACH (based on the protocol to assess for exercise-induced bronchoconstriction)^{30,31} was undertaken as the provoking stimulus with which to induce pulmonary vasospasm. Three minutes of isocapnic hyperventilation at rest was performed at 60% of maximum voluntary ventilation (with a gas mixture of 5% CO₂, 21% O₂, and 73% nitrogen) with the TurboAire Challenger device (VacuMed, Ventura, CA). This portable handheld device utilizes a series of geometrically arranged internal "fins" to alter airflow kinetic energy and achieve rapid air cooling. As measured by a temperature probe at the mouthpiece, inhaled-air temperature was maintained at –10° to –15°C.

PBF measurement. PBF measurement using IGR was performed with the Innocor device (Innovision, Odense, Denmark). IGR (based on the Fick principle) involves the inhalation of a gas mixture containing a soluble and an insoluble gas, with PBF proportional to the rate of decline of the soluble compound.^{23,24} With inline photoacoustic gas analysis, concentrations of nitrous oxide (N₂O; blood soluble) and sulphur hexafluoride (SF₆; blood insoluble) can be rapidly measured, with PBF proportional to the rate of decline of N₂O as it is cleared by the pulmonary circulation. PBF measurements were performed at baseline (PBF_{pre-CACH}) and serially (every 5–10 minutes) after CACH.

DE-CTPA. Dual-energy CT enables simultaneous acquisition of data at differing x-ray tube voltages, and with contrast enhancement, DE-CTPA allows evaluation of pulmonary arteries and lung parenchyma from a single examination.²⁷

Image acquisition. Thirty patients underwent DE-CTPA, which used a dual-source, dual-energy CT scanner (Somatom Definition Flash; Siemens Medical Systems, Forchheim, Germany). Pulmonary arterial opacification was achieved by injecting 50 mL of 370-mg I/mL iodinated contrast medium (Ultravist 370, Bayer Healthcare, Pittsburgh), followed by 50 mL of saline, at a rate of 5–6 mL/s, with a high-speed dual-head injection pump. Examinations were triggered by a bolus-tracking technique, with contrast arrival in the pulmonary trunk detected with a threshold of 100 Hounsfield units (HU). DE-CTPA was performed at baseline (DE-CTPA_{pre-CACH}) and then 10–20 minutes after the CACH (DE-CTPA_{post-CACH}).

Image analysis. To determine whether overall lung density changed after cold-air inhalation, two images from each of the DE-CTPA_{pre-CACH} and DE-CTPA_{post-CACH} 80-kVp axial data sets were selected for analysis (Fig. 2). The superior image was selected at the level of the origin of the right upper lobe bronchus, and the inferior image was the caudalmost image on which the diaphragm was not visible and there were no motion artifacts. Images were transferred to a postprocessing workstation (Leonardo, Siemens), and quantitative lung density analysis was performed with the Pulmo CT program (ver. 2; Siemens), which automatically segments the lung and calculates pixel attenuation coefficients as previously described,³² with minimum and maximum segmentation thresholds of -200 and $-1,024$ HU, respectively (Fig. 3). The MLA generated by the program (based on the two slices) was used for evaluation.

Change in MLA (Δ MLA) was calculated by subtracting the DE-CTPA_{pre-CACH} MLA from the DE-CTPA_{post-CACH} MLA, providing a measure of change in global pulmonary perfusion. Post-processing analysis of advanced image-subtraction techniques allowed the calculation of the number of pixels with intensity ratios of between 0 and 160 (ΔI), expressed in megapixels (1×10^6 pixels), enabling change in regional pulmonary perfusion to be assessed (Fig. 2C). Detailed image acquisition parameters and postprocessing techniques are described in the supplement, available online.

RESULTS

Baseline characteristics

Twenty-two patients with SSc (mean age: 58 ± 9 years, 17 females) and 9 healthy volunteers (mean age: 36 ± 10 years, 4 females) partici-

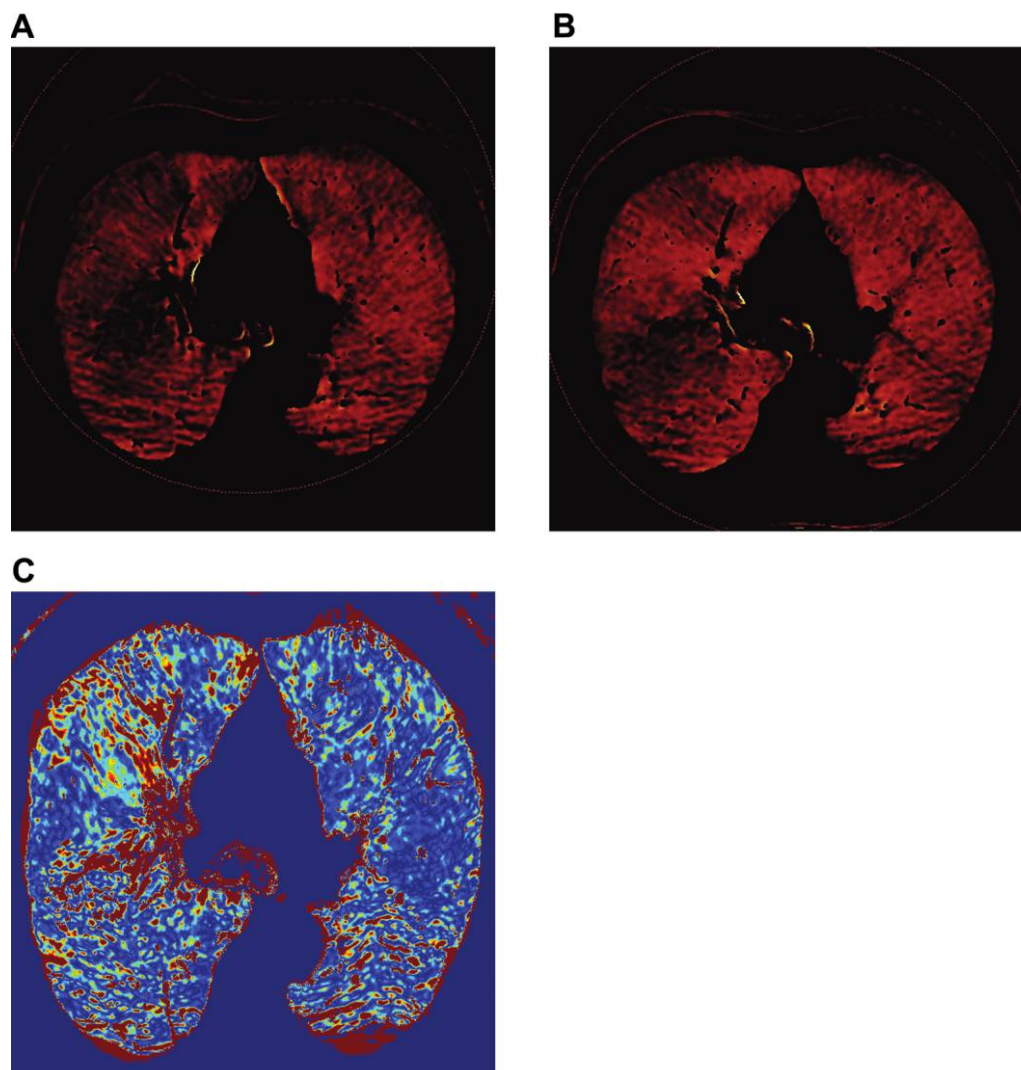


Figure 2. Dual-energy postprocessing and image subtraction on a patient from group A (with a decrease in pulmonary blood flow following cold-air inhalation). Images demonstrate dual energy-derived lung iodine maps from the superior computed-tomography slices (at the level of the origin of the right upper lobe bronchus) before (A) and 15 minutes after (B) cold challenge, with iodine color-coded orange. The subtracted image (C) demonstrates areas of low intensity change as “cold” colors (e.g., blue, green) and areas of high intensity change as “warm” colors (e.g., red); however, areas of high intensity change can also be seen around misregistered vessels, a recognized artifact.

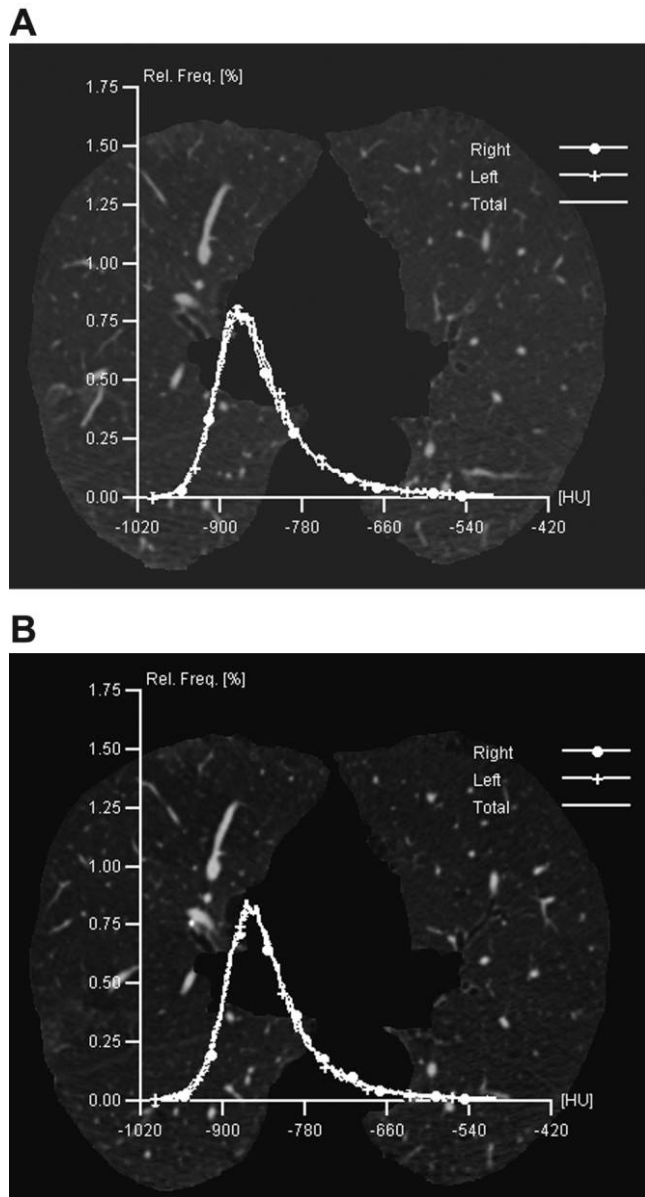


Figure 3. Quantitative computed-tomography (CT) lung density analysis on a patient from group A, using a single CT image (at the level of the origin of the right upper lobe bronchus). The resultant density histograms before (A) and 15 minutes after (B) cold challenge demonstrate no significant change in mean lung attenuation between the 2 CT studies, despite a demonstrated reduction in pulmonary blood flow measured during inert-gas rebreathing. HU: Hounsfield units.

pated in the study. All SSc patients reported a history of digital RP, and all had undergone screening echocardiogram in the previous 12 months (with a normal mean right ventricular systolic pressure of 24.1 ± 8.0 mmHg and no other echocardiographic signs of pulmonary hypertension).

Group A (SSc patients with cold-air sensitivity) included 11 patients (mean age: 58 ± 9 years, 8 females) with a median SSc disease

duration of 4 years (range: 1–13 years). Six patients had limited cutaneous SSc (lcSSc), and 5 had diffuse cutaneous SSc (dcSSc). On CT, 5 patients had no evidence of ILD, 5 patients had radiographic appearances of nonspecific interstitial pneumonia (NSIP), and 1 patient had overlapping appearances of usual interstitial pneumonia (UIP) and NSIP. The mean predicted FVC was $92\% \pm 11\%$. Group B (SSc patients without cold-air sensitivity) included 11 patients (mean age: 60 ± 8 years, 9 females) with a median disease duration of 4 years (range: 1–27 years). Seven patients had lcSSc. On CT, 5 patients had no radiographic evidence of ILD, 5 patients had NSIP, and 1 patient had UIP. The mean predicted FVC was $87\% \pm 10\%$. Baseline demographic and clinical information is summarized in Table 1.

PBF

Median change in PBF from baseline was compared between groups at predefined time intervals, with a significant decline in PBF in group A after CACH (Fig. 4). There was no statistically significant difference in baseline PBF between groups A and B (median: 4.6 [range: 2.6–5.1] and 4.1 [3.0–7.0] L/min, respectively; $P = 0.8$), although PBF was higher in group C, at 6.5 (4.5–7.1) L/min. Ten minutes after CACH, there was a decrease in PBF of 10.0% (–52.2% to 4.0%) in group A, compared to a 2.6% increase (–7.1% to 25.0%; $P < 0.01$) in group B and no change (0.0%; –9.0% to 10.0%; $P < 0.01$) in group C. At 20 minutes, there was a decrease in PBF of 17.4% (–27.9% to 0.0%) in group A, compared to a 4.9% increase (–8.6% to 20.0%; $P < 0.01$) in group B and a 2.2% decrease (–10.0% to 1.5%; $P < 0.01$) in group C. At 30 minutes after CACH, there was a median decrease in PBF of 8.5% (–34.4% to 2.0%) in group A, compared to a 1.4% increase (–5.3% to 16.1%; $P < 0.01$) in group B and no change (0.0%; –11.3% to 1.3%; $P < 0.01$) in group C. Median change in PBF after CACH did not differ significantly between group B and C patients at any time point (Table 2), and no patient experienced a significant change in FEV₁ (defined as a change from baseline of at least 10%) after CACH.

DE-CTPA image analysis

Preliminary analysis of DE-CTPA data in 22 study participants revealed no correlation between change in PBF (Δ PBF) and change in DE-CTPA parameters. Thus, DE-CTPA analysis was not performed in the remaining study participants. In one case, a technical malfunction with bolus triggering resulted in suboptimal DE-CTPA contrast enhancement, and these data were not included in analysis; thus, 21 patients had DE-CTPA examinations suitable for image analysis. No patient had evidence of acute or chronic pulmonary thromboembolism. The mean Δ PBF for the 21 patients was $-3.2\% \pm 11.2\%$ (median: 0%; range: –28.0% to 16.0%). When change in regional pulmonary perfusion after CACH was assessed, no correlation was noted between ΔI and Δ PBF (Spearman’s $\rho = -0.06$; $P = 0.79$). No correlation was found between Δ MLA and ΔI (Spearman’s $\rho = -0.14$; $P = 0.55$), suggesting that changes in lung enhancement as measured by DE-CTPA postprocessing did not simply reflect changes in lung density. When change in global pulmonary perfusion was assessed, the mean Δ MLA was -8.6 ± 30.2 HU (median: –10.7 HU; range: –68.2 to 70.6 HU), and no correlation

Table 1. Baseline clinical and demographic information

	Group A (n = 11)	Group B (n = 11)	Group C (n = 9)
Age, years, mean \pm SD	56.1 \pm 9.0	60.3 \pm 8.1	36.5 \pm 10.2
lcSSc, n	6	7	NA
dcSSc, n	5	5	NA
Disease duration, years (range)	4.1 (1–13)	4.4 (1–27)	NA
Echocardiogram RVSP, mmHg	26.3 \pm 5.6	21.0 \pm 6.4	NA
ILD pattern, n			
No ILD	5	5	9
NSIP	5	5	...
Other	1 ^a	1 ^b	...
FEV ₁ , % predicted	79	82	104
FVC, % predicted	92	87	106
Baseline PBF, L/min (range)	4.6 (2.6–5.1)	4.1 (3.0–7.0)	6.5 (4.5–7.1)

Note: The groups were well matched, other than the younger age and higher baseline PBF in the healthy volunteers (group C). dcSSc: diffuse cutaneous systemic sclerosis; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; ILD: interstitial lung disease; lcSSc: limited cutaneous systemic sclerosis; NSIP: nonspecific interstitial pneumonia; PBF: pulmonary blood flow; RVSP: right ventricular systolic pressure; UIP: usual interstitial pneumonia.

^a UIP/NSIP overlap.

^b UIP.

was demonstrated between Δ MLA and Δ PBF (Spearman's $\rho = -0.04$; $P = 0.85$). No correlations were found between ΔI and Δ PBF, between ΔI and Δ MLA, or between Δ MLA and Δ PBF, in

the group as a whole, or between subgroups A, B, and C (tables S1, S2, available online).

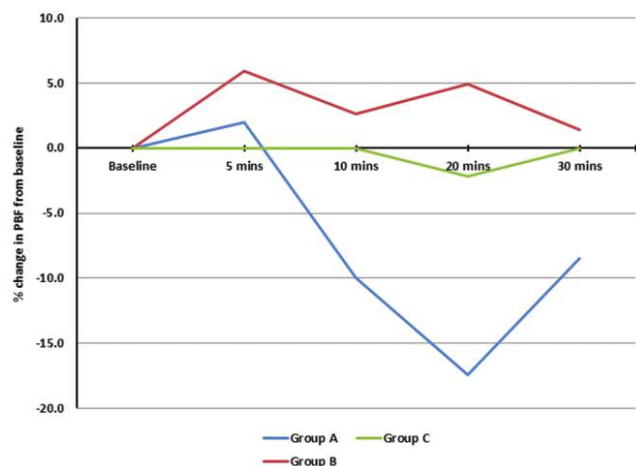


Figure 4. Median percentage change in pulmonary blood flow from baseline after cold-air inhalation challenge. In group A (systemic sclerosis [SSc] patients with cold sensitivity), compared to group B (SSc patients without cold sensitivity) and group C (healthy volunteers), there was a median change in PBF of -10.0% (range: -52.2% to 4.0%) versus $+2.6\%$ (-7.1% to 25.0%) versus 0.0% (-9.0% to 10.0%) at 10 minutes, -17.4% (-27.9% to 0.0%) versus $+4.9\%$ (-8.6% to 20.0%) versus -2.2% (-10.0% to 1.5%) at 20 minutes, and -8.5% (-34.4% to 2.0%) versus $+1.4\%$ (-5.3% to 16.1%) versus 0.0% (-11.3% to 1.3%) at 30 minutes.

DISCUSSION

Pulmonary hypertension develops in 10%–15% of SSc patients and warrants early detection to allow optimal treatment and follow-up. Predicting which patients are at risk of PH is imprecise, and several methods of stratifying at-risk patients have been proposed, including autoantibody profile and SSc phenotype.¹ While repetitive pulmonary vasospasm is one plausible pathophysiologic mechanism that may contribute to PH in SSc, this hypothesis remains controversial, and lability of the pulmonary vasculature has proven difficult to demonstrate conclusively. At our institution, a national ILD referral center with a large SSc cohort, we have identified a subgroup of patients who describe a clear temporal relationship between worsening respiratory symptoms (including dyspnea) and exposure to cold. Utilizing IGR, we were able to identify a clear reduction in PBF in a predefined subgroup of SSc patients following a CACH, suggesting that pulmonary vasospasm may be the physiologic explanation for these symptoms.

Previous efforts to identify pulmonary vasospasm have yielded inconsistent findings. Following cold-pressor testing in patients with RP, several authors^{14–16} have reported a reduction in DLCO, which could be explained by reduced pulmonary capillary blood volume resulting from pulmonary vasospasm. Lampert¹⁷ reported a reduction in DLCO in similar patients, although this was associated with a reduction in mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) at RHC, suggesting that vasodilatation and intrapulmonary blood redistribution may be the un-

Table 2. Change in PBF and FEV₁ after CACH, compared to baseline measurements

	Group A (n = 11)	Group B (n = 11)	Group C (n = 9)
Change in PBF, %			
10 minutes after CACH	-10.0 (-52.2 to 4.0)*	+2.6 (-7.1 to 25.0)	0.0 (-9.0 to 10.0)
20 minutes after CACH	-17.4 (-27.9 to 0.0)*	+4.9 (-8.6 to 20.0)	-2.2 (-10.0 to 1.5)
30 minutes after CACH	-8.5 (-34.4 to 2.0)*	+1.4 (-5.3 to 16.1)	0.0 (-11.3 to 1.3)
Change in FEV ₁ , %	-1.9 (-9.6 to 1.4%)	+1.2 (-4.1 to 2.7%)	-5.6 (-6.6 to 2.1%)

Note: Data are median (range). In group A patients, there was a statistically significant change in PBF from baseline at 10, 20, and 30 minutes after CACH. PBF did not change significantly in group B or C patients. There was no statistically or clinically significant change in FEV₁ in any group after CACH. CACH: cold-air challenge; FEV₁: forced expiratory volume in 1 second; PBF: pulmonary blood flow.

* $P < 0.01$, Wilcoxon sign-rank test.

derlying pathophysiological process. Conversely, neither Miller¹⁸ nor Wise¹³ detected change in DLCO in SSc patients after provocation testing. Other measurement techniques, including krypton perfusion lung scan (demonstrating reduced pulmonary perfusion)²⁰ and RHC (demonstrating an increase in mPAP and PVR in a subgroup of patients),²¹ have provided support for the notion of pulmonary vasospasm, in at least a subgroup of patients. More recently, in SSc patients with established pulmonary hypertension, Coghlan and colleagues²² found no change in right heart catheter parameters or circulating markers of endothelial cell activation after cold-pressor testing.

These conflicting results have created understandable confusion, and a major limitation in identifying pulmonary vasospasm remains the lack of a readily available, validated measure of PBF. DLCO, used as a surrogate for PBF, depends on the area and thickness of the blood-gas barrier (as described by Fick's law of diffusion) and the volume of blood within the pulmonary capillaries. A reduction in pulmonary capillary blood volume results in a reduction in DLCO.³³ However, the use of DLCO for the detection of pulmonary vasospasm has yielded inconsistent findings, with confounders such as increased cardiac output, regional pulmonary vasodilatation, and shift in intrapulmonary blood distribution creating measurement difficulties.

The myocardium,²⁻⁵ brain,⁶⁻⁹ and kidneys¹⁰ have all been shown to experience cold-induced vasospasm in at least a subgroup of SSc patients. LeRoy and colleagues¹⁰ demonstrated a reduction in renal perfusion after cold water hand immersion, while Long² and Alexander³ reported cold-induced reversible myocardial perfusion abnormalities during thallium scintigraphy. The presence of "cardiac RP" has been reported to be a strong independent predictor of subsequent left ventricular dysfunction in SSc patients.⁴ Interestingly, one patient in our cohort (who experienced a 20% reduction in PBF after cold-air inhalation) had received a diagnosis of cardiac syndrome X (recurrent episodes of ischemic chest pain with normal coronary arteries at angiography) several years previously.

Our study is unique in several aspects, including the use of noninvasive measurement techniques allowing the assessment of both regional and global change in pulmonary perfusion. PBF mea-

surement with IGR has been validated against RHC and cardiac MRI^{23,24} and has been shown to detect treatment response after initiation of vasodilator therapy in pulmonary hypertension.³⁴ DE-CTPA perfusion has demonstrated good correlation with CT-derived PBF in porcine models,³⁵ and in our study postprocessing techniques were employed to assess for change in both regional and global pulmonary perfusion. We sought to improve pretest probability by identifying a subgroup of SSc patients with symptoms (worsening dyspnea after cold exposure) plausibly explained by pulmonary vasospasm. After an inhalational CACH as the provoking stimulus (selected to mimic the physiological trigger reported by our patients), we detected a significant and sustained decline in PBF in a subgroup of SSc patients, in clear contrast to healthy volunteers and SSc patients without cold-air sensitivity (in whom PBF did not change). Importantly, FEV₁ did not change after cold-air inhalation, suggesting that cold-induced bronchospasm was not the explanation for worsening dyspnea in our patients.

Utilizing DE-CTPA, we were not able to demonstrate a significant correlation between the changes in MLA and those in PBF, which may be expected with reduced pulmonary capillary blood volume secondary to pulmonary vasospasm. It is possible that the changes in lung perfusion are at the microscopic level and thus too subtle to be reflected in changes of MLA. The lack of a correlation between DE-CTPA-derived intensity changes and MLA changes suggests that subtle changes in perfusion do not contribute to measurable changes in lung density in a predictable manner. While previous studies in emphysema subjects have demonstrated moderate correlations between MLA and DE-CTPA-derived perfusion,³⁶⁻³⁸ these correlations have been observed in regions of increasing emphysema severity. It is also possible that differing postures adopted with each measurement technique (IGR was performed in the seated upright position, while DE-CTPA was performed supine) may have resulted in changes in pulmonary perfusion and ventilation, hampering direct comparison of the two techniques.

This study has a number of important limitations. Significantly, there is no accepted gold-standard measure of pulmonary vasospasm against which to validate novel measurements techniques. While we evaluated techniques that may identify both physiologic and radio-

logic changes in pulmonary perfusion (at both regional and global perfusion levels), the lack of a gold-standard comparator does not allow us to reach definitive conclusions from our data. Furthermore, the optimal stimulus with which to provoke pulmonary vasospasm is not known. Cold-air inhalation was chosen as the provoking stimulus in our study, as this most closely resembled the trigger described by our patients.

We sought to limit confounders (particularly airflow obstruction or ILD) that may impair interpretation of DE-CTPA and IGR findings by recruiting only patients with limited ILD on high-resolution CT and well-preserved spirometry. While it is possible that cold-air inhalation may have resulted in unexpected physiologic consequences (such as bronchoconstriction, which was not detectable as a change in FEV₁) that may affect gas mixing and IGR measurements, we think that this is unlikely.

A further potential confounder is the use of hypercapnic gas mixture (5% CO₂) and its possible effect on pulmonary vascular tone. The net effect of CO₂ on pulmonary vascular tone is dependent on coexistent hypoxia and pH, and, analogous to the CO₂ rebreathing protocol we performed, Fishman³⁹ reported no change in right heart catheter hemodynamics in healthy human controls after they had breathed a 5% CO₂ mixture for 20 minutes under normoxic conditions. As all participants in our study underwent an identical cold-air inhalation protocol, any effect of hypercapnic gas inhalation on pulmonary vascular tone should be consistent across all groups.

Conclusion. Pulmonary vasospasm may explain worsening respiratory symptoms in a subgroup of SSc patients on exposure to cold. While we identified a reduction in PBF using IGR techniques, the utilization of novel measurement techniques and the lack of a gold-standard comparator do not allow us to draw a firm conclusion proving (or disproving) our hypothesis. Furthermore, whether pulmonary vasospasm represents a precursor to eventual fixed pulmonary hypertension in a subgroup of SSc patients is an intriguing hypothesis and warrants further evaluation in a larger cohort followed longitudinally over time.

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Conflict of Interest: None declared.

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