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Early View

Research letter

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Global Lung Initiative equations in pulmonary hypertension screening in systemic sclerosis

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Take home message

Global Lung Initiative equations provide new cut-offs for TLCO for detection of pulmonary hypertension in patients with systemic sclerosis, either with or without interstitial lung disease.

To the Editor:

Systemic sclerosis (SSc) is a connective tissue disease characterised by widespread vasculopathy and excessive fibrosis in multiple organs, including the lungs [1]. The most frequent pulmonary involvement in SSc is interstitial lung disease (ILD), but the most harmful is pulmonary hypertension (PH), a complication found in about 10% of SSc patients [2]. In patients with SSc, early diagnosis and prompt therapy of PH (either isolated or associated with ILD) are beneficial from a prognostic standpoint, and recommendations for active screening of PH in SSc have therefore been established [3].

Pulmonary function tests (PFTs) are one of the key tools used for PH screening in SSc patients [4], and transfer factor of the lung for carbon monoxide (TLCO) and forced vital capacity (FVC) are the two tests most widely used for this purpose [2, 5]. As these two PFTs are expressed as percentages of predicted value (% pred), reference equations to calculate predicted values are of critical importance for interpretation.

New reference equations for FVC and for TLCO, based on a large sample of normal subjects, have recently been published by the Global Lung Function Initiative (GLI) group [6, 7]. By analysing a large multicentre sample of unselected patients with SSc, we aimed to compare the optimal thresholds of TLCO and of the FVC/TLCO ratio for identification of PH in these patients, using either previous reference equations [8, 9] or the latest GLI equations [6, 7]. The population analysed here has been fully described elsewhere [2]. Briefly, PFTs were carried out in SSc patients under stable conditions with standard equipment according to the latest guidelines [10, 11]. All patients underwent Doppler echocardiography at the time of PFTs, and right heart catheterisation was performed if PH was suspected. Of the 572 SSc patients who were included, 58 had pulmonary hypertension (35 had both ILD and PH, while

23 had PH without ILD) and 514 did not have pulmonary hypertension (313 had no pulmonary involvement, i.e., neither ILD nor PH, and 201 had ILD without PH). The area under the receiver operating characteristic (ROC) curve was used to assess the ability of TLCO and of the FVC/TLCO ratio to discriminate between the presence and the absence of PH. As TLCO is modified not only by PH but also by ILD, we performed two analyses, one in SSc patients without ILD (n=336) and another in SSc patients with ILD (n=236). The optimal thresholds for both analyses were assessed according to the Youden index of ROC curve analysis in order to maximise both sensitivity and specificity.

By comparison with the previous equations for TLCO [8] and for FVC [9], we observed that with the GLI equations, mean values of TLCO (% pred) were significantly higher (by 4 to 9%, depending on the presence of PH and/or ILD) and mean values of FVC (% pred) were significantly lower (by 9 to 12%). Use of the GLI equations also resulted in much lower FVC (% pred)/TLCO (% pred) ratios than with the previous equations.

In SSc patients without ILD, analysis of the ROC curves regarding the probability of PH showed that the optimal threshold of TLCO was higher (70% *vs.* 60% pred) with the GLI equation compared with the previous equation (Table 1); optimal thresholds were however similar with the GLI and with the previous equation for SSc patients with ILD. The area under the ROC curve was significantly higher for SSc patients without ILD than for SSc patients with ILD. When TLCO was expressed as z-score, optimal threshold value was ~ -2.00 for SSc patients without ILD and ~ -3.50 for SSc patients with ILD.
For the FVC/TLCO ratio (FVC and TLCO both being expressed as % pred), we identified an optimal threshold that was similar for SSc patients without ILD whatever the equations used.

This threshold was however ~15% lower for SSc patients with ILD with the GLI equations compared with the previous equations (Table 1).

As other authors have recently remarked, PFTs are used for diagnosis and monitoring at the patient level, and percentage of predicted value is the most common way to express results, to define normal status and/or to grade disease severity [12]. Consistency in interpretation of PFTs from one laboratory to another depends at least in part on the choice of reference equation used to standardise measurements [12]. The GLI was formed in 2008 with the aim of improving reference equations in order to standardise the interpretation of PFTs worldwide. The GLI reference equations have been endorsed by all major international respiratory societies and adopted as the recommended reference equations by many national respiratory societies [12]. Given the crucial role of PFTs in screening for PH in SSc, it was important to make a comprehensive evaluation of the diagnostic value of TLCO and FVC/TLCO with these new equations that are likely to be the most largely used worldwide in the near future.

There are both pragmatic and pathophysiological reasons for using TLCO as a screening test for PH. Firstly, TLCO is a non-invasive test widely available in pulmonary function laboratories where SSc patients are followed. Secondly, TLCO is very strongly correlated with pulmonary capillary blood volume [2]. This is impaired when pulmonary vessels are remodelled, as is the case in SSc-related PH. In contrast, use of the FVC/TLCO ratio is less pertinent from a pathophysiological point of view. It should be remembered that TLCO is calculated by the product of KCO (the transfer coefficient of the lung for carbon monoxide) and VA (the alveolar volume). VA is at least in part dependent on vital capacity, and thus depends on FVC. Taken together, the FVC/TLCO ratio, which by design inversely correlates with TLCO/VA, can be considered as a surrogate of KCO. The FVC/TLCO ratio (instead of

KCO) has been used mainly in order to take into consideration the fact that in SSc, TLCO can be decreased not only because of vascular involvement (i.e., decreased pulmonary capillary blood volume in PH) but also because of a restrictive pattern (i.e., decreased FVC in ILD). Nevertheless, when we took into consideration the presence of ILD – information that is in many cases available in patients with SSc – we found that the FVC/TLCO ratio did not have a better diagnostic power for PH than TLCO alone; the usefulness of measuring FVC in this context is therefore unclear.

In conclusion, we provide here cut-off values obtained with the latest GLI prediction equations for the screening of pulmonary hypertension. For this purpose, we suggest taking into account TLCO only (and not the FVC/TLCO ratio), with a cut-off of 70% predicted (or a z-score of -2.00) in SSc subjects without ILD and of 50% predicted (or a z-score of -3.50) in SSc patients with ILD.

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TABLE 1 Performance of transfer factor of the lung for carbon monoxide and of forced vital capacity with different thresholds for detecting the probability of pulmonary hypertension in patients with systemic sclerosis, with or without interstitial lung disease (ILD)

	SSc patients **without ILD**						SSc patients **with ILD**					
	AUC [95% CI]	Cutoff	Se %	Sp %	PPV %	NPV %	AUC [95% CI]	Cutoff	Se %	Sp %	PPV %	NPV %
TLCO % pred (Crapo)	0.89 [0.84-0.95]	60 %	78	84	26	98	0.76 [0.68-0.84]	55 %	83	58	26	95
TLCO % pred (GLI)	0.91 [0.86-0.95]	70 %	83	82	26	98	0.76 [0.68-0.84]	52 %	74	72	32	94
TLCO z-score (GLI)	0.90 [0.85-0.95]	-2.02	87	79	23	99	0.74 [0.66-0.82]	-3.55	77	66	28	94
		-1.96	87	77	22	99		-1.96	91	43	22	97
		-1.64	87	72	19	99		-1.64	94	36	20	97
FVC % pred/TLCO % pred (Quanjer/Crapo)	0.86 [0.77-0.95]	1.66	77	87	29	98	0.73 [0.65-0.81]	1.69	80	60	26	94
FVC % pred/TLCO % pred (GLI)	0.87 [0.79-0.95]	1.50	77	87	30	98	0.73 [0.65-0.81]	1.45	71	67	27	93

AUC: area under the receiver operating characteristic (ROC) curve; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; TLCO: transfer factor of the lung for carbon monoxide; FVC: forced vital capacity; % pred: percentage of the predicted value; GLI: Global Lung Initiative. z-score = -1.96: results from 2.5% of healthy individuals will be below a cut-off identified as the lower limit of normal (LLN). z-score = -1.64: results from 5% of healthy individuals will be below a cut-off identified as LLN.