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Impact of anticentromere antibodies on pulmonary function test results in patients with systemic sclerosis without established or suspected pulmonary disease

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Abstract

Pulmonary arterial hypertension (PAH) occurs in approximately 10% of patients with systemic sclerosis (SSc). Annual screening with pulmonary function tests (PFT) is recommended to help identify those patients at risk of PAH. We have noted that patients with SSc who carry anti-centromere autoantibodies (ACA) often have PFT abnormalities, in the absence of clinical evidence of PAH. To evaluate this further, we undertook a retrospective case-control study evaluating PFT results in patients with SSc in whom pulmonary complications have neither been diagnosed nor suspected. Patients were divided according to ACA carriage and groups compared for PFT results. The median forced vital capacity (FVC) was higher in ACA positive patients (106% vs. 93%, p=0.004). The gas transfer factor (TLco) was significantly lower in the ACA group (62.5% vs. 71%, p=0.013). The resulting FVC:TLco was significantly higher for ACA positive vs. ACA negative patients with SSc (1.70 vs. 1.29, p<0.001). Our findings suggest patients carrying ACA, without established or suspected pulmonary complications, have PFT abnormalities consistent with indolent increased pulmonary vascular resistance despite the majority of such patients not subsequently developing PAH. The long-term sequalae of PFT abnormalities in those patients with ACA who do not subsequently develop PAH is unknown.

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Introduction

Pulmonary arterial hypertension (PAH) is a recognised complication of systemic sclerosis (SSc) with an estimated prevalence of between twelve and fifteen percent (1, 2). Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure of >25mmHg at rest with a pulmonary capillary wedge pressure of less than or equal to 15mmHg and a pulmonary vascular resistance greater than 3 Wood units (3). Assessment of pulmonary arterial pressure (PAP) requires invasive right heart catheterisation (RHC) which has led to the emergence of non-invasive techniques, such as trans-thoracic echocardiography (TTE), as screening tools in the assessment of possible PAH. Annual assessment of PFT and TTE is recommended as screening for PAH in asymptomatic patients with SSc (4). We have noted that patients with SSc who carry anti-centromere autoantibodies (ACA) often have pulmonary function test abnormalities in the absence of clinical evidence of PAH. To confirm these observations, we have undertaken a retrospective case-control study evaluating PFT results of SSc patients, with or without ACA, in whom pulmonary complications have neither been diagnosed nor suspected.

Materials and Methods

A retrospective review of all patients with systemic sclerosis who had attended out-patient clinic over the previous year was undertaken. Case notes of patients who had provided written consent for inclusion on our CTD database were reviewed. The use of such retrospective clinical data has received approval from the Bath Research Ethics Committee. Notes were scrutinised for autoantibody specificity, age, most recent PFT and TTE results, and extent of cutaneous involvement according to the LeRoy and Medsger criteria.(5) We were unable to verify the presence of respiratory symptoms due to inconsistent documentation. Patients with established ILD

(confirmed on HRCT) or PAH (mean PAP at RHC of >25mmHg) were excluded from analysis. Similarly, patients awaiting investigation for these complications were excluded from subsequent analysis. The remaining patients were divided according to ACA carriage and a comparison of clinical features and PFT results from the 2 groups was undertaken.

Statistical analysis

All data is presented as median [IQR] unless otherwise stated. All PFT data is reported as % predicted. The Mann Whitney U test was used to compare the distribution of values across ACA positive and ACA negative patient populations. All tests were 2-tailed and a p value of <0.05 was considered statistically significant.

Results

The case-notes of 93 patients with SSc were reviewed. Thirty patients were excluded; 17 with ILD, 9 with PAH, 2 with coexistent ILD and PAH, and 1 patient who was awaiting RHC assessment for possible PAH. One patient with systemic sclerosis secondary to post-bone marrow transplantation graft versus host disease was also excluded. Of the remaining 63 patients, 34 patients (53.9%) were ACA positive. The remainder carried a variety of anti-nuclear antibody (ANA) specificities which included anti-Scl-70 (n=5), anti-U3-RNP (n=4), anti-PM-Scl (n=3) anti-U1-RNP (n=2), anti-RNA Polymerase III (n=1), anti-Th/To (n=1), other SSc-related ANA (n=4), uncharacterised ANA (n=8) and one patient with negative ANA (n=1) The majority of patients in each group had limited cutaneous involvement (33/34 vs. 27/29, *p*=0.59). As expected, the median age was higher in the ACA group (63 vs. 57 years, *p*=0.031).

Fifty-nine patients (59/63, 93.6%) had undergone previous PFTs (a median number of 231 [147-523] days prior to assessment). The median FVC was higher in patients carrying ACA (106% [21.5] vs. 93% [18.75], *p*=0.004). The TLco meanwhile was significantly lower in the ACA group (62.5% [14.75] vs.

71% [16.65], p=0.013). The resulting FVC:TLco was significantly higher in the ACA group (1.7 [0.45] vs. 1.29 [0.30], p<0.001, Figure 1.). Fifty-nine patients (59 /63, 93.6%) had undergone a previous echo (median of 364 [144-659] days prior to assessment). An estimated RVSP was reported in 22/59 (37.3%) of cases (n=17 for ACA positive and n=5 for ACA negative patients). The median estimated RVSP on TTE, when available from the TTE report, did not differ between groups (24 [11] mmHg vs. 30 [12]mmHg, p=0.45).

Discussion

PFT findings have been shown to be major predictors of PAH in SSc, particularly when the FVC:TLco ratio exceeds 2.0 (2, 7). To our knowledge, this is the first case-control study to evaluate the influence of ACA-carriage on PFT results in patients with SSc, in whom pulmonary disease has neither been diagnosed nor suspected. In our cohort ACA carriage was associated with a higher FVC, lower TLco and an elevated FVC:TLco. The higher FVC may be explained by a lower prevalence of sub-clinical lung fibrosis in patients with ACA. Alternative explanations for the apparent supranormal FVC in ACA positive patients could be sought from further studies incorporating imaging assessment of these patient groups. The reduced TLco and elevated FVC:TLco are suggestive of sub-clinical pulmonary vasculopathy in patients carrying ACA.

The major limitation of this study is our inability to report PFT associations with a more robust assessment of dyspnoea and exercise tolerance. Nonetheless, we carefully excluded all patients with established pulmonary disease and those in which pulmonary complications had been suspected. Furthermore, the case notes of all patients with an FVC:TLCO ratio >2.0 were scrutinised to ensure that there were no additional grounds for further investigation of this finding. It could be argued that our findings include a number of patients carrying ACA who will subsequently develop established PAH. Whilst this is possible, previous studies have shown that the frequency of PAH is similar in ACA-positive and ACA-negative patients with SSc (6). Furthermore, the ACA-negative group comprised a large number of patients

with anti-nucleolar auto-antibodies (17.2%) who have a comparable, if not greater, risk of future pulmonary vascular complications (2). The TTE data did not suggest the ACA-positive group were more likely to develop PAH than the ACA-negative group, although estimated RSVP values were only available in 37% of assessments, highlighting an important limitation of TTE screening for PAH in SSc.

Our findings suggest patients with ACA, without pulmonary complications, have PFT abnormalities consistent with indolent increased pulmonary vascular resistance, despite the majority of these patients not going on to develop PAH. The long-term sequalae of PFT abnormalities in patients with ACA who do not subsequently develop PAH, is unknown.

References

1.   Mukerjee D, St George D, Coleiro B, Knight C, Denton CP, Davar J, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis. 2003 Nov;62(11):1088-93.
2.   Steen V, Medsger TA, Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. Arthritis Rheum. 2003 Feb;48(2):516-22.
3.   McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation. 2009 Apr 28;119(16):2250-94.
4.   Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. Heart. 2008 Mar;94 Suppl 1:i1-41.
5.   LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr., et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988 Feb;15(2):202-5.
6.   Steen VD, Powell DL, Medsger TA, Jr. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. Arthritis Rheum. 1988 Feb;31(2):196-203.
7.   Hsu VM, Moreyra AE, Wilson AC, Shinnar M, Shindler DM, Wilson JE, et al. Assessment of pulmonary arterial hypertension in patients with systemic sclerosis: comparison of noninvasive tests with results of right-heart catheterization. J Rheumatol. 2008 Mar;35(3):458-65.

Figure 1. Differences in the FVC:TLco ratio in patients who are ACA positive and ACA negative. The median, interquartile range and range are represented by the horizontal bar, box plots and whiskers respectively. FVC, forced vital capacity; TLco, gas transfer factor; ACA, anticentromere antibodies.