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Letter to the Editor re: Combined pulmonary fibrosis and emphysema in scleroderma-related lung disease has a major confounding effect on lung physiology and screening for pulmonary hypertension

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Dear Editors

We heartily applaud Antoniou et al for this important query into these poorly understood associations in the natural history of systemic sclerosis (SSc) cardiopulmonary manifestations. The authors found that SSc patients with combined pulmonary fibrosis and emphysema (CPFE) had lower diffusion capacity (DL_{CO}) and higher $FVC\%/DL_{CO}\%$ ratios than SSc patients with isolated interstitial lung disease (ILD) (1). Although not based on right heart catheterization (RHC) hemodynamics, these findings raise key concerns which may impact clinical trials and practice. We would like to introduce these additional points.

Regarding spirometry between the groups, it is striking that forced vital capacity (FVC), a heavily relied upon clinical trial measure in SSc-ILD (2), was not lower in the SSc-CPFE group despite having a larger extent of ILD than the patients without emphysema. This is consistent with prior CPFE descriptions, which have demonstrated relatively normal FVC values despite significant ILD, perhaps due to a balance of restriction and gas trapping which preserves lung volumes (3). The authors feel that the presence of emphysema is unlikely to confound the use of FVC as a prognostic variable in SSc-ILD, but these relatively normal lung volumes may lead to under recognition of ILD when PFTs are used as a screening test. Also, using change in FVC as an outcome measure may be influenced by

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these PFT differences, and prospective study is warranted to determine change in FVC over time in this unique cohort.

Regarding risk for PH and CPFE, though the DL_{CO} and FVC/DL_{CO} ratios seen in SSc-CPFE may be caused by the presence of emphysema itself, it is equally plausible that SSc-CPFE patients more commonly have pulmonary hypertension or more severe PH than the non-CPFE SSc-ILD cohort. In the non-connective tissue disease (CTD) CPFE literature, approximately 50% of CPFE patients have PH (3) which tends to be severe (4,5). In fact, patients with CTD-CPFE (predominantly SSc and rheumatoid arthritis) had more severe elevations in estimated PAP compared to isolated CTD-ILD without emphysema (6). Although in this study there was no statistically significant difference in echo-defined PH rates between the two cohorts, PH occurred at 50% higher rates in the SSc-CPFE group compared to the SSc-ILD without emphysema group (24% vs. 16%); actual RHC-defined PH rates and the severity of existent PH were not reported.

Thus, rather than disregarding an elevated $FVC\%/DL_{CO}\%$ ratio in SSc patients with CPFE as being confounded by emphysema, perhaps this patient cohort should be screened even more aggressively for PH development. Instead of questioning the reliability of gas transfer and $FVC\%/DL_{CO}\%$ ratio as a screening variable, this study may suggest further support for RHC despite non-supportive echocardiogram findings. In the DETECT cohort, 20% with RHC-confirmed SSc-PH had a TRJ less than 2.5m/s (thus, with high likelihood of falling well below the PASP cutoff of 40mmHg in the Antoniou study); and as high as 7% in the DETECT cohort had an undetectable TRJ (7). This study also prompts consideration that gas transfer variables may demonstrate superiority as non-invasive predictors of the development or presence of PH in SSc. Ultimately, without RHC data the differences found in DL_{CO} and $FVC\%/DL_{CO}\%$ ratio between these groups cannot be confidently attributed to a higher rate of PH or more severe elevations in PAP in the SSc-CPFE group nor, without longitudinal follow-up, can the risk of having PH or *future development* of PH be determined. We look forward to future studies utilizing RHC in this important patient cohort, along with serial follow up for PH development and FVC change.

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