ESAT-6 and complement fixation protein-10 (CFP-10) have been suggested as standard triggers for IFN-γ release from lymphocytes, but the employment of BCG and PPD for this purpose warrants further research. The higher specificity of ESAT-6 and CFP-10 (ESAT-6 in this study) as compared with other triggers is reflected in the authors’ observation that among the 100 patients with tuberculosis skin test induration of <5 mm, only 7% showed IFN-γ production in response to ESAT-6. On the other hand, 74% of the BCG subgroup and 65% of the PPD subgroup had positive IFN-γ production. This rather highlights the redundant nature of in vitro and in vivo assays, provided the antigens used are only ESAT-6 and CFP-10, although the higher specificity of these IFN-γ release assays is well proven.

Latent TB infection has been a gray area for decades now because of the heterogeneous prevalence of the disease and infection around the globe. We need further studies to reach definite conclusions.

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Response

To the Editor:

Two interesting points are raised by Drs Khurana and Khurana about our study in CHEST (May 2010). As correctly pointed out, we did not attempt to verify the Bacillus Calmette-Guérin (BCG) vaccination status of our study subjects. However, BCG vaccination at birth has been mandatory in the study area since 1975, and vaccine coverage in the Western Cape is very high at 90% (95% CI, 90%-99.5%). Hence, we can safely assume that the majority of our study subjects were BCG vaccinated.

The other point concerns redundancy of in vivo and in vitro assays. Our study was not designed to evaluate the possible redundancy of cutoff points and positive vs negative responses. Rather, we focused on the correlation in the extent of responsiveness between assays and detected low correlation between assay readouts. From this, we inferred biologic nonredundancy of the different assays. We agree that further studies into the mycobacterial host responses, including the immune assays currently used for diagnosis of latent TB infection, are needed.

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Is Pulmonary Arterial Hypertension Really a Late Complication of Systemic Sclerosis?

To the Editor:

We read with great interest the report by Hachulla et al in CHEST (May 2009) regarding the time of presentation of pulmonary arterial hypertension (PAH) during the course of scleroderma disease (SSc). In their cohort of 75 patients with SSc-associated PAH (PAH-SSc), the authors found the following: (1) 55% of the patients had early-onset PAH (ie, within the first 5 years of SSc-related non-Raynaud symptoms); (2) these patients were older at the time of SSc diagnosis and presented with more severe hemodynamics, although functional class (FC) and mortality outcomes were similar to those of patients with late-onset PAH; (3) Diffusing capacity of the lung for carbon monoxide (DLco) <35% and FC class 4 were the only predictors for survival
in this cohort; and (4) There was a relatively high proportion (22%) of patients with diffuse subtype SSc (dSSc).

We recently described survival outcomes of a cohort of 76 patients with PAH-SSc followed at our center. Although the proportion of early-onset PAH in our cohort was lower (36%), 25% of these patients were diagnosed with PAH within the first 3 years and 11% within the same year of SSc diagnosis. Similar to findings by Hachulla et al, our patients with early-onset PAH were older at the time of SSc presentation compared with patients developing PAH later (59 vs 43 years; P < .01); however, there were no differences in hemodynamics or survival between the groups. Nonetheless, findings from both studies reinforce the need for early screening for PAH in these patients.

In addition, in the study by Hachulla et al, DLco < 35% and FC were the only predictors for survival. This finding may be biased by inclusion of patients with more than mild interstitial lung disease (ILD), because criteria for excluding ILD were based only on FVC or total lung capacity < 60% without consideration of radiologic findings. ILD clearly has an impact on survival in SSc, in particular when complicated by pulmonary hypertension, as recently demonstrated. Thus, one cannot exclude the fact that poorer outcomes related to DLco < 35% might reflect more significant ILD than suggested by pulmonary function tests alteration alone. In this context, the relatively high proportion of patients with dSSc (22%), compared with other studies of PAH-SSc (8%-13%) with stricter criteria for ILD exclusion, may indicate inclusion of patients with significant ILD (more common with this SS subset).

In summary, we wish to emphasize the need for a rigorous phenotypic characterization in order to identify the exact factors responsible for very poor outcomes in PAH-SSc, while avoiding confounders.

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Response

To the Editor:

The correspondence by Campo et al regarding our recent publication in CHEST (November 2009) emphasizing that systemic sclerosis-associated pulmonary arterial hypertension (PAH-SSc) may occur early in the course of the disease (ie, within the first 3 years of systemic sclerosis [SSc]-related, non-Raynaud phenomenon symptoms) is of great interest. Indeed, for the first time, two teams, one in the European Union and one in the United States, independently have shown that PAH-SSc may be an early complication of SSc in up to one-half of the cases. As a consequence, we both recommend that screening for pulmonary arterial hypertension (PAH) should be considered immediately after the occurrence of the first SSc-related non-Raynaud phenomenon symptom.

Campo et al then focus their discussion on the threshold of the diffusion capacity of carbon monoxide (DLco) (35% of predicted value) that we have found to be an independent risk of death in our population of patients with PAH-SSc (hazard ratio, 2.587; 95% CI, 1.029-6.501; P = .04). Obviously, DLco may be reduced not only because of pulmonary vascular disease but also because of comorbid interstitial lung disease (ILD), which is not uncommon in such patients. Distinguishing pure PAH from pulmonary hypertension (PH) due to hypoxia associated with lung fibrosis in patients with SSc may be challenging, and both conditions are sometimes associated. Patients with evidence of ILD, as demonstrated by abnormal high-resolution CT scans of the chest and total lung capacity (TLC) ranging from 60% to 70% with elevated mean pulmonary arterial pressure > 25 mm Hg at rest, were kept in the analysis set in case of the absence of extensive ILD or severe lung fibrosis, based on the expertise of our team, because they were considered more likely to have PAH-SSc rather than ILD-associated PH. We agree that such patients may be difficult to classify and that some may have quite severe ILD, which could contribute to PH. In order to address this comment, we have reanalyzed our data after exclusion of all patients with a TLC < 70% and found a 40% cutoff of predicted DLco value to be an independent risk of death at 3 years in patients with PAH-SSc (hazard ratio, 11.25; 95% CI, 1.38-91.60; P = .02). These consistent results suggest...