Bronchiolitis obliterans syndrome leads to a functional deterioration of the acinus post lung transplant

ABSTRACT

Bronchiolitis obliterans syndrome (BOS) limits long-term survival of lung transplant recipients, and airflow obstruction in these patients likely originates in the small airways. 61 double lung transplant recipients performed multiple breath nitrogen washouts to obtain indices of acinar and conductive ventilation heterogeneity (Sacin, Scond). There was a significant association of BOS status with Sacin (Kruskal-Wallis; p<0.001) but not with Scond (p=0.1). These results demonstrate that it is the structural alteration of the terminal bronchioles, generating ventilation heterogeneity at the level of the diffusion front, and not the bronchioles located more proximally, that is driving the airflow obstruction that determines BOS status.

METHODS

Subject recruitment

Sixty-one bilateral lung transplant recipients (40 male and 21 female) with varying degrees of BOS were recruited for the study.

Multiple breath nitrogen washout (MBNW)

MBNW provides indices that can separate gas mixing in the airways at the level of the diffusion front (Sacin)—likely to be located around the acinar entrance—and that generated more proximally (Scond); an increase in either Sacin or Scond reflects an increased degree of ventilation heterogeneity, that is, a deterioration in lung function.

RESULTS

Individual values of Sacin and Scond against BOS stage can be appreciated from figure 1. All subjects with a BOS stage ≥1 showed a significantly greater Sacin versus BOS=0 patients, and BOS=3 patients showed significantly greater Sacin than BOS=1 or BOS=2 patients (figure 1A). There was no significant dependence of Scond on BOS status (figure 1B). There was a strong correlation of FEV₁/FVC with Sacin (Spearman rho=-0.72; p<0.001) but not with Scond (p=0.097).

DISCUSSION

We have identified a functional correlate of airflow obstruction in patients who fit the strict definition of BOS ¹ by observing increased acinar ventilation heterogeneity (Sacin) with BOS stage. Based on mathematical modelling, Sacin is assumed to be generated around the terminal bronchioles,³ hence our functional findings are in agreement with recent observations from micro CT on explanted lungs obtained from six patients with BOS undergoing retransplantation.⁴ In this preliminary study published in abstract form,⁴ obliterating lesions are reported in the airways immediately proximal to the terminal bronchioles, that is, preterminal bronchioles, of patients with BOS. Beyond these, a normal airway structure leading into the alveolated zone was observed. One could speculate that excessive narrowing of preterminal bronchioles airways shifts the diffusion front, which is the basis of Sacin measurement. Coincidently, recent mathematical modelling work published in abstract form by Murphy et al ⁵ indicated that even with up to 50% airway narrowing in the preterminal bronchioles the diffusion front hardly moved (by ~1 generation proximally). This provides compelling support to the fact that the measured Sacin increases with increasing BOS stage are indeed the result of worsening ventilation heterogeneity generated at the level of the acinar entrance.
CONCLUSION

In a cross-sectional study, the reduction in FEV1 seen with BOS is associated with functional changes generated around the acinar entrance.

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