A spirometric journey following lung transplantation
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Abstract
Spirometry is regarded as the primary tool for the evaluation of lung function in lung transplant (LTx) recipients. Spirometry is crucial in detecting the various phenotypes of chronic lung allograft dysfunction (CLAD), including restrictive allograft syndrome (RAS) and bronchiolitis obliterans syndrome (BOS) – note that these phenotypes potentially have different etiologies and therapies. Following LTx for idiopathic pulmonary fibrosis, a 60-year-old male recipient’s lung function began to gradually improve, peaking at 5 months post-LTx. Subsequently, with increasing impairment of graft function, the diagnosis of BOS was made. A second LTx was performed and lung function subsequently began to increase again. Unfortunately, another year on, lung function deteriorated again – this time due to the development of RAS, antibody-mediated rejection was implicated as the possible underlying cause. This case report highlights the importance of spirometry in assessing the patterns of CLAD following LTx.

Introduction
Following lung transplant (LTx), spirometry is the most commonly utilized method of monitoring the function of the allograft. This convenient measurement of pulmonary function can be assessed at each clinic visit, as a sentinel for the early detection of allograft dysfunction. The development of chronic rejection remains the major barrier to long-term survival following LTx. The term chronic lung allograft dysfunction (CLAD) [1] has recently been introduced to encompass the differing phenotypes of chronic rejection including bronchiolitis obliterans syndrome (BOS) [2] and the recently described restrictive allograft syndrome (RAS) [3]. These CLAD phenotypes are defined primarily by their differing patterns of abnormal spirometry and further characterized by their associated histological and radiological features. To illustrate the pivotal role that spirometry plays in defining both the success and the failure of LTx, we describe a LTx recipient in whom abnormal patterns of spirometry were critical in defining the cause of allograft dysfunction following both his first and second LTx.

Case Report
A 60-year-old man with idiopathic pulmonary fibrosis (IPF) was referred in August 2010 for consideration of lung transplantation. Consistent with the underlying diagnosis, he developed a progressive restrictive decline in pulmonary function tests and a typical computed tomography (CT) scan (Fig. 1A). A bilobar LTx (right and left lower lobes) was performed in August 2012 and histopathology of the explanted lung confirmed the diagnosis of IPF.

Despite a prolonged period of recovery, at 3 months post-transplant, spirometry demonstrated a forced expiratory volume in one second (FEV1) of 1.87 L (56% predicted) and 2.26 L (52% predicted), respectively. Spirometric measures continued to improve, with FEV1 peaking after 5 months at 2.12 L (64%) and FVC peaking after 12 months at 2.81 L (64%). This first year was complicated by recurrent infection, necessitating...
alterations in immunosuppression and hospital admissions for intravenous antibiotics. Following the spirometric peak at 5 months, he developed progressive shortness of breath and decreased exercise tolerance, with a progressive and irreversible decline in spirometry in an obstructive pattern with a FEV₁ nadir of 1.17 L (30%). Further investigation ruled out infection or acute rejection, and he was diagnosed with CLAD due to BOS. Despite treatment, including augmentation of immunosuppression, the progressive decline in pulmonary function continued consistent with the diagnosis of BOS and he was listed for re-LTx (Fig. 1B). In February 2013, 23 months after the initial LTx, a second size-matched bilateral LTx (without lobar cutdown) was performed with histopathology of the explanted lung confirming the diagnosis of obliterative bronchiolitis, the histopathological hallmark of BOS.

Postoperative recovery from the second transplant was complicated by gastrointestinal hemorrhage and the need for large volume blood transfusion. Three months post-retransplant, his lung function peaked with a FEV₁ and FVC of 1.90 L (58%) and 2.27 L (52%), which remained stable for the following 8 months. One year post-retransplant, he developed antibody-mediated rejection as evidenced by the development of de novo anti-HLA donor-specific antibodies, radiologic infiltrates, and declining lung function in a restrictive pattern. Augmentation of immunosuppression including plasmapheresis has not arrested the decline in pulmonary function with spirometry, radiology, and transbronchial biopsy changes, suggestive of RAS as the cause of his CLAD (Fig. 1C). The longitudinal changes in spirometry from pretransplant through the course of his two lung transplants are shown in Figure 2.

Discussion

Historically, the histological description of obliterative bronchiolitis has been synonymous with chronic lung allograft rejection. Its clinical correlate BOS describes the deterioration in graft function defined spirometrically as persistent airflow obstruction. BOS is thought to occur as a result of damage to the respiratory epithelium resulting in a fibroproliferative response [2]. The radiological findings of BOS are those of small airways pathology, namely bronchial dilatation, bronchial wall thickening, and air trapping (mosaic pattern). Spirometry and radiology suggest RAS as the cause of allograft failure following the second transplant and an association with antibody-mediated rejection as a possible etiological factor (Fig. 1C).

Recently, it has become apparent that there are other phenotypes of chronic rejection beyond those described by BOS and thus the term CLAD was introduced to describe all causes of chronic lung failure. RAS is characterized by restrictive physiology and changes on imaging inconsistent with BOS, including the presence of ground glass and interstitial fibrosis [3]. Spirometry and radiology suggest RAS as the cause of graft failure following the second transplant and an association with antibody-mediated rejection as a possible etiological factor (Fig. 1C).

In summary, using spirometry to measure lung function is critically important in lung transplantation, with regard
to assessing both the timing for transplant prior to surgery and the allograft function following transplant. This case illustrates that maximal lung function is typically not achieved for many months following transplant, largely related to issues such as pain, wound healing, and deconditioning. Importantly, however, changes in spirometry are often the first sign of a failing graft and the development of either obstructive or restrictive ventilatory defects differentiates the different forms of CLAD.

Disclosure Statements
No conflict of interest declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

References

Figure 2. Spirometry course overview. Significant deviations in both forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) over the 4-year period. Notably, improvements in both values are evident following first and second lung transplantations. Subsequent decreases are prominent, highlighting involvement of chronic lung allograft dysfunction.