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Calling Time on Spirometry: Unlocking the Silent Zone in Acute Rejection after Lung Transplantation

Lung transplantation is the only effective treatment for patients with end-stage lung disease, yet median survival is only 6 years and significantly shorter than that observed with other solid-organ transplants (1). Acute cellular rejection (ACR) causing graft failure is the major cause of death in the first year, and is also a risk factor for chronic lung allograft dysfunction (CLAD) (2). The International Society for Heart and Lung Transplantation reported that 28% of lung transplant recipients experience at least one episode of treated ACR within the first year (1). Graft rejection and transplant failure place an immense burden on both patients and healthcare systems, so the detection and treatment of ACR is paramount.

Transplant centers monitor patients routinely with spirometry indices, primarily FEV_1. Both ACR and CLAD begin in the small airways, yet FEV_1 only gives information relevant to large- and medium-sized airways and is rather insensitive and nonspecific to changes within the small airways (3). Progressive immunopathological disease in the "silent zone" may therefore go unnoticed until it is significantly advanced before a change in FEV_1 occurs or the patient experiences symptoms (4). The role of routine surveillance bronchoscopy in screening asymptomatic patients for histopathological ACR remains controversial and varies among transplant centers (5). There is a real need to track changes in the small airways and lung parenchyma, preferably noninvasively, to identify disease early and thus allow a prompt diagnosis and timely intervention, but efforts have been limited by the lack of accurate techniques and accessible tools.

Recent years have seen the development and validation of physiological tests of small airway function, and commercially available machines that can monitor the lung periphery are being used in clinical practice (6). Indices of ventilation distribution reflecting small airway dysfunction have been studied in lung transplant recipients (7, 8) and shown to be abnormal 1 year before a 20% decrease in FEV_1 (9). Oscillometry has been available for over 50 years and can be used to detect small and large airway disease in patients with obstructive lung disease (10). Low-frequency signals (5 Hz) penetrate out to the lung periphery (all airways), whereas high-frequency signals (19 Hz) only reach the proximal airways, such that resistance at 5 Hz (R5) reflects the total airway resistance and the difference (R5–19 Hz) probes the distal smaller airways (Figure 1) (11). Studies of oscillometry in lung transplant recipients are limited.

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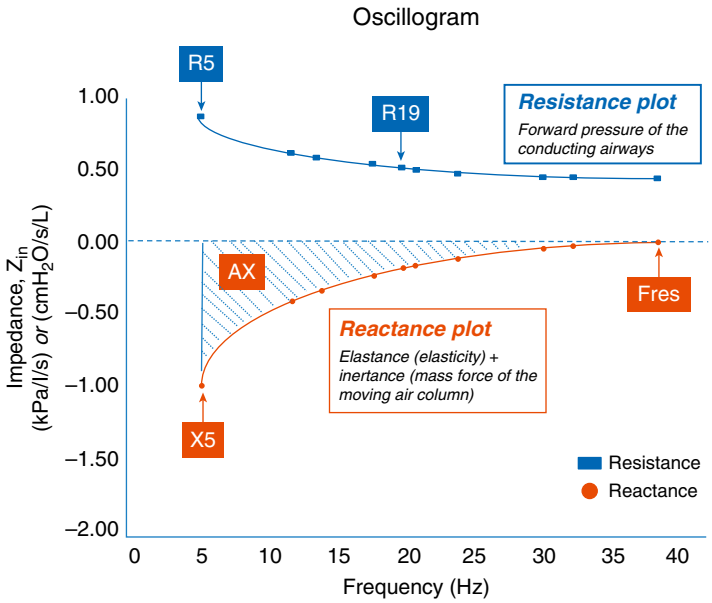

Figure 1. An oscillogram depicting key lung mechanics indices: resistance (R), reactance (X), resonant frequency (Fres), and area under the reactance curve (AX).

In this issue of the *Journal*, Cho and colleagues (pp. 1536–1544) report their work to characterize oscillometry measurements in clearly defined grade 2 ACR compared with "no acute rejection" grade 0 ACR, both established on transbronchial biopsy (12). They investigated 138 lung transplant recipients who had completed a 3-month follow-up with spirometry, oscillometry, and surveillance transbronchial biopsies for rejection episodes. Fifteen patients experienced 16 episodes of grade 2 ACR, and in 15 of 16 rejection episodes, the oscillometry distal airway measurement of R5–19 was markedly abnormal and significantly different from that observed in grade 0 ACR episodes (64 episodes in 44 patients), and occurred at the time when FEV_1 was either stable or improving. This implies that ACR of the transplant would have been missed if the patients had been monitored with spirometry alone or by clinically driven transbronchial biopsies that relied on a fall in FEV_1.

In addition, the authors reported that 2 weeks after transbronchial biopsy in patients who had received treatment with high-dose methylprednisolone daily for grade 2 ACR, R5–19 had improved and was similar to values in the grade 0 ACR group, suggesting resolution of grade 2 ACR. These observations provide a logical rationale for treating grade 2 ACR established on transbronchial biopsy, even with an unaltered FEV_1. Similar findings were obtained with regard to the oscillometry measurement area of reactance, which is the integrated area of the reactance curve between the lowest frequency (X_5) and the resonant frequency, and also reflects the small airways and the soft tissue of the peripheral lung parenchyma (Figure 1).

The data of Cho and colleagues support R5–19 as a valuable airway measurement in lung transplant recipients to provide early evidence of acute rejection, and the utility of oscillometry as an essential adjunct to spirometry in these patients, particularly in centers that do not perform routine surveillance bronchoscopy with transbronchial biopsy. The authors were unable to determine the sensitivity and specificity of oscillometry for detecting acute rejection, which would require a greater number of patients with episodes of grade 2 ACR. Furthermore, the characterization undertaken here was a retrospective diagnosis, and the authors propose to undertake a follow-up validation study to prospectively evaluate the clinical utility, sensitivity, and specificity of oscillometry in predicting grade 2 ACR.

In a broader context, the difficulty in our discipline of respiratory medicine is that we use a routine test, spirometry, to classify, diagnose, and monitor lung disease that is based on a wholly unnatural maneuver of the organ in question. The lungs do not work in a forced exhalation mode; rather, they function with tidal breathing. The dependency of spirometry on a forced expiratory maneuver leads to test variability, resulting in the need to take the best of three measures, as well as the inability of both young and old patients to reproducibly perform the test. The disconnect between FEV_1 and symptoms, exercise tolerance, exacerbations, and quality of life in patients with obstructive airway disease is well recognized, and FEV_1 does not capture the complexity of lung diseases such as chronic obstructive pulmonary disease (13). In contrast, oscillometry assesses the lungs in their natural tidal breathing state and is a simple procedure that can be performed on both young and old patients. Just like the spirogram and flow–volume loop, the "oscillogram" requires pattern recognition to decipher abnormal lung mechanics based on key physiological indices (Figure 1). Although there is a paucity of normal reference values for oscillometry compared with conventional lung function tests, the Global Lung Function Initiative supported by the European Respiratory Society is currently developing reference equations for oscillometry measurements.

With the spirometer now in its 175th year since Hutchinson's pioneering invention and descriptions of "forced expiration" (14), is it not about time that we reconsider our current dependence on spirometry and its role in managing a patient's clinical state

in the context of this work and other respiratory diseases (10)? Graham Hall and Charlie Irvin recently challenged the profession by asking, "As health professionals, do we have an obligation to reflect on what the actual pathophysiology for a specific lung disease is and considering this, look at different physiological outcomes beyond FEV_1?" (15). Indeed, within the realm of lung transplantation, should we call time on our obedience to a test that is "too little, too late"? Being cognizant of the devastating potential consequences for the transplanted patient, we need to embrace and incorporate a more physiologically relevant and structurally accurate noninvasive test to detect the site of pathology early, to finally unleash the noise of the silent zone. ■

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suPAR Surprises as a Biomarker of Invasive Outcomes in Pleural Infection

Pleural infection is a major healthcare burden worldwide. Adhesions and loculations, often present in pleural infection, have fascinated pulmonologists for centuries. Their pathogenesis and best management are still debated.

The fibrinolytic pathway has been the subject of active research, and derangements of the local fibrinolytic system can influence the pathogenesis of pleural organization and fibrotic repair, as reviewed elsewhere (1). The suPAR (soluble urokinase-type plasminogen activator receptor) represents a potential clinical application of the cumulative knowledge gained to date. In this issue of the *Journal* (p. 1545–1553), Arnold and colleagues (2) explore the measurement of suPAR as a new biomarker in pleural infection. Their findings merit further investigation.

suPAR occurs in biologic fluids, including plasma, urine, and pleural fluids, and is proteolytically cleaved from the surface of cells bearing the uPAR (urokinase-type plasminogen activator receptor), which regulates cellular proteolysis, viability, movement, and proliferation (3). It is also possible that an alternatively spliced variant of suPAR may contribute to the suPAR concentrations seen in pleural fluids, as has previously been demonstrated in cancer cell lines (4). suPAR concentrations increase in

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