different disease states, including atherosclerosis, obesity, diabetes, and sepsis (5). These results provide important insights for potential epigenetic therapeutics for IPF treatment. ■

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Using Automated Radiographic Signatures to Prognosticate Chronic Lung Allograft Dysfunction

What Does the Future Hold?

Lung transplantation is a life-saving procedure that is associated with a significant improvement in health-related quality of life and physical function (1, 2). However, at 6.2 years, the median survival of lung transplant recipients worldwide lags behind other solid organ transplant recipients (3). The main contributor to decreased survival is chronic lung allograft dysfunction (CLAD), with about half of transplant recipients developing CLAD within the first 5 years (4, 5). Unfortunately, once CLAD develops, the prognosis is poor, with ongoing loss of function in most patients (5). Thus, early identification of graft injury at the time of potential CLAD, represented by an initial drop of 10–20% from baseline FEV_1, may allow for treatment strategies that may help mitigate graft loss and, potentially, reduce morbidity (5, 6). Presently, there is no effective treatment for CLAD other than retransplantation (5, 7).

The recent International Society of Heart and Lung Transplant consensus statement recommends a high-resolution computed tomography (HRCT) evaluation at the time of potential CLAD (5). Although HRCT is most helpful for excluding non-CLAD causes of lung function decline, the systematic use of HRCT at baseline and at CLAD onset can facilitate the identification of imaging biomarkers for earlier discovery of graft dysfunction, CLAD phenotyping, and prognosis. A promising quantitative approach described by Belloli and colleagues (pp. 967–976) in this issue of the *Journal* is parametric response mapping (PRM) (8). PRM is a voxel-wise analysis of paired HRCT inspiratory and expiratory images to identify both air trapping and parenchymal lung diseases, some of which may not be detectable

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with the human eye. The PRM technique has been applied in patients with chronic obstructive pulmonary disease (9), bone marrow transplant recipients (10), and lung transplant recipients with definite CLAD (11) but has not been previously evaluated in those with potential CLAD.

In this issue of the *Journal*, Belloli and colleagues evaluate the prognostic utility of PRM with HRCT scans in predicting CLAD-free survival and all-cause mortality (8). Building on their previous work using an algorithm developed at their center in lung transplant recipients with definite CLAD (11), the authors applied a cut-off value of PRM $\geq$ 30% to define an abnormal pattern in a retrospective cohort of 61 lung transplant recipients from their center with potential CLAD (FEV_1, 80–90% of baseline). The investigators identified three radiographic signatures: *1*) functional small airway disease (PRM^{fSAD}, 11.5%), *2*) parenchymal disease (PRM^{PD}, 41%), and *3*) normal pattern (PRM^{normal}, 47.5%). CLAD-free survival of the PRM^{fSAD} and PRM^{PD} groups was significantly shorter (approximately 0.5 years for both) than that of the PRM^{normal} group (2 years). This association was independent of transplant type, age, body mass index, and HRCT timing after transplant. Of the patients who underwent bronchoscopy (69%) or transbronchial biopsies (48%), there were no differences observed among PRM groups with respect to infection or acute rejection, which underscores the fact that clinical risk factors of CLAD were not associated with PRM signatures. The investigators also demonstrated the challenges of radiological interpretation, with slight to fair agreement among radiologists and a high prevalence of gas trapping observed in two-thirds of lung transplant recipients. Gas trapping was similar among PRM groups and was not prognostic of CLAD-free survival.

PRM signatures provide novel prognostic information not available from clinical or standard radiological assessments in the evaluation of graft function. Indeed, the PRM analysis was superior to routine radiological assessment, which proved to have limited sensitivity: 41% had PRM changes that were undetectable during visual interpretation by radiologists. Furthermore, radiological assessments only yielded ground glass opacities as the marker associated with CLAD-free survival. The present study highlights the importance of reproducible, quantitative image analysis to improve the characterization of structural changes associated with CLAD phenotypes (12).

There are several limitations that need to be highlighted in the work by Bolleli and colleagues. First, this was a single-center cohort study with a modest cohort size from 2004 to 2016. Second, the PRM application presently lacks external validation; future investigation will be needed to explore the prognostic utility of this radiological application in larger, multicentered cohorts. Third, the investigators compared PRM with other radiological assessments (i.e., gas trapping, nodules, ground glass) but did not have other physiological assessments such as oscillometry, which is known to be a sensitive marker of early small airway changes and acute cellular rejection in lung transplant recipients (13). Furthermore, donor-specific antibodies were not available in the current cohort, which will be an important consideration for future work given their association with CLAD (14). The investigators observed a trend toward differences in body mass index among PRM groups at the time of potential CLAD, which was an important covariate of posttransplant survival. The contribution of body composition to these PRM signatures and graft function requires further study.

The work by Belloli and colleagues provides a novel application of an existing diagnostic tool that could improve clinical care in lung transplantation. It highlights the benefits of using PRM on HRCT to characterize the lung parenchyma for earlier detection of graft injury and prognostication. The ability to apply different assessment techniques to clinical HRCT scans in this population may allow other morphometric parameters, such as body composition (i.e., skeletal muscle mass or adiposity) (15), to be evaluated, which may help delineate the role of body composition in posttransplant survival. Thus, the use of HRCT beyond the traditional radiological assessments is a significant advancement in offsetting the morbidity and mortality associated with CLAD, and PRM may provide an important radiological marker in clinical trials. ■

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Epinephrine Administration Intervals: Seeing the Forest for the Trees

The current pediatric and adult life support recommendations suggest an epinephrine administration interval (EAI) of 3–5 minutes during cardiopulmonary resuscitation (CPR) (1, 2). These recommendations are expert opinion based on the half-life of epinephrine in animal studies, but there are few clinical data about EAI during CPR. Adult observational data are inconsistent, reporting better outcomes with shorter EAI (3), longer EAI (4, 5), or neither (6). A practical approach uses a fixed 4-minute EAI that allows providers to synchronize with the 2-minute chest compressor change, rhythm check, and defibrillation. Thus, pediatric intensivists have a range of choices for a fixed or variable EAI and little evidence to guide their practice.

A 2017 retrospective review of 1,630 pediatric in-hospital cardiac arrests in a large national database related EAI to the rates of return of spontaneous circulation (ROSC) and survival to hospital discharge (7). They calculated EAI as the duration of CPR after the first epinephrine dose divided by the total number of epinephrine doses. ROSC and survival were better with EAIs from 5 to 8 minutes and best with EAIs from 8 to 10 minutes compared with the 1-to-5-minute EAI group. The duration of CPR was longer in the 5-to-8-minute group and longest in the 8-to-10-minute group. The time to first epinephrine administration was 2.4 minutes in all three groups. Worse outcomes were associated with total epinephrine dosage administered. The authors concluded that the administration of less epinephrine with less frequency was associated with better outcomes.

In this issue of the *Journal*, Kienzle and colleagues (pp. 977–985) provide contradictory findings on the association of EAI with outcomes in pediatric cardiac arrest (8). This 2021 retrospective review of an institutional database of 125 pediatric in-hospital cardiac arrests examined the effects of the EAI during CPR on the rates of ROSC, survival to hospital discharge, and return to neurologic baseline (8). Their method for determining the EAI was to round epinephrine administration times to the closest minute and average the intervals from the first epinephrine dose to the end of resuscitation. They compared the frequent administration of epinephrine (EAIs ⩽2 min) with standard EAIs (⩾3 min) and found that frequent epinephrine administration was associated with better rates of ROSC, survival, and return to neurologic baseline. They found that CPR duration was shorter in the frequent epinephrine group and was associated with better outcomes. The time to first epinephrine dose—1 minute in the frequent group and 2 minutes in the standard group—was not statistically different. The authors concluded that more frequent epinephrine dosing (⩽2-min intervals) was associated with better outcomes.

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