Physiology of chronic lung allograft dysfunction: back to the future?

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Chronic lung allograft dysfunction (CLAD) is, in one sense, a term without a true consensus definition, although its common usage in the field of lung transplantation implies a base understanding throughout the community that it describes a lung allograft that does not work (well) [1]. There appears to be general agreement that CLAD most commonly occurs in a time-dependent fashion after transplant and is a harbinger of a foreshortened survival [2]. However, different phenotypes have been described based on a combination of physiological and radiological features [3]. A restrictive ventilatory defect, with or without interstitial pulmonary infiltrates and/or pleural thickening, has the worst prognosis and is also associated with inferior results from attempts at salvage by retransplantation [4]. One curious feature of the natural history of CLAD is the chameleon-like property of morphing from one predominant phenotype to another [5]. Perhaps this bespeaks our simplistic understanding of the root causative mechanisms, but emphasises there is still much to learn about this dominant complication of lung transplantation, which is the major risk factor for death in those who survive the perioperative period. The article by Kneidinger *et al.* [6] in this issue of the *European Respiratory Journal* attempts to fine-tune our insight into CLAD phenotypes and provides valuable information regarding the prognostic value of gas trapping in CLAD. Once again, the precision of pulmonary physiology assessment as a longitudinal tool is shown to provide a useful guide to survival. In this way, repeated measures of a safe and noninvasive test can assist individual patient management by highlighting early trends. Whether effective therapies are currently available is another question, but at least some stratification of those individuals less likely to deteriorate can be carried out. One perennial problem in this type of long-term retrospective single-centre analysis is the potential for variable adherence to testing schedules and the relatively small number of patients in each group. In this case, 20 had restrictive physiology (defined by a 10% reduction in total lung capacity (TLC) from baseline) and 21 had gas trapping (defined as a residual volume/TLC ⩾50%) at CLAD onset. Both of these phenotypes had inferior survival compared with other patients with CLAD who predominantly had bronchiolitis obliterans syndrome (BOS), as defined recently in the Journal [7]. Is this surprising? Although the finding of a poor outcome with gas trapping has not been widely reported previously after lung transplantation, it makes biological sense and resonates with conventional knowledge that accepts that gas trapping is associated with an increased risk of dynamic hyperinflation (an increase in TLC) and thereby an increase in mechanical load on the inspiratory muscles, reduced mechanical advantage and increased oxygen cost of breathing [8]. The result is impaired exercise performance and greater levels of dyspnoea. Ultimately, respiratory cachexia and hypercapnoeic respiratory failure develop, with death commonly from respiratory tract infection. Conversely, there is now a building body of evidence regarding

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the adverse prognosis of restrictive CLAD – whether associated with pleuroparenchymal disease or not. Upper lobe fibrosis was first described by Konen *et al.* [9] in 2003, and later, restrictive allograft syndrome (RAS) was described by Sato *et al.* [10], combining changes in TLC with computed tomography (CT) evidence to examine outcomes. A number of other authors have employed different physiological criteria of restriction, not always measuring lung volumes, and broadly found similar outcomes [11]. There are nuances of course, and while a case can be made for the expedience of measuring lung mechanics alone (spirometrically determined variables) to assess likelihood of the presence of a restrictive defect, it is refreshing to see the diligence of the current report, where full lung function testing was performed at least every 3 months using body plethysmography – recognised as the preferred laboratory tool for assessing lung volumes, as opposed to helium dilution, which may underestimate trapped gas and TLC.

All groups cannot afford such rigorous serial evaluation, or so it would seem, but weighed against the cost of CT scanning and bronchoscopy, perhaps a favourable cost–utility ratio could be determined.

Why is it so? What causes CLAD and are there different mechanisms for each phenotype? Likely there are, and we do have some specific outcomes. Both timing and severity of the development appear prognostically important and therein lies a clue (or two). As does distribution [12]. We know that severe primary graft dysfunction is a significant risk factor, as is cellular rejection, particularly lymphocytic bronchiolitis, but also antibody-mediated rejection – both HLA-related and associated with autoantibodies – although the full picture is only beginning to emerge [13–17]. Even the air that we breathe is important, let alone community-acquired viral infection [18–22]. Perhaps matching therapies to individual recipients may one day provide a tailored approach with greater efficacy as there remains a firm conviction that one size does not fit all. It is always possible that some commonly employed immune suppressive therapies may be profibrotic in some individuals with specific genetic polymorphisms, and this may in part explain the variable incidence of restrictive physiology reported throughout the globe [23].

How should we incorporate the knowledge gained from the current study? In practice, it is a reminder of what we always knew. A deep understanding of pulmonary physiology with sensitive pattern recognition informs function of the lung, and perhaps nowhere else do we have such a predictable and compressed model of lung dysfunction to examine prospectively. The gauntlet has been thrown down as a challenge to us all to rethink our somewhat antediluvian approach to lung physiology of the pulmonary allograft and develop specific approaches to specific phenotypes based solidly on mechanistic principles, thereby availing our patients of the panoply of diagnostic and therapeutic strategies available at a stage where stabilisation may be associated with acceptable quality-of-life outcomes.

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