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CONSENSUS STATEMENT

Chronic lung allograft dysfunction: Definition and update of restrictive allograft syndrome—A consensus report from the Pulmonary Council of the ISHLT

Allan R. Glanville, MBBS, MD,[a,1] Geert M. Verleden, MD, PhD,[b,1] Jamie L. Todd, MD,[c] Christian Benden, MD, FCCP,[d] Fiorella Calabrese, MD,[e] Jens Gottlieb, MD,[f] Ramsey R. Hachem, MD,[g] Deborah Levine, MD,[h] Federica Meloni, MD, PhD,[i] Scott M. Palmer, MD, MHS,[c] Antonio Roman, MD,[j] Masaaki Sato, MD, PhD,[k] Lianne G. Singer, MD, FRCPC,[l] Sofya Tokman, MD,[m] Stijn E. Verleden, PhD,[b] Jan von der Thüsen, MBBS, PhD,[n] Robin Vos, MD, PhD,[b] and Gregory Snell, MD[o]

From the [a]Lung Transplant Unit, St. Vincent's Hospital, Sydney, New South Wales, Australia; [b]University Hospital Gasthuisberg, Leuven, Belgium; [c]Division of Pulmonary, Allergy and Critical Care Medicine, Duke University, Durham, North Carolina, USA; [d]University Hospital Zurich, Zurich, Switzerland; [e]Department of Cardiothoracic and Vascular Sciences, University of Padova Medical School, Padova, Italy; [f]Department of Respiratory Medicine, Hannover Medical School, Member of the German Center for Lung Research, Hannover, Germany; [g]Division of Pulmonary & Critical Care, Washington University in St. Louis, St. Louis, Missouri, USA; [h]Pulmonary Disease and Critical Care Medicine, University of Texas Health Science Center San Antonio, San Antonio, Texas, USA; [i]Department of Respiratory Diseases Policlinico San Matteo Foundation & University of Pavia, Pavia, Italy; [j]Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain; [k]Department of Thoracic Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan; [l]Toronto Lung Transplant Program, University Health Network, University of Toronto, Toronto, Ontario, Canada; [m]Norton Thoracic Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona, USA; [n]Department of Pathology, University Medical Center, Rotterdam, The Netherlands; and the [o]Lung Transplant Service, The Alfred Hospital, Melbourne, Victoria, Australia.

Since the inception of lung transplantation (LTx), serial pulmonary function testing (PFT) has been the primary method of quantifying the physiologic performance of the allograft. The spirometric indices have since been the standard benchmark to detect the emergence of chronic allograft dysfunction (CLAD). Historic descriptions of physiologic and histologic findings in the first heart–lung transplant (HLTx) recipients formed the basis for our initial understanding of chronic dysfunction of the pulmonary allograft. In 1984, Burke et al described 14 long-term survivors of combined HLTx, 5 of whom developed airflow limitation.[1] The authors noted that 3 of the latter patients also developed a superimposed progressive restrictive ventilatory defect. In 1985, Yousem et al described the histopathologic features in these HLTx recipients based on analysis of 2 open lung biopsies, 2 autopsies, and 1 explant.[2] Morphologically, the allografts showed extensive bronchiolitis obliterans (BO) and interstitial and pleural fibrosis, with both arterial and venous vasculopathy. In a prescient statement, Yousem opined that BO may prove to be a significant complication of HLTx. In 1988, Glanville et al examined 12 HLTx patients with a non-progressive restrictive ventilatory defect and concluded that a stable restrictive defect post-HLTx was determined primarily by chest wall mechanics.[3] Patients with progressive restrictive physiology were not examined in that study.

[1]These authors have contributed equally to this work.

Reprint requests: Geert Verleden, MD, PhD, Lung Transplantation Unit, University Hospital Gasthuisberg, 49 Herestraat, B-3000 Leuven, Belgium. Telephone: +32-16-346802. Fax: +32-16-346803.

E-mail address: geert.verleden@uzleuven.be

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In 1993, the International Society for Heart and Lung Transplantation (ISHLT) established an ad-hoc working group that published a working formulation to describe chronic dysfunction of the allograft. The group concluded that a decline in the forced expiratory volume in 1 second (FEV_1) was the most reliable and consistent indicator of allograft dysfunction after other identifiable causes were excluded.[4] The acronym BOS (bronchiolitis obliterans syndrome) was introduced to describe such dysfunction, but the previously described restrictive physiology related to parenchymal with or without pleural fibrosis was not included in the syndrome. The BOS update published by Estenne et al in 2002 did not include a definition for restrictive mechanics either.[5] By the time Meyer et al published their clinical practice guideline on the diagnosis and management of BOS in 2014, recognition of the clinical importance of a restrictive defect was emerging.[6] Indeed, in 2005, Pakhale et al described 13 LTx patients, out of a cohort of 686, who developed radiographic findings of upper lobe fibrosis.[7] Pulmonary function tests demonstrated predominantly a progressive restrictive pattern. Open lung biopsy specimens revealed dense interstitial fibrosis, with occasional features of BO, organizing pneumonia (OP), and aspiration. Nine patients died at a median follow-up of 2,310 (range 266−3,740) days, 8 due to respiratory failure. The authors concluded that upper lobe fibrosis was a novel presentation of CLAD, which could be differentiated from BOS on the basis of physiologic and radiologic findings. One year later, Martinu et al described pathologic changes in 12 patients undergoing retransplantation for BOS and found a wide range of pathologic processes of potential clinical significance, including severe pulmonary fibrosis ($n = 2$).[8] They concluded that "end-stage" BOS displayed significant histologic heterogeneity, which may contribute to variability of treatment responses. Recognizing the emerging evidence for a diversity of phenotypes, and possibly endotypes of allograft dysfunction after LTx, the acronym CLAD was first introduced in 2010 by Glanville as an umbrella term to include both obstructive and restrictive phenotypes.[9] A seminal report by Sato et al in 2011, introduced the term restrictive allograft syndrome (RAS).[10,11] In the series, RAS was diagnosed in 30% of bilateral LTx patients with CLAD. The diagnosis was based on finding a restrictive ventilatory defect, defined as FEV_1 ≤80% and total lung capacity (TLC) ≤90% of baseline values. Many patients with RAS had radiographic findings of interstitial or ground-glass opacities, of whom 41% had upper zone involvement. Patients with RAS had an inferior median survival from diagnosis compared to patients with BOS.[12−14] A slightly earlier publication by Woodrow et al showed that single LTx patients were less likely to be categorized by either phenotype using the radiographic and spirometry criteria proposed by Sato.

Building on the these findings, a broader global vision of chronic allograft dysfunction was constructed using the collection of physiologic evidence of phenotypes and their associated outcomes.[15,16] In 2014, a definition of CLAD was proposed to define a persistent decrease in FEV_1 and/or forced vital capacity (FVC) of at least 20% with respect to baseline (defined as the mean of the best 2 measurements after LTx, obtained at least 3 weeks apart).[17] At that time, a number of known causes of allograft dysfunction were included under the umbrella of CLAD, in keeping with the common usage meaning. However, the most recent consensus definition of CLAD now excludes acute onset of treatable causes of graft dysfunction but recognizes that these episodes are risk factors for the eventual development of CLAD.[18] To best understand how RAS fits in with the revised definition of CLAD, it is strongly advised to read the current RAS article in conjunction with the CLAD consensus article.

In this article, we provide a consensus standardized definition of RAS for use across centers; provide a state-of-the-art literature review supporting the development of the definition; and describe in detail the current understanding of clinical, physiologic, radiologic, and histologic manifestations of RAS. In addition, we discuss available data on risk factors and treatment approaches to RAS and identify key research priorities for future consideration in areas where critical data are still lacking.

RAS definition

We propose that RAS (formerly also termed r[restrictive] CLAD) is defined as the restrictive phenotype of CLAD, which is defined in the CLAD consensus document (Table 1).[18] The restrictive phenotype of CLAD is defined physiologically by:

1. A persistent ≥20% decline in FEV_1 compared with the reference or baseline value, which is computed as the mean of the best 2 post-operative FEV_1 measurements (taken ≥3 weeks apart).
2. A concomitant ≥10% decline in TLC, compared with the reference or baseline value, which is computed as the mean of the 2 TLC measurements taken at the time

Table 1 Definition of Restrictive Allograft Syndrome

Criterion	
1	Persistent ≥20% decline in FEV_1, compared with baseline
2	Concomitant ≥10% decline in TLC, compared with baseline
3	Persistent opacities on chest imaging

CLAD, chronic lung allograft dysfunction; FEV_1, forced expiratory volume in 1 second; TLC, total lung capacity. Once CLAD is diagnosed,[18] phenotype should be determined. Restrictive allograft syndrome (RAS) is defined by the combination of all 3 of the criteria listed. Post-operative FEV_1 baseline is computed as the mean of the best 2 post-operative FEV_1 values, at least 3 weeks apart. The post-operative TLC baseline is computed as the mean of 2 post-operative TLC values taken at the time of or very near to the best 2 post-operative FEV_1 measurements, at least 3 weeks apart. Consistent with the definition of CLAD, the date of RAS onset is defined as the date at which the first value of FEV_1 ≤80% of baseline is recorded, when subsequent values also fall below the threshold.

of, or very near to, the best 2 post-operative FEV_1 measurements.
3. The presence of persistent opacities on chest imaging. In the current definition, once the patient qualifies for CLAD,[18] we propose that an additional essential requirement for RAS diagnosis is the presence of parenchymal with or without pleural-based opacities, on high-resolution (HR) chest CT scan (preferred) or on chest X-ray (CXR) if HRCT is unavailable.

If restrictive physiology and CXR/CT opacities persist after 3 months despite appropriate therapeutic efforts, the diagnosis of CLAD with the phenotype of RAS is confirmed. Note that this definition applies to de-novo RAS. Where RAS develops after BOS has been established (mixed phenotype CLAD), the baseline for TLC should be taken as the last TLC measured in BOS to minimize the effect that gas trapping may have on calculation of the FVC. If a restrictive defect is implied by changes in spirometry, as discussed in what follows, then an appellation of "probable" RAS can be applied, if facilities to measure TLC are not available.

Diagnosis and Outcome of RAS

Plethysmography is the preferred means to measure TLC to further define the emergence of a restrictive ventilatory defect, but serial TLC monitoring is not routinely performed in most LTx centers. Moreover, diagnostic criteria for pulmonary restriction may be obscured in single LTx recipients due to the dual effects of allograft dysfunction and mechanics of the native lung. A number of studies have assessed alternative methodologies of making a RAS diagnosis. The first study, detailed in what follows, examined the FEV_1/FVC ratio (assuming it will remain stable or increase in a restrictive ventilatory defect), and the second study examined the FVC at CLAD onset relative to the FVC baseline.[16,19] A subsequent report combined the FVC loss criterion with computed tomography (CT) findings of pleural or parenchymal fibrosis, and validated the utility of FVC loss in predicting the outcome of CLAD, both in bilateral and single LTx recipients.[20] A single-center retrospective study showed that loss of >10% TLC with respect to baseline, or air trapping (defined as residual volume [RV]/TLC ≥50%), was associated with inferior survival.[21,22] Severity of the restrictive ventilatory defect and the extent of CT changes were associated with poorer survival in the study by Suhling et al, as was FVC loss at CLAD onset, a predictor also confirmed by Verleden et al.[23,24] It appears some RAS patients may present with a mixed phenotype *ab initio*, whereas others may demonstrate a shift from the original phenotype (usually BOS) to a mixed phenotype over time. Taken together, and acknowledging the slight differences between each set of diagnostic criteria, studies to date have confirmed 18% to 30% of all CLAD patients have a restrictive ventilatory defect at diagnosis with CT findings of parenchymal with or without pleural fibrosis. Universally, a diagnosis of RAS portends a worse prognosis than BOS.[16,25] In one series of 53 patients with RAS, predictors of decreased survival included the presence of lower lobe dominant or diffuse infiltrates on CT scan, increased bronchoalveolar lavage (BAL) neutrophilia or eosinophilia, the presence of a discernible trigger, and a history of lymphocytic bronchiolitis (LB).[25]

Clinical features

Patients with RAS report shortness of breath (either insidious or acute onset), fever, non-productive cough, pleurisy, chest tightness, and weight loss. Signs of RAS may include coarse crackles or bronchial breath sounds on auscultation in combination with hypoxemia and impaired exercise capacity.[13]

The natural history and prognosis of RAS is highly variable, although 3 general patterns of progression have been described:

1. A subset of patients present with acute hypoxemic respiratory failure, akin to adult respiratory distress syndrome, which leads to rapid deterioration and death or retransplant. The Leuven and Hannover group described 21 LTx recipients with acute late-onset allograft failure characterized by bilateral radiographic opacities and severe hypoxemia. Explanted lungs revealed acute fibrinoid organizing pneumonia (AFOP), organizing pneumonia (OP), and diffuse alveolar damage (DAD), but also identified BO. All patients who survived to discharge without retransplantation ($n = 2$, 9%) subsequently developed RAS.[26]
2. Another subset of patients are characterized by a less fulminant course and a "stair-step" pattern of lung function decline and disease progression. Sato et al[13] described 25 patients with this pattern of RAS progression distinguished by recurrent episodes of acute-onset hypoxemia, hospital admission, and/or mechanical ventilation. These exacerbations were followed by intervals of relative clinical stability. During these intervals, pulmonary function improved, remained stable, or continued to decline. Radiographically, ground-glass opacities and/or consolidation predominated during acute exacerbations and subsequently evolved to progressive changes compatible with fibrosis. None of the patients fully recovered, and the mean ± SD time from the initial acute exacerbation to death or retransplant was 558 ± 441 days (range 104 to 1,612 days, median 457 days).
3. A third subset of patients present with radiographic changes and a gradually progressive decline in lung function. In a smaller study, Pakhale et al[7] described 13 patients with a predominance of upper lobe fibrosis and a slow but steady decline in TLC, which, over time, resulted in a better prognosis compared with the type 1 or type 2 patients just described.

Physiology of RAS

In the initial description of RAS, Sato et al examined serial post-transplant lung volume measurements by

plethysmography in 468 bilateral LTx recipients, 156 of whom developed chronic graft dysfunction as defined by a sustained impairment in FEV_1.[11] A threshold decline in TLC to ≤90% of the baseline value demonstrated the best operating characteristics for correctly classifying an irreversible loss.[11] Thirty percent of the CLAD cohort had a sustained decline in TLC to ≤90% of the baseline TLC. Furthermore, these patients had distinct radiographic and histologic findings, including upper lung zone opacities compatible with fibrosis on imaging and features of DAD on pathology.[11] This observation was confirmed by Verleden et al, who evaluated the impact of a ≥10% TLC decline on survival in 71 lung recipients, including 23 single LTx recipients.[19]

This initial report prompted other centers to provide independent validation and refinement of physiologic criteria. Two studies, in particular, have added to our understanding of TLC changes in association with CLAD. Suhling et al reported 89 patients with CLAD, as defined by persistent loss of FEV_1; 28% of their cohort developed RAS, defined as TLC ≤90% of the baseline value. In the study, patients with TLC loss to ≤80% had the shortest graft survival.[23] However, before CLAD onset, 52 patients (58%) exhibited an FEV_1/FVC ratio of <0.7, increasing to 0.76 (85%) at CLAD diagnosis and 0.85 (95%) at last follow-up. These data indicate a proportion of patients display a mixed restrictive and obstructive phenotype at CLAD onset, which could impact survival. Kneidinger et al confirmed that a decline in TLC to ≤90% of baseline was adversely associated with survival after onset of graft dysfunction in bilateral LTx recipients.[27] Moreover, the TLC/$TLC_{baseline}$ ratio, when modeled as a continuous rather than categorical variable, was also associated with a higher hazard for death.[27]

Although TLC remains the primary criterion for the diagnosis of a restrictive ventilatory defect, TLC monitoring is not always obtained as part of standard post-transplant care. Also, some patients are unable to undergo body plethysmography. In the absence of utilizing the TLC, a restrictive disorder can be identified from spirometry if the FVC is reduced from baseline and the ratio of FEV_1/FVC is elevated or increasing from baseline.[28] Todd et al performed a retrospective clinical trial in 216 bilateral LTx recipients with CLAD to determine whether the spirometric pattern present at the time of CLAD onset could be utilized to meaningfully determine survival.[16] FVC loss was determined by FVC_{CLAD}/FVC_{best} <0.8 at CLAD onset, where FVC_{best} was the average of the 2 FVC measurements that paired with the 2 best post-LTx FEV_1 values used to determine the FEV_1 baseline.[16] Within this cohort, 30% of patients met spirometric criteria for FVC loss, the majority of whom simultaneously demonstrated interstitial opacities on CT. Patients who had measured decreases in FVC at onset of CLAD had significantly worse survival compared with those who had preserved FVC (median survival 309 vs 1,070 days).[16] The true overlap of patients identified by FVC loss and those meeting criteria for RAS, as defined by TLC loss, could not be described due to the lack of formal lung volumes in the study.

A declining FVC could also be attributable to air trapping and hyperinflation, which are the hallmarks of airflow limitation.[22,29] Subsequent studies have validated the association of FVC loss with poor survival after the onset of CLAD in independent cohorts of bilateral LTx recipients, and also extended these observations for the first time to a multicenter cohort of single LTx recipients.[20,30] Together, these studies support the idea that, whenever TLC data are not available, a decline in FVC at CLAD diagnosis is a useful clinical tool to identify LTx patients at risk for poor clinical outcomes at the onset of CLAD and during follow-up. However, it should be clear that not all these patients have RAS. These data identify a population in whom further evaluation with formal lung volumes by plethysmography and HRCT may provide additional valuable information to definitely phenotype such patients. Single LTx recipients are an important target group for further detailed examination given the risk of native lung hyperinflation in patients with contralateral emphysema, and, conversely, volume loss in patients with contralateral pulmonary fibrosis.

Imaging of RAS

The first radiologic report by Konen et al in 2002 of a "RAS-like" phenotype described 7 patients with opacities and honeycombing predominantly in the upper lobes on HRCT scans.[31] In 2005, 13 cases (12 bilateral LTxs) of "upper lobe fibrosis" were described by the Toronto and Duke group.[7] In 9 of 13 cases, the aforementioned CT findings correlated with a reduced TLC measured by body plethysmography, but 7 of 13 also had an FEV_1/FVC <0.7. Signs of airway disease, such as air trapping, "tree-in-bud" opacities, centrilobular nodules, airway thickening, and bronchiectasis, were present in a considerable proportion of patients with CT features of upper lobe fibrosis, which is in accord with physiologic evidence of a mixed phenotype in some patients.[18]

Sato et al observed ground-glass opacities and reticular changes more often were associated with patients with a TLC loss than in patients with BOS and preserved TLC or stable LTx recipients, respectively.[11] Subsequently, in a study of radiographic findings in a 2-center cohort of 225 patients with CLAD, 43% of whom had pleural abnormalities, 26% had consolidation, 41% had ground-glass opacities, and 25% had reticulation or septal thickening. CT abnormalities were more frequent in patients with a reduced FVC at CLAD diagnosis and were associated with worse survival. DerHovanessian et al later demonstrated that patients with preserved FVC at CLAD onset who had pleural or parenchymal fibrosis demonstrated on CT also had poor survival.[20] In 23 bilateral LTx and HLTx recipients with TLC ≤90% or FEV_1/FVC ratio >0.70 with low FVC, the Leuven group compared CT findings before CLAD onset, at CLAD diagnosis, and during the course of CLAD. In the early stages of RAS, ground-glass opacities were the most prominent feature on CT (>50% of patients), whereas, in the later stages, consolidation (>60% of patients) and volume loss were observed. Simultaneous radiographic

signs of airway disease, including bronchiectasis and air trapping, were detected in most cases.[24]

Dettmer et al reported a single-center cohort of 52 patients with CLAD and found that patients who later developed RAS had significantly more CT abnormalities at CLAD onset than patients without this phenotype. Specifically, consolidation (57% vs 4%, $p < 0.001$) and ground-glass opacities (71% vs 7%, $p < 0.001$) were more common.[32] Suhling et al reported that 55 of 89 (62%) restrictive CLAD patients had persistent moderate and severe reticular changes and consolidation without the upper lobe predominance seen in Konen's cohort.[23] Severe and multilobar consolidation was associated with a reduced TLC and a poor prognosis. Other changes, including ground-glass opacities, were not associated with survival, but this finding was possibly biased by the limited availability of early CT scans. In another single-center analysis of 22 CLAD patients with TLC ≤90% of baseline, diffuse peripheral patchy consolidation, often with the presence of ground-glass attenuation, was described on serial CTs.[33] In 64% of the patients studied, upper lobe disease was predominant on the CT images. Survival and clinical disease progression were associated with the presence of pleural thickening and volume loss in the upper lobes.

Investigators have explored whether machine-learning analysis is able to detect CLAD earlier and with higher sensitivity than the current interpretation methodologies. In 2 studies from Toronto, Horie et al used software-based analysis of low-dose CT scans in a cohort of CLAD patients with TLC ≤90% baseline, and compared them to CLAD patients without a restrictive ventilatory defect. Increasing lung density and lung deformation identified patients with RAS and was associated with lower survival.[34,35] Voskrebenzev et al explored the utility of Fourier decomposition magnetic resonance imaging (MRI) in the quantitation of RAS.[36] Although MRI is an promising technique for the future to allow serial assessment without radiation exposure and use of contrast media, its utility has not yet been established.

Based on the results of these studies, inspiratory thin section HRCT scans (maximum 3-mm sections) without contrast media are recommended in all CLAD patients with a decline in TLC, FVC loss, or persistent opacities on CXR. Persistent (≥3 months) multilobar opacities, with or without pleural changes, are the hallmark of RAS. Although the RAS literature to date has often employed the term "infiltrates" in descriptions of radiologic changes of RAS, we acknowledge there is some debate about the precision of this term.[37] Hence, we support using the term "opacities" to describe results of imaging studies and have adopted this terminology accordingly in the RAS definition.[38]

Pathology of RAS

RAS has complex histopathologic manifestations, consisting of more than one distinct pattern of parenchymal fibrosis and airway obliteration. Acute morphologic changes or acute cellular rejection (ACR) may also be found.

Fibrotic changes

Most studies of RAS have shown a pattern of intra-alveolar fibroelastosis (IAFE) adjacent to bronchioles, the pleura, and the interlobular septa with or without concomitant BO.[14,39–41] A fibrotic pattern of non-specific interstitial pneumonia (NSIP) has also been found in up to 25% of RAS patients.[14,41] Fibrosis-induced sub-pleural and/or paraseptal emphysema has also been recognized recently as a potential third histopathologic pattern in a substantial number of cases, and appears to be associated with a relatively good prognosis.[41] A high, but variable prevalence of BO has been found in RAS lungs (62%−100%).[14,39–43] The variability may in part reflect sampling bias.

Acute morphologic changes

Late-onset DAD with hyaline membrane formation has been described in patients with RAS, and is often associated with IAFE, but may also be an early finding associated with the later development of RAS.[12,44] The prevalence of DAD in patients with RAS is variable and may relates to the timing of the biopsy.[1,4,7,8] AFOP has also been detected in RAS and was shown to be associated with restrictive pulmonary function and a poor survival.[41,45] AFOP is characterized by a peribronchiolar, sub-pleural, or paraseptal deposition of intra-alveolar fibrin with some fibroblastic proliferation within the alveolar space, and minimal inflammatory infiltrates. These areas are often immediately adjacent to areas of fibroelastosis, which suggests that acute lung injury may precede the development of fibrosis, particulary secondary to microvascular damage, including within alveoli.[40,41] It is plausible that microvascular damage may result from chronic (sub-clinical) antibody-mediated rejection (AMR), but more work is needed to establish a clear relationship between AMR and RAS (refer to subsection on risk factors in what follows).

The pathogenesis of RAS is speculative. AFOP appears to be the early phase of the disease process wherein fibrin is deposited due to microvascular injury. Incomplete resolution may then result from defective clearance, perhaps related to defective macrophage function, and/or repetitive injury, leading to an IAFE pattern.[39] Theoretically, this may explain the stepwise pattern of physiologic decline, as noted by Sato et al.[13] Clinically, it is also of interest that AFOP has been associated with worse survival after the diagnosis of RAS while a pattern of fibrosis with emphysema-like changes seems to be associated with a better survival and reduced inflammation in bronchoalveolar lavage (BAL) at the time of diagnosis.[39]

Changes related to ACR

ACR has been described commonly in RAS. Indeed, in one case series, ACR was present in all investigated lungs, wherein a variable degree of BO was also observed.[8] ACR is regarded as a temporal exclusion criterion for the diagnosis of CLAD, but is recognized as perhaps the greatest risk

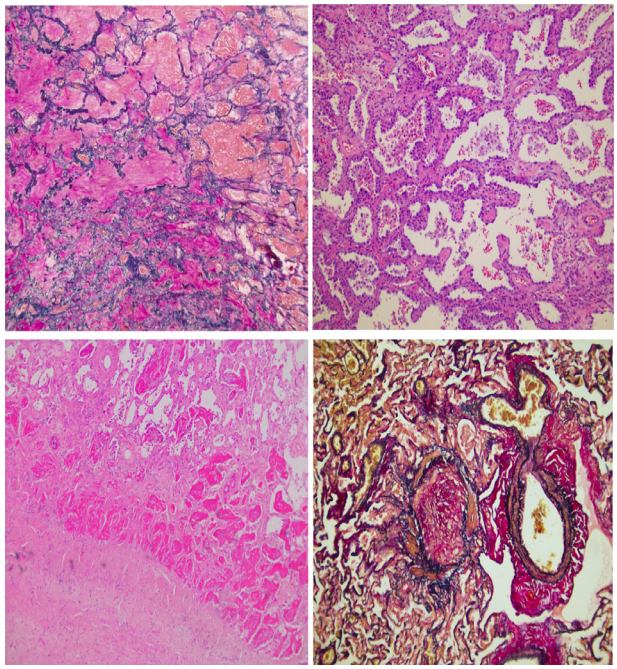

Figure 1 Histopathologic changes commonly encountered in RAS. (A) Intra-alveolar fibroelastosis (IAFE). (B) Non-specific interstitial pneumonia (NSIP). (C) Acute fibrinous and organizing pneumonia (AFOP). (D) Obliterative bronchiolitis (OB).

factor for the subsequent development of CLAD. The potential role of chronic vascular rejection in the development of fibrotic lung disease after LTx is appealing but has not been well studied.

In summary, the histopathologic spectrum of RAS is variable (Figure 1) and the array of different pathologies in RAS specimens may provide clues to the temporal development of the disease from cellular rejection, to allograft injury, to fibrosis. The juxtaposition of chronic fibrotic and more acute changes may reflect the dynamic response of the lung allograft to acute or ongoing injury irrespective of the specific cause. As discussed in the next subsection, the exact injuries predisposing to RAS development are still being determined.

Risk factors for RAS

The body of evidence for risk factors specific for RAS is substantially smaller than for BOS, likely due to the fact that RAS has only been defined recently and that previous research pooled the different phenotypes. However, Verleden et al demonstrated that many risk factors are shared between BOS and RAS. Previously defined risk factors for BOS, such as ACR, LB, chronic pulmonary infection with *Pseudomonas aeruginosa*, infection, and increased BAL neutrophilia, were more prevalent in RAS patients compared with stable patients. However, except for severe LB (LB $\geq$2), there was no difference in the prevalence of these risk factors compared to patients with BOS.[46] ACR was confirmed previously by Shino et al as a risk factor for RAS.[44] Females were more likely to develop RAS in studies by Todd et al and DerHovanessian et al.[16,20] RAS patients were younger than the BOS patients in studies by Verleden et al and Sato et al.[11,19] Cytomegalovirus (CMV) mismatch was a risk factor for RAS in the Sato et al study.[11] Underlying disease, specifically chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), were associated with RAS in a study by Koutsokera et al.[47] Elevated BAL and blood eosinophilia were also associated with future RAS development,[48] but cytokine expression in the pre-implanted lung was not associated with RAS.[49]

A larger body of evidence supports a role for donor-specific antibodies (DSA) and AMR as risk factors for RAS, as described by Todd et al, who found a higher incidence of newly detected human leukocyte antigen (HLA) antibodies, some of which were donor-specific, temporally associated with CLAD onset in the RAS group.[16] These findings were later confirmed by Roux et al, who showed that a significant number of patients who survived AMR subsequently developed RAS.[50] In contrast, a recent study found that only 35% of RAS patients had donor-specific HLA antibodies and there was no appreciable staining for C4d.[41] In another recent study, Koutsokera et al found that detection of DSA at 1 year post-LTx predisposed to CLAD, but did not discriminate between BOS and RAS.[47] Verleden et al demonstrated that DSA were not only associated with reduced CLAD-free and graft survival, but that this was associated specifically with RAS.[51] Further evidence provided by Walton et al showed that HLA matching at the eplet level was a major risk factor.[52] Mismatch at HLA-DRB1/3/4/5 + DQA/B was specifically associated with RAS, but not BOS, thereby further supporting the role of DSA as risk factor for RAS.

The largest body of evidence has been derived from analysis of transbronchial biopsies. Both Sato et al and Shino et al showed that late-onset DAD (>3 months after LTx) was associated with RAS but not BOS development.[12,44] Early-onset DAD (within 3 months of LTx), however, was more often associated with BOS.[12] AFOP, first defined in an LTx cohort by Paraskeva et al, is also considered a risk factor for RAS, as progression from AFOP to RAS has been demonstrated in 2 separate reports.[26,45,53]

Potential mechanisms of RAS

The pathogenesis of RAS remains to be elucidated. There is a large degree of overlap in the mechanism of airway disease in RAS and BOS as BO is a common denominator, which may include a fibroproliferative process affecting the terminal bronchioles in particular.[14,40–42] A gene expression analysis of lung biopsies led to speculation that a non-specific fibrin-rich reaction to an injury pattern (irrespective of cause) triggers the influx of pro-inflammatory cells, leading to fibroblast recruitment and activation and ultimately remodeling of the extracellular matrix.[39] Evidence for a pro-inflammatory environment is robust as several groups have shown significant increases in interleukin-5 (IL-5), alarmins (S100A9, S100A8/A9, S100A12, S100P, and HMGB1), neutrophil elastase, pentraxin-3, IL-6, and C-X-C

Table 2 Studies Describing Impact of Treatment for RAS and Outcomes

Study	*N*	Centers	Treatments[a]	Outcomes
Pakhale et al[7]	13	2	High-dose steroids (2), ATG (2), change CsA to tacrolimus (8), change azathioprine to sirolimus (1)	No apparent impact on progression of upper lobe fibrosis
Sato et al[11]	47	1	No details on treatment beyond description of pulse steroids	"Stair-step" decline/progression, inconsistent response to treatment
Kohno et al[67]	4	1	Alemtuzumab (4)	Probable RAS, improved interstitial changes and lung function
Sato et al[13]	25	1	High-dose steroids (24), change to tacrolimus (4), change to MMF (1), ATG (2), PEx (3), azithromycin (8)	Efficacy of treatment "inconclusive," general progression
Greer et al[68]	22	1	CLAD progression after azithromycin, ECP (22)	6 of 22 stabilized with ECP
Vos et al[64]	1	1	Pirfenidone (1) for <3 months	Less rapid decline in FEV_1 and FVC, improvement in TLC and imaging; no symptomatic improvement
Vos et al[65]	11	1	Pirfenidone up to 46.6 months	Attenuation in decline of FEV_1 and FVC, improvement in imaging (CT and ^{18}F-FDG PET)
Todd et al[16]	65	1	Azithromycin (37), ATG (20), alemtuzumab (69), fundoplication (3)	No analysis of specific treatment and outcome but general progression
Del Fante et al[69]	14	1	ECP (14)	Worse survival for RAS compared with BOS
Verleden et al[70]	49	Multiple	Retransplantation (49)	RAS patients redeveloped CLAD faster than those with BOS and had worse survival after retransplantation
Hall et al[71]	18	1	Retransplantation (18)	Patients with RAS had worse survival compared to those with BOS

ATG, anti-thymocyte globulin; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; CsA, cyclosporine A; ECP, extracorporeal photopheresis; ^{18}F-FDG PET, 18-flourodeoxyglucose positron emission tomography; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMF, mycophenolate mofetil; PEx, plasmapheresis; RAS, restrictive allograft syndrome; TLC, total lung capacity.

[a]Number of patients in parentheses.

motif ligand 10 in RAS, when compared with BOS.[54–58] Interestingly, vascular endothelial growth factor (VEGF), a marker of neo-angiogenesis, was decreased in RAS. Vascular injury was also implicated by pathologic examination of RAS lungs with evidence of a reduction in the number of capillaries and the presence of small lymphocytes and plasma cells associated with fibrointimal thickening of arteries and veins.[40] Intriguingly, there is also strong evidence for a role of humoral immunity in RAS. In addition to the association between circulating de-novo DSA and the development of RAS mentioned earlier, immunohistochemical staining of RAS explants has revealed the presence of B-cell organization into follicles.[59] Moreover, BAL at RAS diagnosis has shown specific increases in total immunoglobulin G (IgG), IgG1–4, and IgM compared with BOS. Further investigation of the underlying mechanism will be crucial to better understand the pathophysiology of RAS. In this respect, it is of note that the orthotopic mouse LTx model, previously used to model BOS, also demonstrates a RAS phenotype.[60]

Treatment of RAS

There are few data to guide the treatment of RAS. To date, there have been no prospective, randomized, controlled trials. To some extent, the absence of a widely accepted and standardized definition for RAS has hindered the design and conduct of such studies. In general, clinicians have used similar treatments for RAS and BOS, as outlined in the CLAD consensus document[18] and summarized in Table 2. However, outcomes for RAS have been consistently inferior to those for BOS, and there remains a lack of robust evidence to suggest efficacy of any treatment option for either phenotype. With more stringent definitions of BOS and RAS phenotypes, future studies will be better able to define response during a therapeutic trial. Clearly, additional studies are necessary to identify treatment options that may provide better outcomes for patients with RAS.

Key research areas and future priorities

There are a number of important research initiatives that should be explored to further our knowledge regarding RAS as a subset of CLAD:

1. Determine exact prevalence, specific risk factors, mechanisms, prognostic variables, and clinical outcomes for RAS and whether they differ from risk factors for BOS.
2. Explore proteomic, immunologic, genetic, and epigenetic profiles among patients with each CLAD phenotype to elucidate common or divergent biologic mechanisms. This may provide a rationale for phenotype-specific therapies.

3. Design future prospective, multicenter, collaborative studies utilizing existing LTx tissue/BAL banks (LTx outcomes group, clinical trials in organ transplant).[20,61,62]
4. Examine preventive strategies by focusing on known risk factors.
5. Design interventional trials to reduce the risk of DSA such as real-time donor/recipient eplet matching, which may reduce the incidence of RAS.
6. Explore utility of anti-fibrotic therapy after pro-fibrotic events such as severe ACR, AMR, or viral pneumonia.[63,64]
7. Use the new definitions of RAS and CLAD phenotypes as per the current RAS and related CLAD consensus definition documents in the design of therapeutic CLAD clinical trials with incorporation of the CLAD staging criteria.[18]
8. Design randomized, non-inferiority clinical trials and analyze outcomes, stratified by CLAD phenotype given the worse survival of RAS.[11,16,19,20]
9. Consider reanalyzing previously published LTx studies using the new definitions, thereby generating novel strategies to test prospectively.[65,66]
10. Determine how best to diagnose RAS after single LTx, particularly as native lung disease may confound the interpretation of physiology.
11. Design therapeutic trials based on the CLAD phenotypes to improve outcomes of patients with RAS, including the role of retransplantation.[26,27]

Finally, it is acknowledged that RAS has protean manifestations, uncertain pathogenetic mechanisms, and almost a universally poor prognosis. The description of the RAS entity is relatively new, thus recommendations regarding therapy must perforce be cautious, until deeper understanding of the pathophysiology of RAS is achieved. This report, when read in conjunction with the CLAD consensus report,[18] will hopefully provide a roadmap for our future approach to reducing rates of lung allograft failure.

Disclosure statement

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