



# Association between the renin–angiotensin system and chronic lung allograft dysfunction

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**Components of the renin–angiotensin system are increased in chronic lung allograft dysfunction (CLAD) fibrosis. Angiotensin II-regulated proteins in bronchoalveolar lavage identify concurrent and predict future CLAD in lung transplant recipients.** <https://bit.ly/3eRYez7>

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## Abstract

Chronic lung allograft dysfunction (CLAD) is the major cause of death after lung transplantation. Angiotensin II (AngII), the main effector of the renin–angiotensin system, elicits fibrosis in both kidney and lung. We identified six AngII-regulated proteins (Ras homolog family member B (RHOB), bone marrow stromal cell antigen 1 (BST1), lysophospholipase 1 (LYPA1), glutamine synthetase (GLNA), thrombospondin 1 (TSP1) and laminin subunit  $\beta$ 2 (LAMB2)) that were increased in urine of patients with kidney allograft fibrosis. We hypothesised that the renin–angiotensin system is active in CLAD and that AngII-regulated proteins are increased in bronchoalveolar lavage fluid (BAL) of CLAD patients.

We performed immunostaining of AngII receptors (AGTR1 and AGTR2), TSP1 and GLNA in 10 CLAD lungs and five controls. Using mass spectrometry, we quantified peptides corresponding to AngII-regulated proteins in BAL of 40 lung transplant recipients (stable, acute lung allograft dysfunction (ALAD) and CLAD). Machine learning algorithms were developed to predict CLAD based on BAL peptide concentrations.

Immunostaining demonstrated significantly more AGTR1<sup>+</sup> cells in CLAD *versus* control lungs ( $p=0.02$ ). TSP1 and GLNA immunostaining positively correlated with the degree of lung fibrosis ( $R^2=0.42$  and  $0.57$ , respectively). In BAL, we noted a trend towards higher concentrations of AngII-regulated peptides in patients with CLAD at the time of bronchoscopy, and significantly higher concentrations of BST1, GLNA and RHOB peptides in patients that developed CLAD at follow-up ( $p<0.05$ ). The support vector machine classifier discriminated CLAD from stable and ALAD patients at the time of bronchoscopy (area under the curve (AUC) 0.86) and accurately predicted subsequent CLAD development (AUC 0.97).

Proteins involved in the renin–angiotensin system are increased in CLAD lungs and BAL. AngII-regulated peptides measured in BAL may accurately identify patients with CLAD and predict subsequent CLAD development.

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