support the high interest in early diagnosis and alleviation of IH in patients with OSA to limit cardiovascular complications.

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**FINANCIAL/NONFINANCIAL DISCLOSURES:** None declared.

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**DOI:** http://dx.doi.org/10.1016/j.chest.2016.05.031

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# Serum Surfactant Protein D as a Marker of Asthma Severity

**To the Editor:**

We have read with great interest the article by Mackay et al[1] published in *CHEST* (May 2016) entitled "Airway Surfactant Protein D Deficiency in Adults with Severe Asthma." As elegantly shown, serum surfactant protein D (SP-D) concentrations were significantly lower in individuals with severe asthma as opposed to individuals with mild asthma and healthy control subjects, and SP-D levels were significantly higher in the BAL of patients with severe asthma compared with those with mild asthma. On this basis, the authors propose that serum SP-D could serve as a biomarker of the most severe forms of asthma. In their article, Mackay et al[1] state that "To the best of our knowledge, this study is the first to investigate the relationship between asthma and SP-D concentration in patients with such severe disease." We respectfully disagree with this statement, since we recently reported that indeed serum SP-D concentrations are significantly higher in individuals with severe asthma as opposed to healthy control subjects and individuals with mild asthma, and their levels correlate with the degree of airway obstruction.[2] In our study, we hypothesized that serum SP-D could increase as a result of inflammation-induced permeability of the bronchial microvasculature, which allows the passage of large macromolecules, such as hydrophilic surfactant proteins, from lung to blood.[3] However, the increased levels of surfactant proteins in serum could also be explained by an increased local synthesis of surfactant proteins induced by local inflammation.[4]

SP-D contributes to pathogen clearance and resolution of inflammation as a component of the innate immune defense within the airway. In this context, Mackay et al[1] propose that the degradation of SP-D would render the airways susceptible to airway infections, thus leading to frequent exacerbations and features of treatment-resistant asthma. To complement the immunologic role, surfactant also acts by stabilizing the conducting airways. In this scenario, the increased surface tension caused by the loss of the surfactant function would oppose the bronchodilatory ability of deep inspirations, which has been demonstrated to decrease with the severity of asthma.[5] The effectiveness of the beneficial effects of lung inflation on airways is dependent on the interdependence between the parenchyma that surrounds and sustains the small airways and the outer airway walls. This is further supported by the significant relationship between serum SP-D levels and functional abnormalities of small airways.[2] We believe that the findings of the two studies could provide a potential explanation to the pathophysiological mechanisms of severe asthma.

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**FINANCIAL/NONFINANCIAL DISCLOSURES:** None declared

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**DOI:** http://dx.doi.org/10.1016/j.chest.2016.05.032

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# Response

**To the Editor:**

We thank Dr Benfante et al for their letter. We are delighted that they have been able to replicate our findings reported in *CHEST*[1] and add to our data that serum surfactant protein D (SP-D) is elevated in severe asthma and as such may act as a biomarker of small airway events. This was indicated by our identification of reduced concentrations of SP-D in BAL, which has implications for small airway function and innate immune defense. Benfante et al questioned our statement that "To the best of our knowledge, this study is the first to investigate the relationship between asthma and SP-D concentration in patients with such severe disease." They respectfully disagree with our statement, referring to their recent report that serum SP-D concentrations are significantly higher in patients with severe asthma as opposed to healthy control subjects and individuals with mild asthma and that their levels correlate with the degree of airflow obstruction.[2] However, our *CHEST* publication, first available as an e-publication in January 2016, predated their e-publication in March 2016, and as such our statement is correct. However, this is not of scientific importance; we highlight this only to provide the correct information and make the record clear. Of more importance is their validation of our findings and considerations about future work to understand the implications and the value of serum SP-D as a biomarker to potentially monitor the impact of therapy on the distal airways. This correspondence brings together similar research at separate sites and highlights the need for further research to investigate possible mechanisms of airway SP-D deficiency in severe asthma. As such, we welcome possible collaborations into understanding the underlying causes. A recent review has highlighted several important areas of further investigation, for example, are the low levels in the airway a result of consumption or cleavage associated with increased airway infection?[3] We recognize that the airways are not sterile and that there is an altered colonization in severe asthma.[4] We have recently reported that some bacterial strains may shield core structures in the lipopolysaccharide, which are targets for SP-D binding by the carbohydrate recognition domain; proteases present in severe asthma may cleave SP-D within the carbohydrate recognition domain and inhibit these innate immune defense functions, contributing to ongoing inflammation and low SP-D levels in the BAL.[5]

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**FINANCIAL/NONFINANCIAL DISCLOSURES:** See earlier cited article for author conflicts of interest.

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**DOI:** http://dx.doi.org/10.1016/j.chest.2016.05.033

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