

Dear Sir,

We were pleased to read the letter from Dr Puxeddu and co-workers, written in response to our observation that an increase pulmonary vessel volume, derived using quantitative CT analysis, strongly predicts mortality in patients with idiopathic pulmonary fibrosis (IPF).¹ Dr Puxeddu and his team highlight a selection of studies that have identified pulmonary vascular alterations in IPF, similar to those seen in pulmonary venous occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH).²⁻⁴ They suggest that when considered in the light of these previous reports, our findings add support to the idea that vascular alterations might be the first pathological lesion in IPF preceding, and leading to, fibrogenesis.

Linkage between fibrosis and alterations in pulmonary vessel density in IPF is not a new observation. The histopathological evaluation of surgical lung biopsy samples performed by Ebina et al established that tissue surrounding regions of fibrosis in IPF is characterised by an increase in vessel profusion, whilst the fibrotic tissue itself demonstrates a reduced number of vessels.² In line with these findings, fibroblastic foci, a pathological hallmark of IPF,⁵ have been shown to be relatively avascular⁶ yet have a network of capillaries at the base of the lesion. Furthermore, within fibrotic regions of histopathological IPF samples, the normal reduction in vessel profusion with increasing distance from the alveoli spaces has been shown to be disrupted.⁷

More recently, in vivo studies in animal models have highlighted the varied effects on pulmonary fibrosis mediated by modifying angiogenic pathways. In a rat model of bleomycin-induced pulmonary fibrosis, vascular endothelial growth factor (VEGF), an

angiogenic mediator, was shown to reduce the severity of pulmonary hypertension yet concomitantly increase the severity of pulmonary fibrosis.⁸ In a similar mouse model, an angiostatic chemokine CXCL11, was found to reduce total lung collagen deposition and overall fibrosis extent on morphometric analysis. However, the reduction in fibrosis rather than being mediated through effects on pulmonary fibroblasts, was linked to reductions in numbers of pulmonary endothelial cells and the inhibition of angiogenesis.⁹ Building on these reports, endostatin, a collagen degradation product that inhibits the VEGF receptor, has been shown to ameliorate bleomycin-induced pulmonary fibrosis possibly by reducing aberrant pulmonary angiogenesis and reducing alveolar epithelial cell apoptosis.¹⁰

Despite the apparent corroboration from these various *in vivo* models, the translation of animal models of pulmonary fibrosis and vascular proliferation to human IPF studies must be guarded. Similarly, extrapolating relationships between the pulmonary microvasculature and fibrosis at a cellular level to the more macroscopic changes identified using quantitative CT analysis is a large, and possibly unwarranted, step. Nevertheless, dynamic or functional imaging studies may further elucidate the complex interactions that exist between the vessels in the lung and the development of fibrosis.

With regard to the specific suggestion that vascular stresses occurring secondary to either PVOD or PCH may be the first pathological lesion in the IPF lung” as Dr Puxeddu et al. states, it is worth pointing out that fibrous intimal narrowing of vessels is frequently seen on a histopathological analysis of pulmonary fibrosis, and

thus adjacent vascular changes could be secondary to, or an epiphenomenon of, the fibrosing process itself. Thus it remains unclear whether vascular proliferation represents a compensatory response to subadjacent pulmonary fibrosis, contributes to fibrogenesis, or represents a combination of the two.

Despite our intentional restraint in suggesting hypotheses to explain our observations about pulmonary vascular volume in IPF, the interest our work has generated is encouraging. Whilst exact relationships are elusive, it is becoming increasingly apparent that understanding the complexities of the pulmonary vasculature is an important but neglected field of study in IPF.

Yours sincerely,

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REFERENCES

1. Jacob J, Bartholmai B, Rajagopalan S, et al. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of automated computer tomographic analysis with conventional severity measures. *Eur Respir J*. 2016;doi: 10.1183/13993003.01011-2016.
2. Ebina M, Shimizukawa M, Shibata N, et al. Heterogeneous Increase in CD34-positive Alveolar Capillaries in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med*. 2004;169:1203-8.
3. Colombat M, Mal H, Groussard O, et al. Pulmonary vascular lesions in end-stage idiopathic pulmonary fibrosis: histopathologic study on lung explant specimens and correlations with pulmonary hemodynamics. *Hum Pathol*. 2007;38:60-5.
4. Kim K-H, Maldonado F, Ryu JH, et al. Iron deposition and increased alveolar septal capillary density in nonfibrotic lung tissue are associated with pulmonary hypertension in idiopathic pulmonary fibrosis. *Respir Res*. 2010;11:37.
5. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183(6):788-824.
6. Lappi-Blanco E, Kaarteenaho-Wilk R, Soini Y, et al. Intraluminal fibromyxoid lesions in bronchiolitis obliterans organizing pneumonia are highly capillarized. *Hum Pathol*. 1999;30:1192-6.
7. Renzoni EA, Walsh DA, Salmon M, et al. Interstitial Vascularity in Fibrosing Alveolitis. *Am J Respir Crit Care Med*. 2003;167:438-43.
8. Farkas L, Farkas D, Ask K, et al. VEGF ameliorates pulmonary hypertension through inhibition of endothelial apoptosis in experimental lung fibrosis in rats. *The Journal of Clinical Investigation*. 2009;119:1298-311.
9. Burdick MD, Murray LA, Keane MP, et al. CXCL11 Attenuates Bleomycin-induced Pulmonary Fibrosis via Inhibition of Vascular Remodeling. *Am J Respir Crit Care Med*. 2005;171:261-8.
10. Wan Y-Y, Tian G-Y, Guo H-S, et al. Endostatin, an angiogenesis inhibitor, ameliorates bleomycin-induced pulmonary fibrosis in rats. *Respir Res*. 2013;14:56.