Gadofosveset-enhanced lung magnetic resonance imaging to detect ongoing vascular leak in pulmonary fibrosis

To the Editor:

Vascular leak is a cardinal response to tissue injury [1, 2]. When dysregulated, vascular leak has been shown to contribute to the development of pulmonary fibrosis in the bleomycin mouse model [3]. Specifically targeting vascular endothelial growth factor, initially described as vascular permeability factor [4] and a key mediator regulating capillary permeability, attenuates the development of pulmonary fibrosis *in vivo* [5]. Gadofosveset (Ablavar; Lantheus Medical Imaging Inc., North Billerica, MA, USA) is a US Food and Drug Administration-approved, gadolinium-based, albumin-binding contrast agent. Gadofosveset has been used to detect vascular permeability in mouse models [6] and to perform vascular imaging clinically. We hypothesised that gadofosveset-enhanced lung magnetic resonance imaging (MRI) could detect albumin extravasation in subjects with pulmonary fibrosis and demonstrate the location of ongoing tissue injury.

This study was approved though the Partners Institutional Review Board (Partners Healthcare, Somerville, MA, USA) and written consent was obtained. Six subjects with pulmonary fibrosis and four healthy subjects were included. Five subjects had idiopathic pulmonary fibrosis (IPF) and one subject had scleroderma-associated interstitial lung disease with a usual interstitial pneumonia (UIP) pattern. Subjects were excluded for congestive heart failure, pneumonia within 6 weeks of study entry, cigarette smoking within 6 months of study entry, or contraindications to undergoing MRI or receiving gadolinium.

MRI was performed using a commercial 3-T MRI scanner (SKYRA; Siemens Healthcare, Boston, MA, USA) with an 18-channel body array and 12-channel spine array. Images were obtained during free breathing, and acquired using pointwise encoding time reduction with radial acquisition with a flip angle of 25°, echo time 0.050 ms, repetition time 2.24 ms, 40 K radials, three-dimensional field of view of 400 mm and pixel resolution of 1.56×1.56×1.56 mm. Baseline imaging was performed followed by intravenous injection of gadofosveset at single dose of 0.03 mmol·kg^{-1} and imaging was repeated for up to 32.5 min post-injection.

Images were analysed using the freeware Dicom reader OsiriX (Pixmeo SARL, Bernex, Switzerland). For each subject, regions of interest (ROIs) were drawn in the ascending and descending aorta at five different standardised locations, two of which were in coronal planes and three of which were in axial planes. ROIs were drawn by hand to outline subpleural regions of each lung, excluding the most medial portions. The lung ROIs were specifically chosen to avoid central blood vessels so as not to confound changes in lung parenchyma signal with potential differences in vasculature between IPF and healthy subjects. The mean signal intensity (SI) of each ROI was measured pre-gadofosveset injection and 5–7.5 min, 10–12.5 min and 15–17.5 min after injection of gadofosveset. We calculated our primary outcome measure, the albumin extravasation index (AEI), as a surrogate measure of pulmonary vascular permeability. The AEI is defined as the change in SI in the parenchyma after gadofosveset injection divided by the change in SI in the aorta after gadofosveset injection.

$$AEI = \frac{(SI\ lung\ post\text{-}gadofosveset) - (SI\ lung\ pre\text{-}gadofosveset)}{(SI\ aorta\ post\text{-}gadofosveset) - (SI\ aorta\ pre\text{-}gadofosveset)}$$
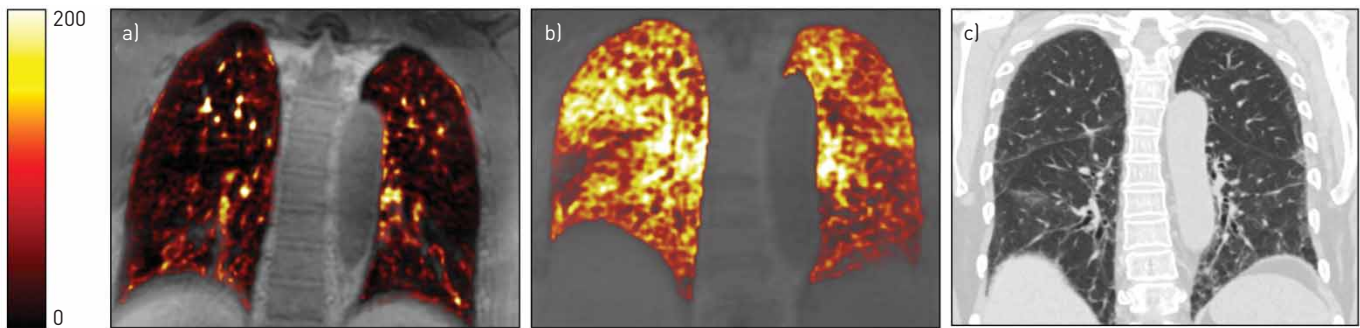
FIGURE 1 Coronal subtraction images with colour overlay. Subtraction of baseline pre-gadofosveset image from 15 min post-gadofosveset image (colour) superimposed on baseline image. a) Healthy control. b) Subject with idiopathic pulmonary fibrosis (IPF). c) Computed tomography image of the same subject with IPF. In a), signal enhancement is isolated to areas of known blood vessels with the majority of the lung unenhanced. In b), regions of signal enhancement extend well beyond major vessels and into the lung parenchyma, consistent with increased albumin extravasation. When comparing b) to c), regions of increased signal intensity occur in areas of radiographically normal lung in addition to areas with known fibrosis.

We averaged the AEIs from the right and left lung at each location and then across the three time points to use for subsequent calculations. We calculated total, coronal and axial AEIs to assess the degree of vascular permeability from measured lung regions, and AEIs for each anatomical section to assess the anatomical distribution of alveolar–capillary permeability. Statistical analyses were performed using Prism 6.0 (GraphPad Software, La Jolla, CA, USA) using Mann–Whitney U and one-way ANOVA as appropriate, with p-values <0.05 considered statistically significant. Data are reported as median (range). To visualise the location of albumin extravasation, subtraction images with colour overlay were constructed (figure 1).

Subjects with pulmonary fibrosis had a total AEI of 0.37 (0.32–0.46) *versus* 0.17 (0.12–0.28) for controls (p=0.01). The AEI was increased in subjects with IPF across coronal (0.34 (0.30–0.42) *versus* 0.16 (0.13–0.26), p=0.01) and axial (0.43 (0.32–0.56) *versus* 0.20 (0.06–0.30), p=0.01) measurements. The AEI was also increased across both anterior (0.39 (0.26–0.45) *versus* 0.15 (0.07–0.22), p=0.01) and posterior (0.32 (0.26–0.39) *versus* 0.18 (0.16–0.30), p=0.02) coronal locations as well as upper (0.45 (0.40–0.51) *versus* 0.21 (0.10–0.32), p=0.01), middle (0.40 (0.31–0.57) *versus* 0.21 (0.05–0.30), p=0.01) and lower (0.44 (0.33–0.56) *versus* 0.20 (0.08–0.30), p=0.01) axial locations in IPF subjects. The AEI was increased similarly across axial locations for UIP subjects. Significance for all AEIs persisted even when excluding the scleroderma–UIP values.

Subtraction images demonstrate a marked increase in SI in IPF patients compared to healthy controls (*e.g.* figure 1). For the healthy control (figure 1a), the majority of the lung is nonenhanced and high signal enhancement areas are limited to areas of the vascular tree consistent with the expected distribution of a blood pool magnetic resonance contrast agent. For the subject with IPF (figure 1b), however, regions of enhancement extend well beyond major vessels, were located diffusely throughout the lung fields, and did not display a basilar nor a subpleural preference. When compared to computed tomography chest imaging (figure 1c), increased signal intensity occurred in radiographically normal lung as well as areas with fibrotic changes.

We present the novel application of gadofosveset-enhanced MRI to detect pulmonary vascular leak by directly imaging albumin extravasation for the first time. We found that vascular leak was increased in the lungs of individuals with pulmonary fibrosis compared to healthy controls. These findings build on previous observations indicating disruption of the alveolar–capillary membrane in IPF [7–9]. By specifically imaging albumin extravasation from the vascular compartment, our results provide potentially important information about the spatial distribution of ongoing lung injury in pulmonary fibrosis.

Gadofosveset is a small molecule gadolinium-based contrast agent that binds reversibly to serum albumin. After administration, about 80–90% of the contrast agent is bound to albumin with a dissociation constant of 90 µM [10]. We hypothesised that in vascular leak, the extravascular, extracellular albumin concentration will increase due to extravasation of albumin, and the unbound gadofosveset would extravasate rapidly from the blood into the lung interstitial space and bind to albumin present there. In the absence of gadofosveset extravasation, the AEI would equal the blood volume fraction in the region of lung tissue analysed. Higher AEI values would indicate vascular leak. While we did not validate our albumin extravasation index with albumin extravasation histologically, gadofosveset has been used to assess vascular permeability and response to treatment in the setting of mouse models of accelerated atherosclerosis with correlation of vessel wall MRI signal changes with Evans blue dye [6].

Albumin extravasation was increased in subjects with pulmonary fibrosis similarly across all regions of the lung. Our results suggest that lung injury occurring in pulmonary fibrosis is more diffuse than traditionally thought, and this finding questions why basilar fibrosis predominates in conditions like IPF. Other factors, such as tractional stress or collapse induration, as have been hypothesised [11–13], may create regional differences in wound healing responses that can promote fibrosis rather than normal repair. Insight into the mechanobiological drivers of fibrosis and signalling pathways upregulated by stretch, including transforming growth factor-β [14], may elucidate this further. Albumin extravasation was not limited to fibrotic regions and occurred in areas of radiographically normal lung. Whether some component of these findings could be explained by very early fibrotic changes or neovascularisation is not known. Lung regions with increased vascular permeability may represent areas at risk of developing radiographically apparent fibrosis. Additional research is needed to assess associations between the amount of vascular leak and disease progression. Our results represent an important step towards the use of molecular imaging to assess known processes directly involved in the development of fibrosis.

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