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Quantitative magnetic particle imaging monitors pulmonary vascular permeability in vivo

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Abstract

Increased pulmonary vascular permeability is a characteristic feature of acute lung injury and some chronic lung diseases. Currently there are no established methods to visualize pulmonary vascular permeability change in vivo in in both research and clinical settings. Terminal assays such as Evans Blue test, lung wet/dry ratio, and bronchoalveolar lavage fluid (BALF) total protein test lack the capability of monitoring the dynamics of vascular injury during disease progression. In this study, we used magnetic particle imaging (MPI)-CT dual-modality imaging combined with quantitative image analysis to noninvasively visualize and evaluate pulmonary vascular permeability in vivo in animal models. Oleic acid (OA) induced acute respiratory distress syndrome (ARDS) model was used for imaging. Based on the in vivo 3D MPI-CT images, we defined pulmonary SPIO extravasation index (SEI) to evaluate the vascular permeability. Significantly increased SEI was observed in the ARDS mice, which correlated well with ex vivo imaging findings. Moreover, quantitative imaging results were validated by ex vivo Evans Blue test, lung wet/dry ratio, BALF total protein concentration measurements and H&E histology. Our results suggest that 3D quantitative MPI-CT can be used to evaluate pulmonary vascular permeability, providing a noninvasive tool to monitor the dynamic change of pulmonary injury in vivo.

I. Introduction

Pulmonary vascular endothelium forms the main barrier between the blood and the interstitium of the lung, prohibiting the passage of liquid and macromolecules from blood to tissue. In acute lung injury and chronic lung diseases, this barrier is often disrupted, resulting in the increased vascular permeability and extravasation of liquid and proteins into the interstitium and pulmonary air spaces [1]. It has been reported that this process significantly contributes to the mortality of acute lung injury and to the development of progressive pulmonary fibrosis [2]. Detecting and evaluating the vascular permeability change could help to better understand the location and severity of endothelium injury, facilitating the diagnosis of acute respiratory distress syndrome (ARDS) and pulmonary fibrosis, and influencing the administration of therapeutics toward repairing the endothelium barrier.

Currently, there are no established imaging techniques that could visualize the pulmonary vascular permeability changes *in vivo* in both research and clini-

cal settings [3]. CT is useful for identifying pulmonary edema, but could not differentiate the hydrostatic pressure edema from permeability edema, especially in elderly patients with cardiac diseases. Pulsed index continuous cardiac output (PiCCO) is a bed-side monitoring device used in intensive care unit to evaluate extravascular lung water, but lacks visualization capability. In research settings, Evans Blue test, lung wet/dry ratio, and bronchoalveolar lavage fluid (BALF) total protein test are gold standard to assess the pulmonary vascular permeability. However, these are all terminal assays that cannot track the dynamic changes of vascular permeability on the same animal.

Recently, magnetic particle imaging (MPI) has shown promise in pulmonary imaging. As a highly sensitive tracer imaging modality, MPI is not affected by the alveolar air-tissue interface in inflated lungs, which is often a significant problem in MRI and ultrasound imaging. Unlike CT or nuclear medicine, MPI uses superparamagnetic iron oxide (SPIO) for imaging which has no ionizing radiation. Previously, MPI has been used to monitor lung perfusion [4], lung ventilation [5], and inhaled aerosol delivery [6]. In this work, we demonstrate the first *in vivo* quantitative MPI of pulmonary vascular permeability using lung injury models.

II. Material and methods

Oleic acid (OA) induced acute respiratory distress syndrome (ARDS) mouse model was used in this work to validate the feasibility of using MPI to monitor pulmonary vascular permeability. Specifically, OA (0.1 ml/kg) was injected intravenously in 7-week-old Kunming mice and ARDS was established within 10 min post injection. For imaging experiments, commercial SPIO Synomag-D (3mg/kg) was injected intravenously. 3D MPI was performed with default mode using the Magnetic Insight Momentum scanner at 6h post SPIO administration. CT images were acquired with our in-house built CT scanner and co-registered with the MPI images. After *in vivo* imaging, mice were euthanized and major organs were extracted. 2D MPI images of the lung, liver, spleen, heart and kidney were acquired.

Based on the 3D-MPI/CT images, we defined SPIO extravasation index (SEI) as the sum of pixel intensities (PXLI) over the pulmonary area divided by the sum of PXLI over the entire body, and normalized by the total volume of the lung:

$$SEI = \frac{\sum_{pulmonary\ area} PXLI_{i,\,j,k}}{\sum_{whole\ body} PXLI_{i,j,k}}, \qquad (1)$$

where i, j, k are the coordinates that identify each pixel. For *ex vivo* 2D MPI images, relative lung signal (RLS) was calculated to confirm the *in vivo* SEI result:

$$RLS = \frac{PXLI_{ave,\,lung}}{PXLI_{ave,\,lung} + PXLI_{ave,\,liver} + PXLI_{ave,\,spleen}} \qquad (2)$$

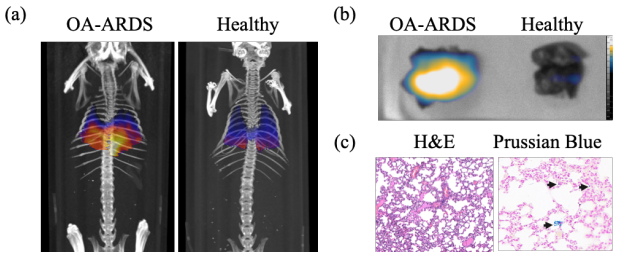

Figure 1: MPI images and histopathological results. (a) Representative in vivo 3D MPI/CT images of the OA induced ARDS mouse (left) and healthy mouse (right); (b) representative ex vivo 2D MPI images of the excised lung tissue of OA induced ARDS mouse (left) and healthy mouse (right); (c) H&E histology and Prussian blue staining of the excised ARDS lung.

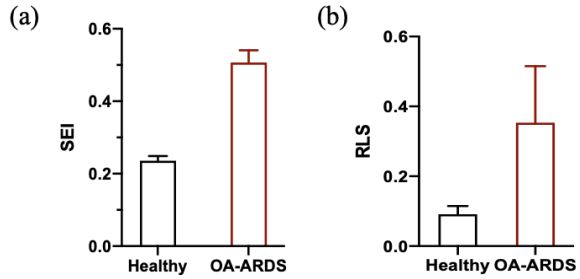

Figure 2: Quantitative analysis of pulmonary vascular permeability based on the in vivo 3D MPI and ex vivo 2D MPI imaging results. (a) SEI of healthy and ARDS mouse quantified from the in vivo 3D MPI/CT images; (b) RLS of healthy and ARDS lung tissue quantified from the ex vivo 2D MPI images.

where $PXLI_{ave,\ lung}$, $PXLI_{ave,\ liver}$, $PXLI_{ave,\ spleen}$ denotes the average pixel intensity of the lung, liver and spleen, respectively.

To further validate our imaging results, Evans Blue test, protein concentration test of the bronchoalveolar lavage fluid (BALF), and lung wet-dry (W/D) ratio were used as gold standard to evaluate the pulmonary vascular permeability.

III. Results and discussion

Representative *in vivo* 3D-MPI/CT images and *ex vivo* 2D MPI images of the excised lung tissue are presented in Fig. 1a and 1b. Significantly increased MPI signal can be observed in the ARDS lung, indicating the leakage of SPIOs into the lung interstitium due to elevated vascular permeability. In H&E histology (Fig. 1c), alveolar wall thickening and vascular leak can be observed in the ARDS lung. Prussian blue staining further confirms the extravasation of SPIOs.

Quantitative image analysis results are presented in Fig. 2. As described in section II, SEI and RLS were calculated based on the *in vivo* and *ex vivo* MPI images, re-

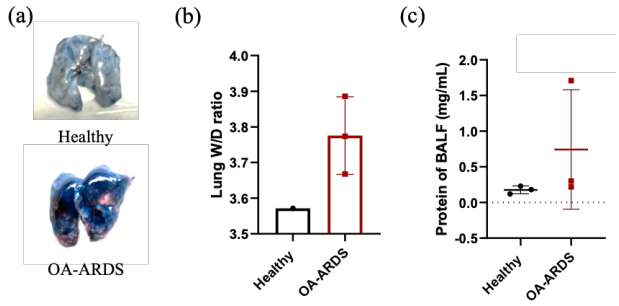

Figure 3: Pulmonary vascular permeability assessment via terminal assays. (a) SEI of healthy and ARDS mouse quantified from the in vivo 3D MPI/CT images; (b) RLS of healthy and ARDS lung tissue quantified from the ex vivo 2D MPI images.

spectively. Our results show that both SEI and RLS of the ARDS group are more than two times higher than those of the healthy group, providing a quantitative method to evaluate the vascular permeability.

Quantitative imaging results of the vascular permeability were compared with results obtained via gold standard terminal assays. In Fig. 3a, Evans Blue extravasation can be visualized clearly in the ARDS lung, confirming the hyperpermeability of the injured lung vasculature. The lung W/D ratio is higher in ARDS model, representing the increased extravascular lung water (Fig. 3b). BALF protein concentration is elevated in the ARDS model, demonstrating the extrusion of protein from blood to the alveolar space (Fig. 3c). Overall, results obtained from the terminal assays are in consistent with our *in vivo* imaging findings, validating the use of MPI imaging and quantitative image analysis to evaluate vascular permeability *in vivo*.

IV. Conclusions

Our results show that 3D MPI imaging successfully tracks the vascular permeability changes *in vivo* in acute lung injury. Quantitative 3D MPI imaging may serve as an *in vivo* tool to monitor the pulmonary vascular permeability. Further studies are underway to investigate the value of this imaging technique in other disease models such as sepsis and pulmonary fibrosis.

Author's statement

Conflict of interest: Authors state no conflict of interest. Ethical approval: The research related to animal use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

References

[1] M. A. Matthay, *Acute respiratory distress syndrome*, Nat. Rev. Dis. Primers, vol. 5, 1 18, Mar. 2019.

[2] C. K. Probst, *Vascular permeability in the fibrotic lung*, Eur. Respir. J., vol 56, 1 1900100, Jul. 2020.

[3] J. Jagtap, *A rapid dynamic in vivo near-infrared fluorescence imaging assay to track lung vascular permeability after acute radiation injury*, Am. J. Physiol. Lung Cell Mol. Physiol., vol. 320, pp. L436-L450, Mar. 2021.

[4] X. Y. Zhou, *First in vivo magnetic particle imaging of lung perfusion in rats*, Phys. Med. Biol., vol. 62, pp. 3510-3522, May 2017.

[5] K. Nishimoto, *Application of Magnetic Particle Imaging to Pulmonary Imaging Using Nebulized Magnetic Nanoparticles*, Open Journal of Medical Imaging, vol. 5, pp. 49-55, Jun. 2015.

[6] Z. W. Tay, *In vivo tracking and quantification of inhaled aerosol using magnetic particle imaging towards inhaled therapeutic monitoring*, Theranostics, vol. 8, pp. 3676-3687, Jun. 2018.

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