Quantification of local lung disease in rat models of cystic fibrosis disease

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BACKGROUND

- Obtaining detailed easily-interpreted quantitative measures of lung function is a common challenge in research and clinical practice.
- Current practice typically involves lung function testing (e.g. FEV1 or FOT) combined with assessment of structural lung disease by CT.
- We have reported on the performance of x-ray velocimetry (XV), a novel technique that combines particle-image velocimetry analysis techniques and propagation-based x-ray phase contrast imaging [1].
- XV provides <u>regional</u> information on tissue displacement across the entire lung through the breath, from which airflow can be derived [1].

AIM

- The aim of this project was to use XV to assess the obstructive effect of agar beads in normal rats, and perform a preliminary respiratory phenotype characterisation in CFTR knockout (KO) rats.

METHODS

- Imaging was performed at the Australian Synchrotron Imaging and Medical Beamline (IMBL; Fig. 1a). XV procedures were adapted from those used in mice [2].
- Normal rats and CFTR KO rats (see Poster 35 for phenotype characterisation) from our Adelaide colony were imaged:
  - All rats were tracheostomised and ventilated at 14 cmH_2O PIP, 2 cmH_2O PEEP, 250 ms inspiration, and 500 ms expiration.
  - Image exposure lengths of ~40 ms were used, and 15 images were collected per breath. A total of 12,133 projections (Fig. 1b) were captured over 182 degrees of rotation, and binned into 15 CT datasets with ~800 projections in each (Fig. 1c).
  - After baseline imaging varying concentrations of sterile agar beads in saline were delivered to the normal rat lungs via a PE10 cannula, and a second XV scan was performed.
- CT volumes were reconstructed with X-TRACT (Fig. 1d) and our XV analysis algorithms were applied to produce a lung expansion map (Fig. 1e and Fig. 2).
- Probability density functions (PDF) of local lung expansion (Fig. 3), were used to calculate metrics for presence of heterogeneous, patchy, or clustered disease in each animal [3].

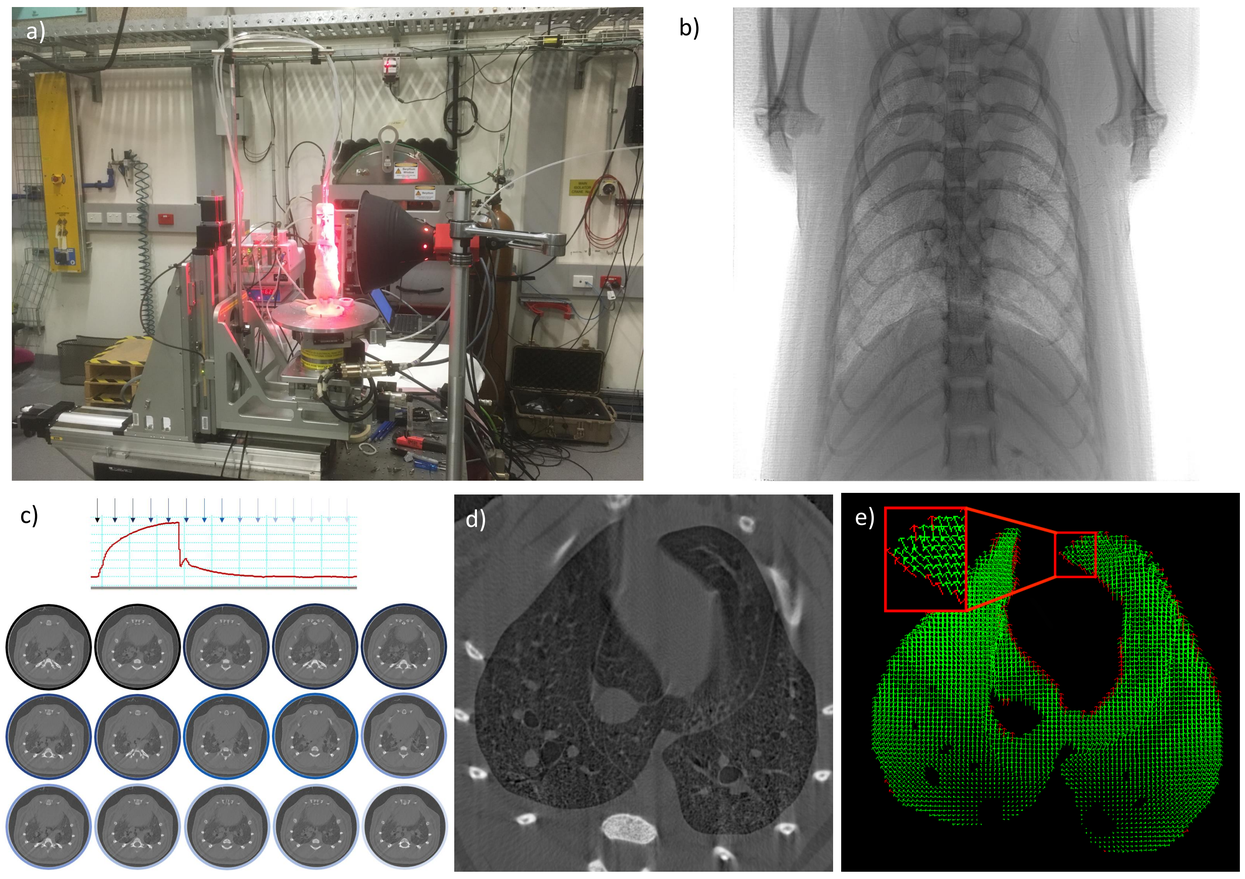

Figure 1: (a) The imaging setup in the IMBL hutch. (b) Example projection image. (c) Projection images are binned into the 15 phases of the breath and reconstructed. (d) Example reconstructed slice. (e) XV analysis produces a vector map that shows how the lung tissue moves during the breath (green indicates a confident measurement, red indicates some uncertainty).

RESULTS

- The effect of agar beads was clearly seen in the lung motion, resulting in local areas of decreased expansion (white arrow in Fig. 2b, which corresponds to the lower peak in Fig. 3a).
- In CFTR KO rats, PDF analysis of XV tissue expansion data (Fig. 3c) reveals an increase in the range of expansion values seen across the lungs compared to normal rats.

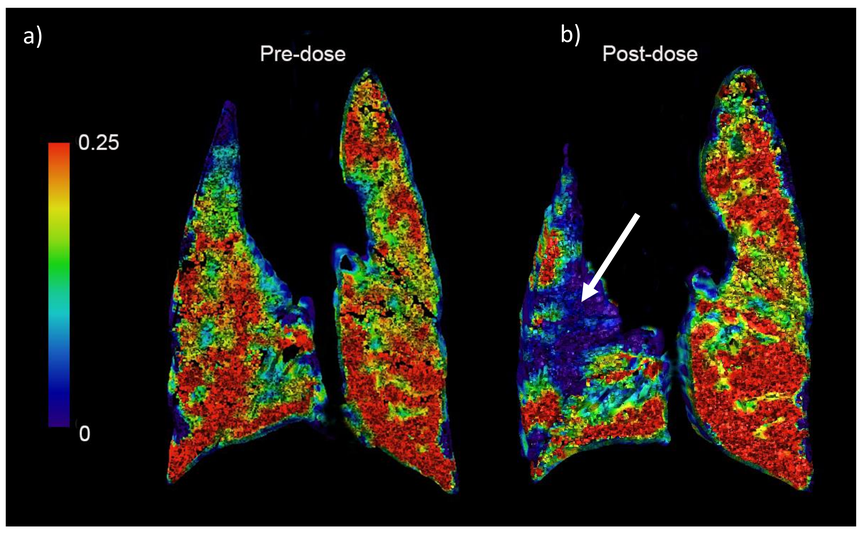

Figure 2: A central slice through the lung showing expansion data from (a) an XV scan before dosing, (b) XV scan after beads were dosed into the trachea and deposited in the right upper lobe.

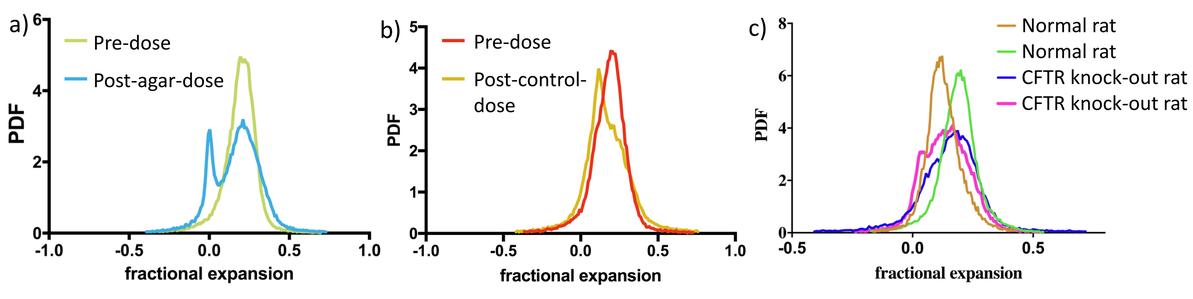

Figure 3: Probability density functions of fractional expansion. (a) Before and after dosing with agar beads, from the same dataset as Figure 2. (b) Before and after dosing with PBS only (as a no-bead control). (c) In normal and CFTR knock-out rats.

CONCLUSIONS

- Successful adaptation of XV to the larger rat animal model represents a significant advance in XV, and shows the potential to utilise our new CF rat models for genetic therapy assessment.
- Preliminary analysis indicates that the presence and location of agar bead lung obstructions can be detected using XV, and that greater expansion heterogeneity is seen in the lungs of CFTR KO rats.

FUTURE DIRECTIONS

- Studies of mouse and rat lung function have now begun in Adelaide using a new 4Dx Permetium small animal XV scanner (Fig. 4).

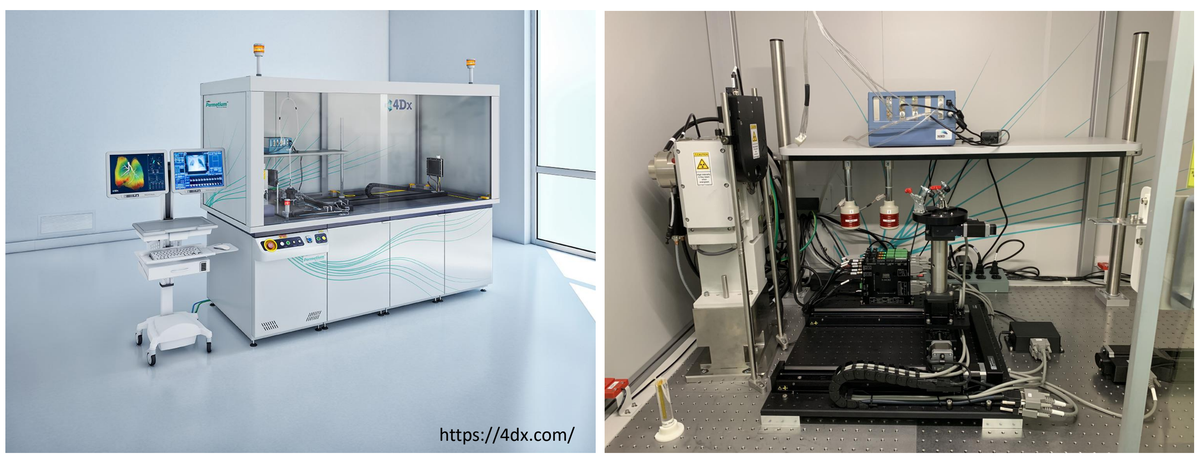

Figure 4: 4Dx Permetium scanner now available at the SAHMRI Gilles Plains Preclinical Imaging and Research Laboratories in Adelaide. The machine allows XV lung function studies to be performed in a range of laboratory animals including rats and mice.

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