

# Phe508del and knockout cystic fibrosis rat lung phenotype assessment via flexiVent and x-ray velocimetry

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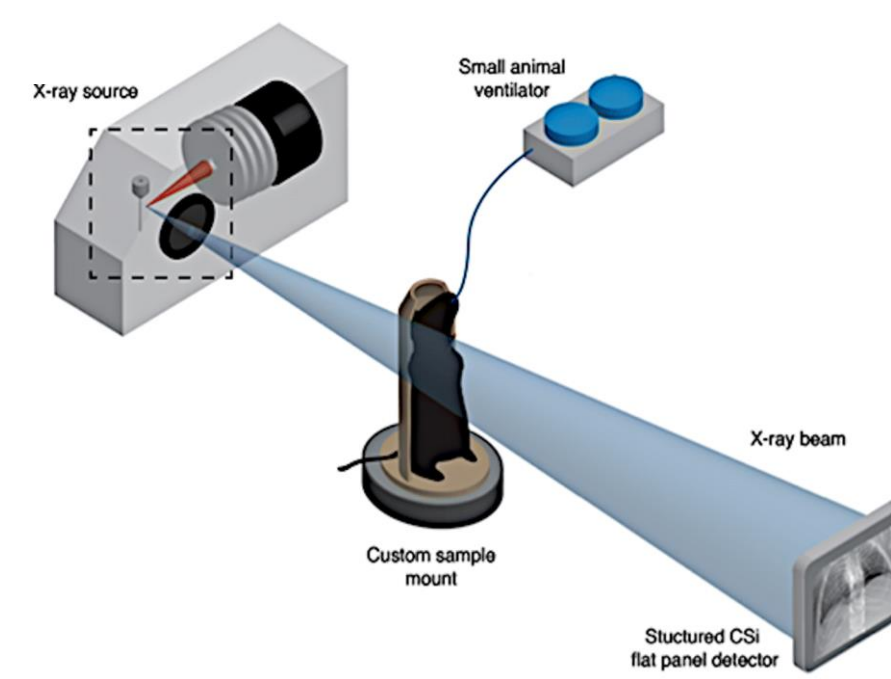
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## BACKGROUND

- We recently generated CF rats with Phe508del and *CFTR* knockout (KO) genotypes that recapitulate important features of human CF disease.
- Both models exhibit CF-related pathologies in a range of organs, with Phe508del rats having milder CF phenotypes than *CFTR* KO rats.
- In the airways, electrophysiological defects are present and *CFTR* mRNA expression in the lungs is significantly reduced when compared to wildtype (WT). A significant increase in acidic mucin and dilated mucus glands in the trachea was observed in KO rats compared to WT, but histologically their lungs appear relatively normal.
- While some aspects of the airways are affected, neither model demonstrates the overt lung disease that is typically seen in humans, or some other CF animal models.

## TECHNOLOGIES

- Scireq flexiVent:** Spirometry has been the gold standard pulmonary function testing method. The flexiVent small animal ventilator enables respiratory mechanics to be assessed in live terminally anaesthetized laboratory animals.
- 4DMedical Permetium:** Lung structure is typically assessed by computed tomography. In contrast, x-ray velocimetry (XV) is an x-ray imaging-based method of measuring lung motion and from that calculating information about regional airflow throughout the respiratory cycle.



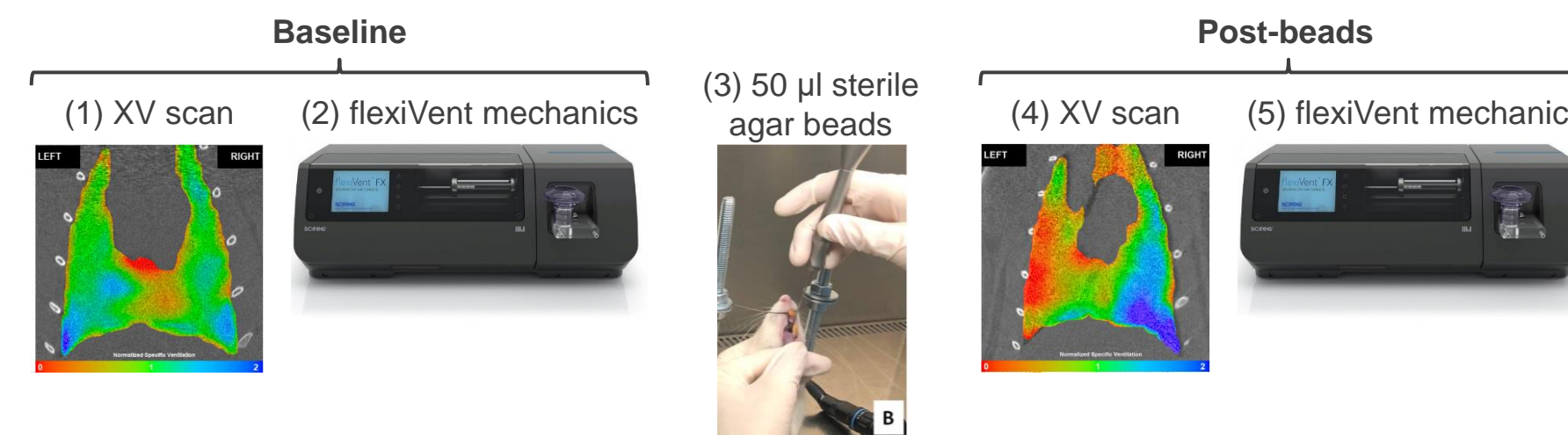
## AIM

- Characterize the lung phenotype of the CF rat models using flexiVent lung mechanics scans and XV imaging.
- Assess the impact of a localised insult to the airways on the measured parameters and validate that XV can determine the location of any resulting airflow defect.

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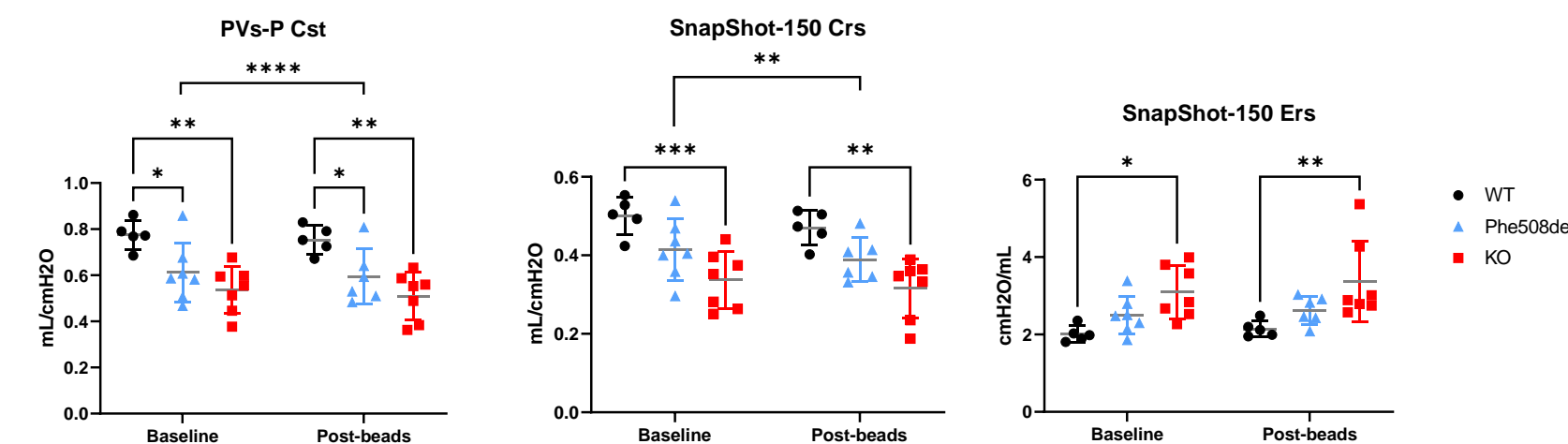
## METHODS

- WT, Phe508del and KO rats (n=5-7 per group) were anaesthetised using a mix of medetomidine and ketamine, and then surgically intubated.
- Rats were placed into a Permetium scanner (4DMedical, Melbourne, Australia), and a single 4D XV scan was acquired.
- Animals were then connected to a flexiVent small animal ventilator (Scireq, Canada) and baseline mechanics scans were performed in triplicate.
- To test the ability of these two systems to detect a regional airflow defect, a 50 µl dose of sterile agar beads (median diameter ~100 µm) in saline was then delivered by miniature bronchoscope into either the left or right main bronchus. The Permetium and flexiVent scans were then repeated.
- Statistical analysis was performed using GraphPad Prism.

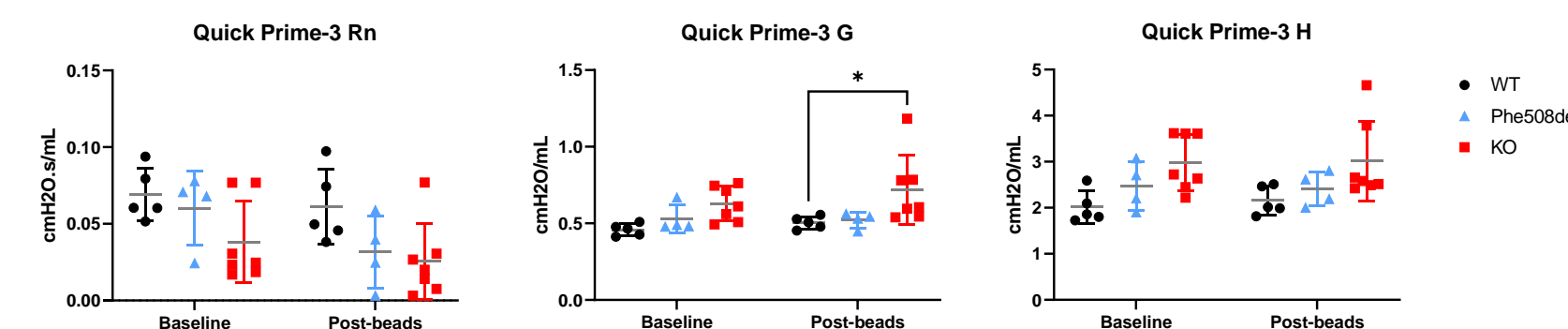


## RESULTS

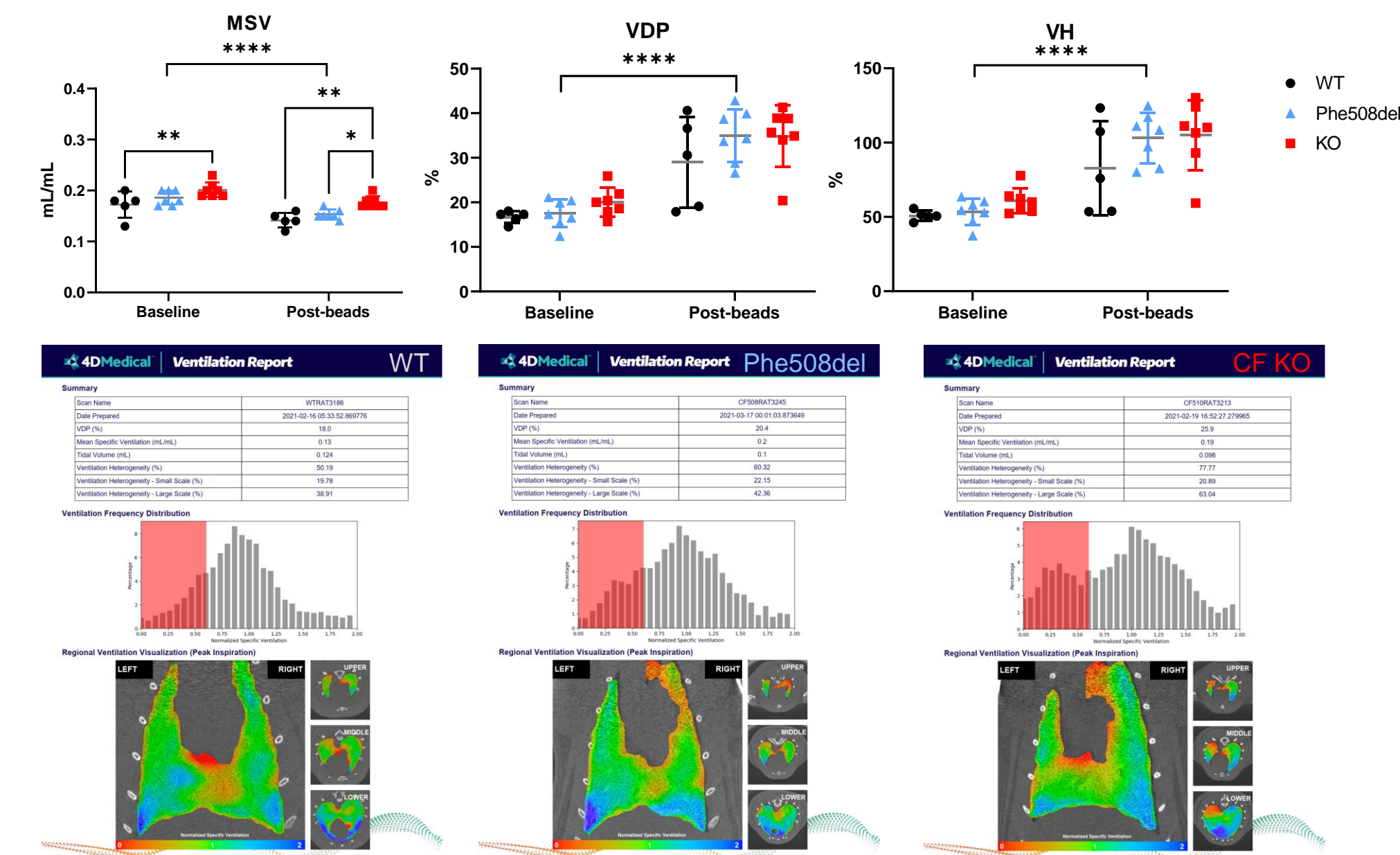
- Using the **flexiVent**, baseline pressure volume loops (PVs-P) showed decreased static compliance (Cst) in the Phe508del (p<0.05) and KO rats (p<0.01) compared to WT. Cst decreased after bead delivery (p<0.0001).
- Compliance (Crs, p<0.001) and Elastance (Ers, p<0.05) measured with the SnapShot single compartment model were also altered in the KO animals compared to WT. Compliance also reduced (p<0.01) following bead delivery.



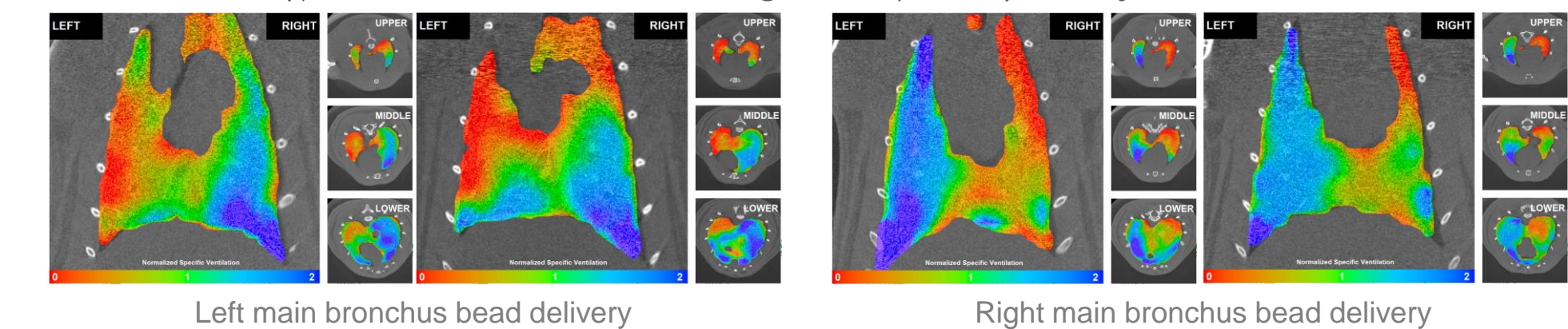
- The forced oscillation technique showed no detectable baseline differences in Newtonian resistance (Rn), damping (G) or elastance (H) in Phe508del or KO rats.



- Baseline **XV imaging** showed increased mean specific ventilation (MSV) in KO rats compared to WT (p<0.01). MSV, ventilation defect percent (VDP), and ventilation heterogeneity (VH) significantly increased after bead delivery.



- XV imaging provides regional information about where in the lung the functional changes from bead delivery originate, with the airflow defect location (↓ ventilation red, normal green, ↑ blue) easily identified in all scans.



## CONCLUSION

- This new data suggests that KO rats have poorer peripheral lung mechanics than WT rats because they have stiffer lungs.
- flexiVent and XV parameters match previously reported CF rat phenotypes.
- This pilot study shows that XV provides a highly sensitive measure of lung function and health, with defect localization information that is not available from traditional lung function methods.

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