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Excess mucus viscosity and airway dehydration impact COPD airway clearance

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ABSTRACT The mechanisms by which cigarette smoking impairs airway mucus clearance are not well understood. We recently established a ferret model of cigarette smoke-induced chronic obstructive pulmonary disease (COPD) exhibiting chronic bronchitis. We investigated the effects of cigarette smoke on mucociliary transport (MCT).

Adult ferrets were exposed to cigarette smoke for 6 months, with *in vivo* mucociliary clearance measured by technetium-labelled DTPA retention. Excised tracheae were imaged with micro-optical coherence tomography. Mucus changes in primary human airway epithelial cells and *ex vivo* ferret airways were assessed by histology and particle tracking microrheology. Linear mixed models for repeated measures identified key determinants of MCT.

Compared to air controls, cigarette smoke-exposed ferrets exhibited mucus hypersecretion, delayed mucociliary clearance (−89.0%, $p<0.01$) and impaired tracheal MCT (−29.4%, $p<0.05$). Cholinergic stimulus augmented airway surface liquid (ASL) depth (5.8±0.3 to 7.3±0.6 µm, $p<0.0001$) and restored MCT (6.8±0.8 to 12.9±1.2 mm·min^{-1}, $p<0.0001$). Mixed model analysis controlling for covariates indicated smoking exposure, mucus hydration (ASL) and ciliary beat frequency were important predictors of MCT. Ferret mucus was hyperviscous following smoke exposure *in vivo* or *in vitro*, and contributed to diminished MCT. Primary cells from smokers with and without COPD recapitulated these findings, which persisted despite the absence of continued smoke exposure.

Cigarette smoke impairs MCT by inducing airway dehydration and increased mucus viscosity, and can be partially abrogated by cholinergic secretion of fluid secretion. These data elucidate the detrimental effects of cigarette smoke exposure on mucus clearance and suggest additional avenues for therapeutic intervention.