The Use of Molecular Imaging Methodology to Develop a Feed Forward Model to Assess Lung Function in Mustard-Induced Lung Injury

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Nitrogen mustard (NM; Tris[2-chloroethyl] amine) is a cytotoxic vesicant known to cause pulmonary damage which progresses to chronic fibrosis. Using computed tomography (CT) and magnetic resonance imaging (MRI) we can monitor NM-induced alterations in the lungs non-invasively as pathology develops. The goal of this study was to use structural changes identified by MRI and CT scanning to predict functional alterations, so as to conduct *in vivo* toxicological assessment. Male Wistar rats were exposed to PBS (control) or NM (0.125 mg/kg) via i.t. instillation. CT and MRI scans were performed prior to exposure and 3, 7, 14 and 28 d post exposure. To correlate pulmonary structure and function rats imaged at 3 and 28 d post NM exposure were assessed for lung function using a SCIREQ flexiVent. Baseline pulmonary mechanics were collected at a positive end expiratory pressure (PEEP) of 3 cm H_2O. Total lung volume was calculated from MRI (W) as it provides an accurate and artifact free assessment of lung tissue volume. The relative volumes of the lung using CT were used to summarize hyperinflation (I), normal lung, and consolidated lung tissue (B) using voxel density as a marker. CT is capable of differentiating between areas of the lung as air and water which are separated by over 1000 Hounsfield units; allowing voxel density to be used as a direct measure of fluid density within the tissue. Using these elements, we constructed a feed forward model to predict respiratory impedance (Z), a measure of airflow through a system, with the equation: Z = ((H(η-j))/(ω^α)) where H =(B/(I+W)). Calculated H revealed lung alterations following NM exposure (1.38 ± 0.08 n=4 in controls vs 0.99 ± 0.16 n=3) as a result of hyperinflation in NM-treated rats. The predicted Z spectra Z spectra generated using the flexiVent at PEEP 3. A strong correlation was observed between predicted and measured Z spectra at 28 d post NM (R^2=0.98 ± 0.01, n=7). Both the predicted and the measured Z spectra were consistent with prior data showing loss of function at higher frequencies. Data was also analyzed at 3, 7, and 14 d to provide longitudinal analysis of the functional pathological changes over time. End expiratory pressure can be used to further assess lung function. These findings indicate that structural imaging data can be used to predict lung function as a toxicological endpoint following exposure to pulmonary toxicants. *Supported by NIH U54AR055073, R01ES004738, P30ES005022.*