Respiratory Assessment Using Intra-Plural Pressure/Head-Out Plethysmography in a Repetitive Bleomycin Challenge Model of Pulmonary Fibrosis in the Conscious Rat

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1 Introduction

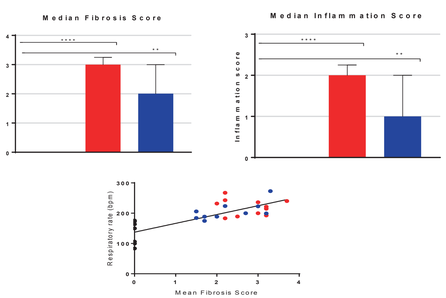
Idiopathic Pulmonary Fibrosis (IPF) is a life threatening lung disease caused by repetitive micro-injuries to the alveolar epithelium. Nintedanib, approved for the treatment of IPF, slows the decline of lung function and extends life. The objective of this study was to use IPP-HOP (Intra-Plural Pressure/Head-Out Plethysmography) to assess changes in respiratory parameters during the acute and fibrosis phases of bleomycin-induced injury. IPP-HOP ventilatory parameters were compared with data from whole body plethysmography (WBP). Respiratory waveform data from HOP were also processed using a novel mathematical method (Modified Attractor Reconstruction, MAR)(Attractor)(1,2).

4 Conclusion

These data demonstrate that the IPP-HOP system detects changes in a respiratory parameters, including compliance, in the acute phase of bleomycin injury and the extent of early change predicted the severity of fibrosis in conscious rats. These data also show that nintedanib protects the lung before the development of fibrosis. However, IPP-HOP did not detect significant changes in compliance in animals with lung fibrosis. Preliminary analysis using modified attractor reconstruction (Refs 1,2) on respiratory waveform data demonstrated that quantification of the morphology and variability of the respiratory waveform using this approach, may be a more sensitive method to detect fibrotic changes in conscious animals.

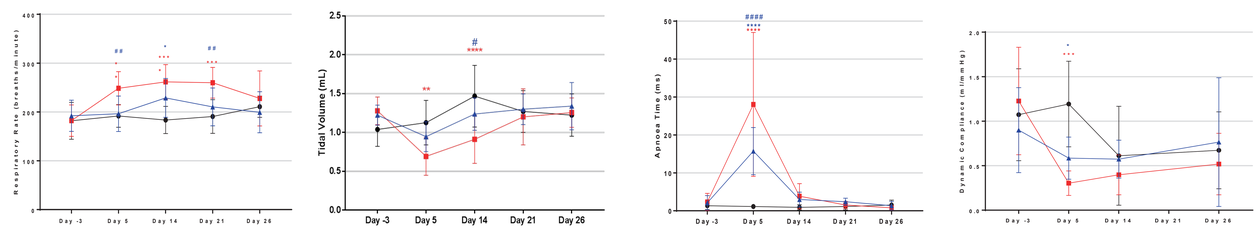
2 Results

Effect of Nintedanib on Bleomycin-Induced Fibrosis and Inflammation Scores (Day 29)



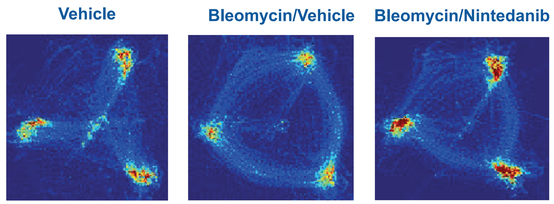
Nintedanib treatment (blue) attenuated bleomycin (red) fibrosis and inflammation score. Respiratory rate (Day 5) was positively correlated with the extent of fibrosis (r^2 = 0.65, P<0.001, Pearson).

Effect of Nintedanib on Bleomycin-Induced Respiratory Changes Using IPP/HOP



During the injury and acute inflammation phase (Week 1), bleomycin (red lines) increased respiratory rate, decreased tidal volume, increased the apnoea time but decreased compliance compared with vehicle controls (black line). During the fibrosis phase (Week 4), all measured parameters were similar to vehicle controls including compliance. Treatment with nintedanib (blue line) attenuated bleomycin–induced respiratory changes. WBP respiratory rate and tidal volumes followed a similar pattern (data not shown).

Attractor Analysis at Day 26



Data were analysed using MAR, a novel mathematical method to enable visualization of waveform morphology and variability (1,2). Bleomycin caused a clear distortion of the attractor shape whereas nintenanib treatment resulted in an attractor that was more similar to the vehicle control. Further work is ongoing to quantify these changes in shape and correlate to extent of lung fibrosis.

3 Methods

Studies were performed in male telemetered SD rats (350 to 400g). Animals were administered vehicle or bleomycin on Days 1, 2, 3 and 6 and treated with nintedanib (60 mg/kg, BID from Day -1 to 27) or vehicle. Respiratory parameters were assessed weekly over the study. Respiratory measurements were obtained by HOP and WBP. At day 29, lungs were removed for fibrosis assessment (modified Ashcroft Score, performed blind). ANOVA with Dunnett's post-test analysis was used to compare differences between groups. The Attractor analysis was performed on the waveform data generated during the IPP-HOP assessments. Refs: (1) Aston et al., 2018 Physiol Meas. 2018 Feb; 39(2): (2) Nandi et al., 2018 Physiol Meas. 2018 Oct 30;39(10):1