Whole body plethysmography-enabled stratification of lung functional deficits in a bleomycin-induced and spirometry-confirmed mouse model of IPF

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BACKGROUND & AIM

Bleomycin (BLEO) induced mouse models of pulmonary fibrosis are widely employed in preclinical drug development. It is well-established that BLEO administration results in a variable disease phenotype. This poses a challenge when designing BLEO-IPF mouse studies sensitive enough to consistently detect treatment effects. Here, we characterized whole-body plethysmography (WBP) as an approach to reduce cohort variability at baseline and thereby enable better stratification to treatment in BLEO-IPF mouse models.

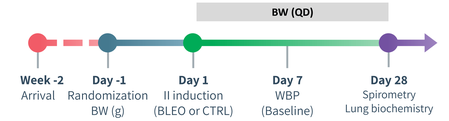
METHODS

Male C57BL/6JRj mice (10-12 weeks old, n=25) were randomized into study groups based on body weight loss at study day -1. BLEO-IPF mice (n=15) received either a single intratracheal instillation (50 µl) of bleomycin (1.75 mg/kg) or saline (CTRL) at study day 1. Body weights were monitored daily. On study day 7 (baseline), lung function was measured in all animals using whole body plethysmography (WBP) (vivoFlow, EMKA, https://emka.scireq.com/vivoflow). Terminal pulmonary endpoints included spirometry (expiratory/inspiratory capacity), total lung weight and hydroxyproline (HP).

CONCLUSION

+ Baseline WBP reliably detected impaired lung function at 7 days post-BLEO administration.
+ Enhanced pause was ranked as the best suitable parameter for stratification.
+ Enhanced pause closely predicted terminal lung function deficits measured by spirometry as well as lung weight.
+ WBP should be applied for baseline stratification of lung disease in BLEO-IPF mouse models.

1 Study outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume	Dosing concentration
1	CTRL	Male	10	**Saline**	II	Single dose	50 µL	-
2	BLEO-IPF	Male	15	**Bleomycin**	II	Single dose	50 µL	**1.75 mg/kg**

Figure 1. Study outline.
Abbreviations: II: Intratracheal instillation; BW: Body weight; QD: once daily. WBP: Whole-body plethysmography.

2 Metabolic and biochemical parameters

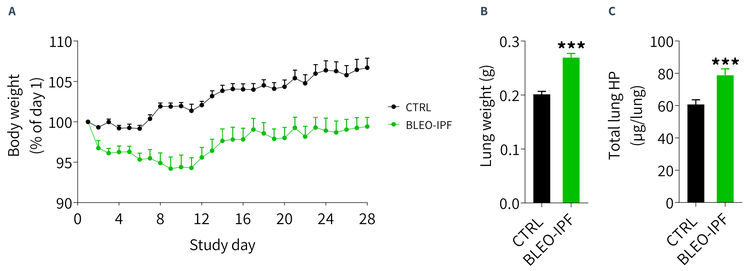


Figure 2. Metabolic and biochemical parameters in CTRL and BLEO-IPF mice.
(A) Body weight change relative to baseline (day 1). **(B)** Terminal lung weight (g). **(C)** Terminal total lung HP. ***p<0.001 compared to CTRL group (Dunnett's test one-factor linear model).

3 Terminal spirometry

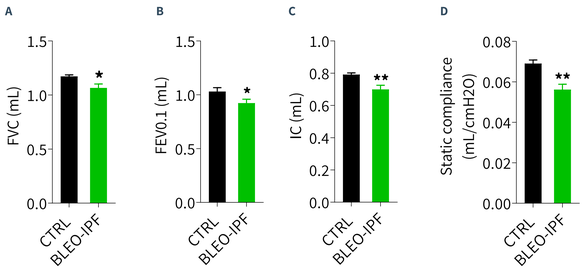


Figure 3. Terminal spirometry parameters in CTRL and BLEO-IPF mice.
(A) Forced vital capacity (FVC). **(B)** Forced expiratory volume in 0.1 seconds (FEV0.1). **(C)** Inspiratory capacity (IC). **(D)** Static compliance. *p<0.05, **p<0.01 compared to CTRL group (Dunnett's test one-factor linear model).

4 Baseline whole body plethysmography

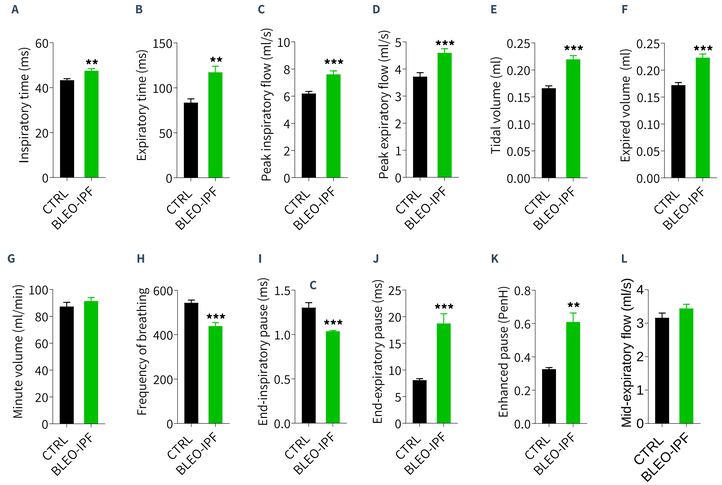


Figure 4. Baseline whole body plethysmography (WBP) in CTRL and BLEO-IPF mice.
(A) Inspiratory time. **(B)** Expiratory time. **(C)** Peak inspiratory flow. **(D)** Peak expiratory flow. **(E)** Tidal volume. **(F)** Expired volume. **(G)** Minute volume. **(H)** Frequency of breathing. **(I)** End-inspiratory pause. **(J)** End-expiratory pause. **(K)** Enhanced pause (PenH). **(L)** Mid-expiratory flow. **p<0.01, ***p<0.001 compared to CTRL group (Dunnett's test one-factor linear model).

5 Enhanced pause is optimal for WBP-based stratification

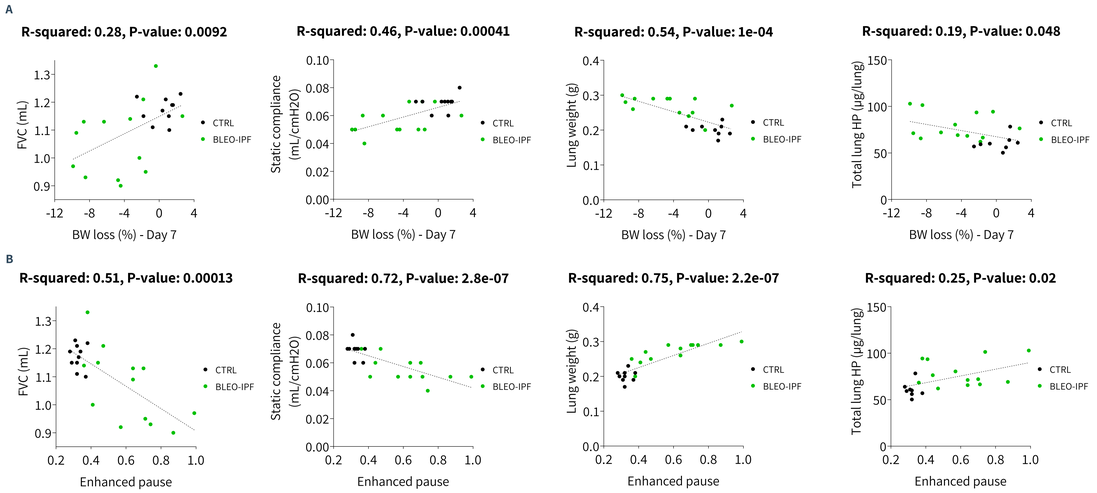


Figure 5. Correlations of relative body weight loss at day 7 post-BLEO administration and enhanced pause to spirometry, metabolic and biochemical parameters.
(A) Forced vital capacity (FVC), static compliance, lung weight or total lung HP plotted against body weight loss at day 7. **(B)** Forced vital capacity (FVC), static compliance, lung weight or total lung HP plotted against enhanced pause.