

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/6J 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 WBP (vivoFlow, EMKA). 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

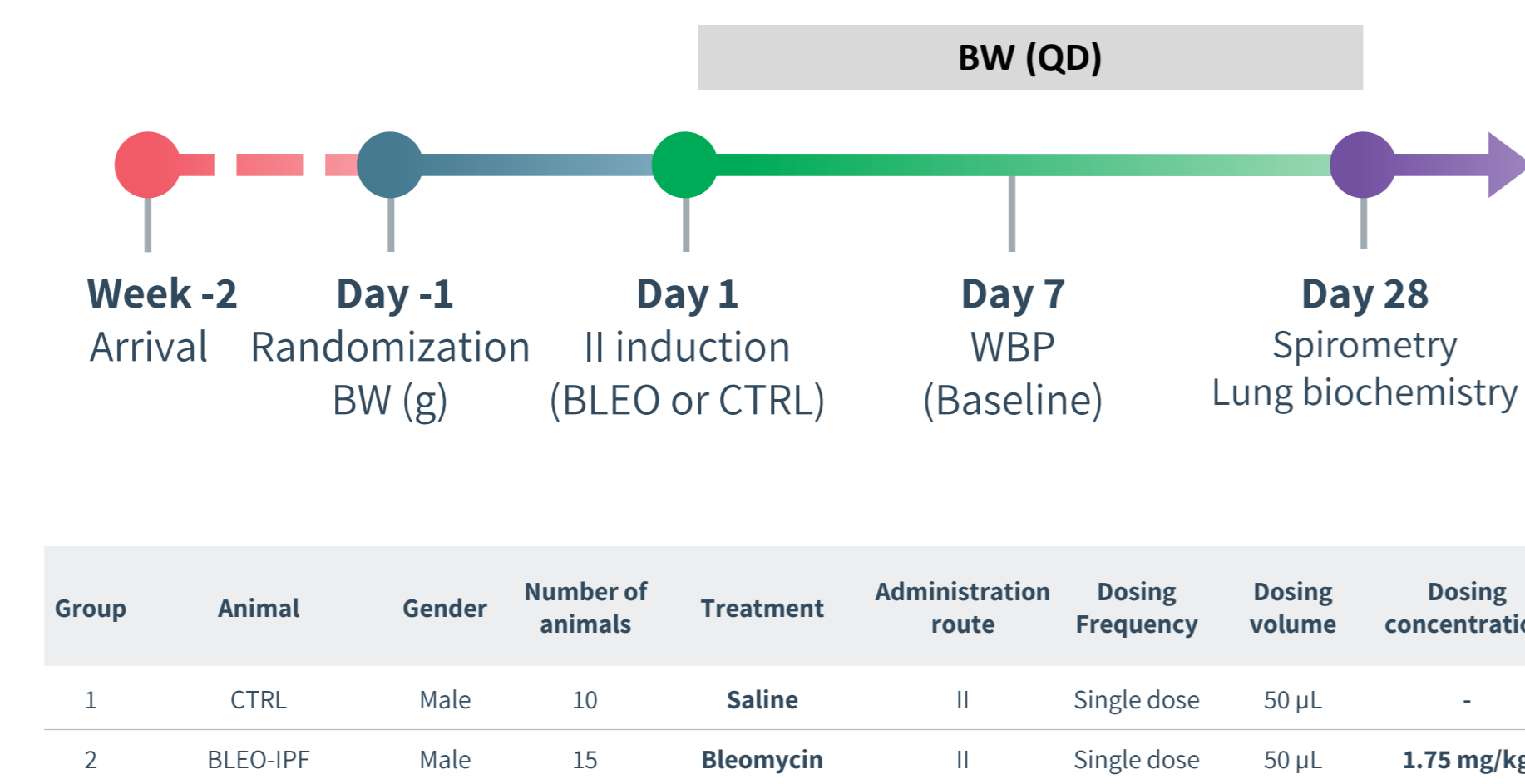


Figure 1. Study outline.

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

2 Metabolic and biochemical parameters

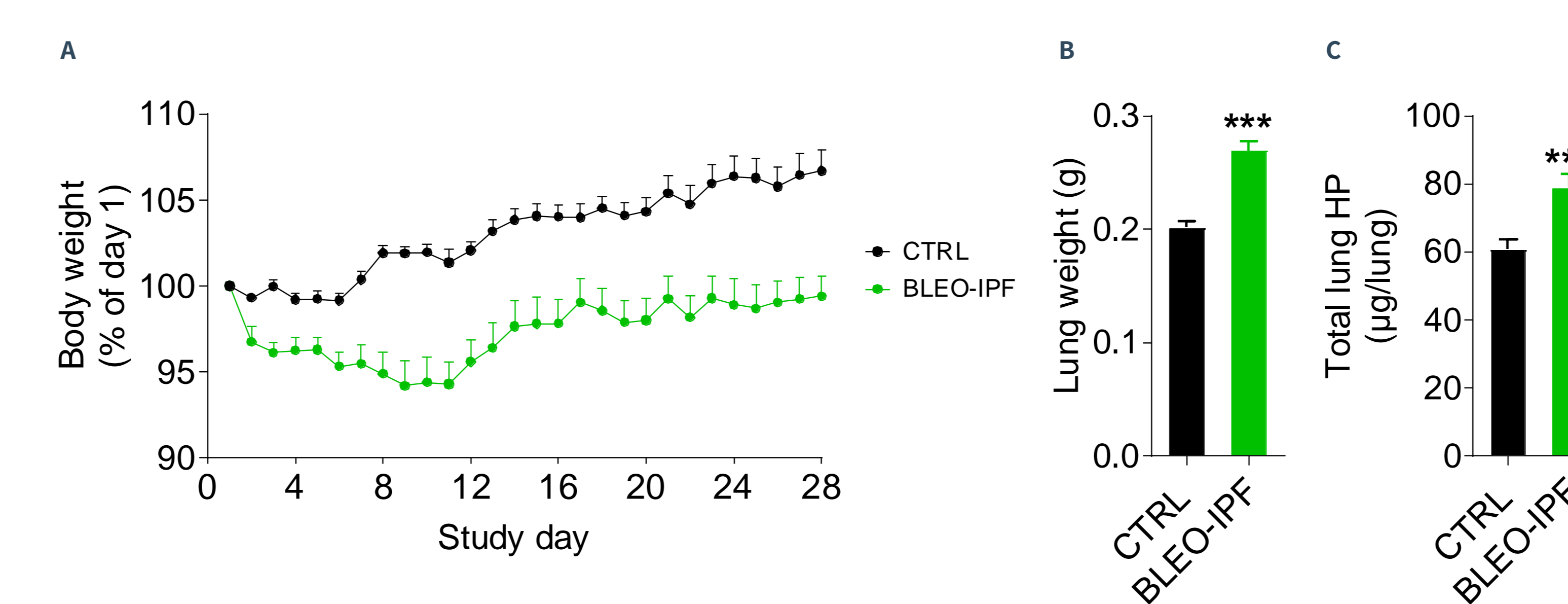


Figure 2. Metabolic and biochemical parameters in CTRL and BLEO-IPF mice.

(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

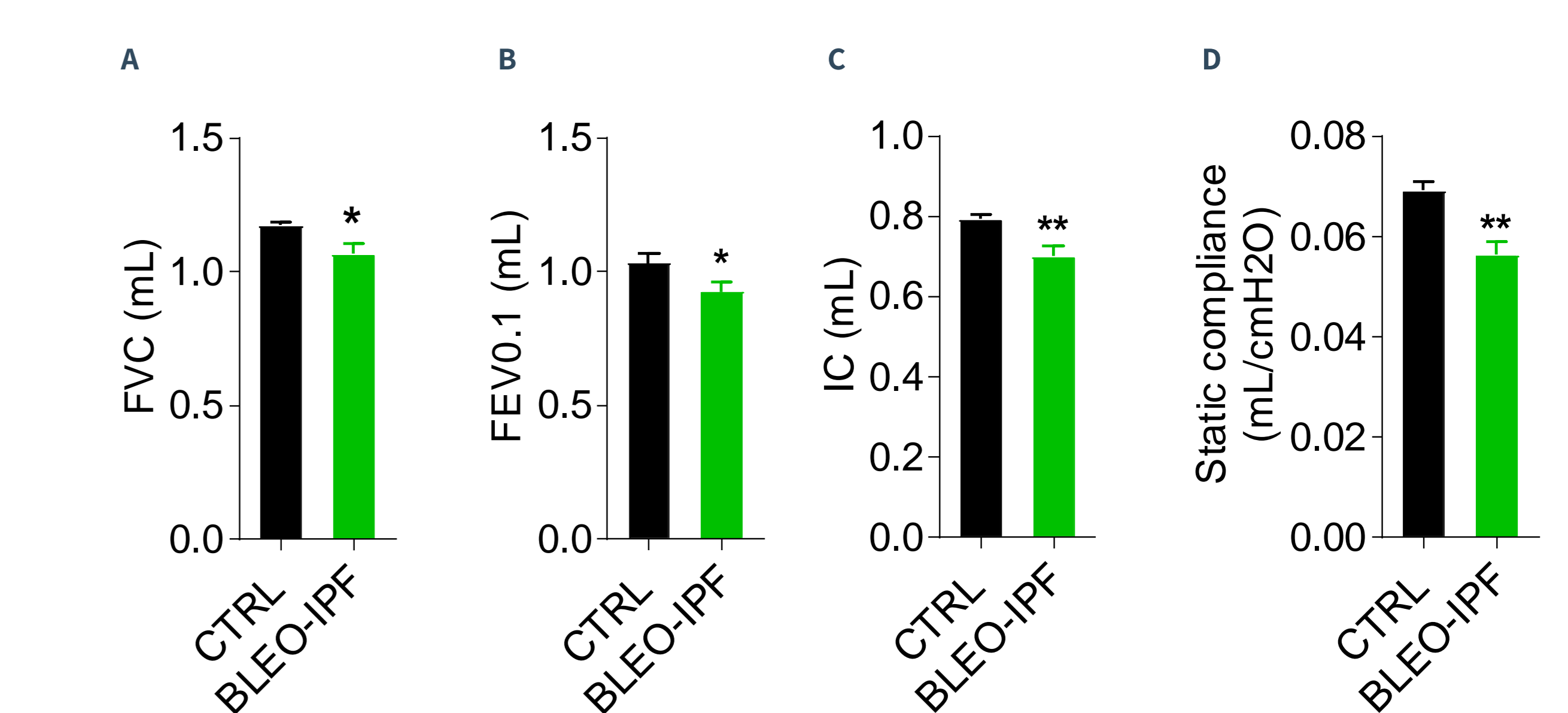


Figure 3. Terminal spirometry parameters in CTRL and BLEO-IPF mice.

(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

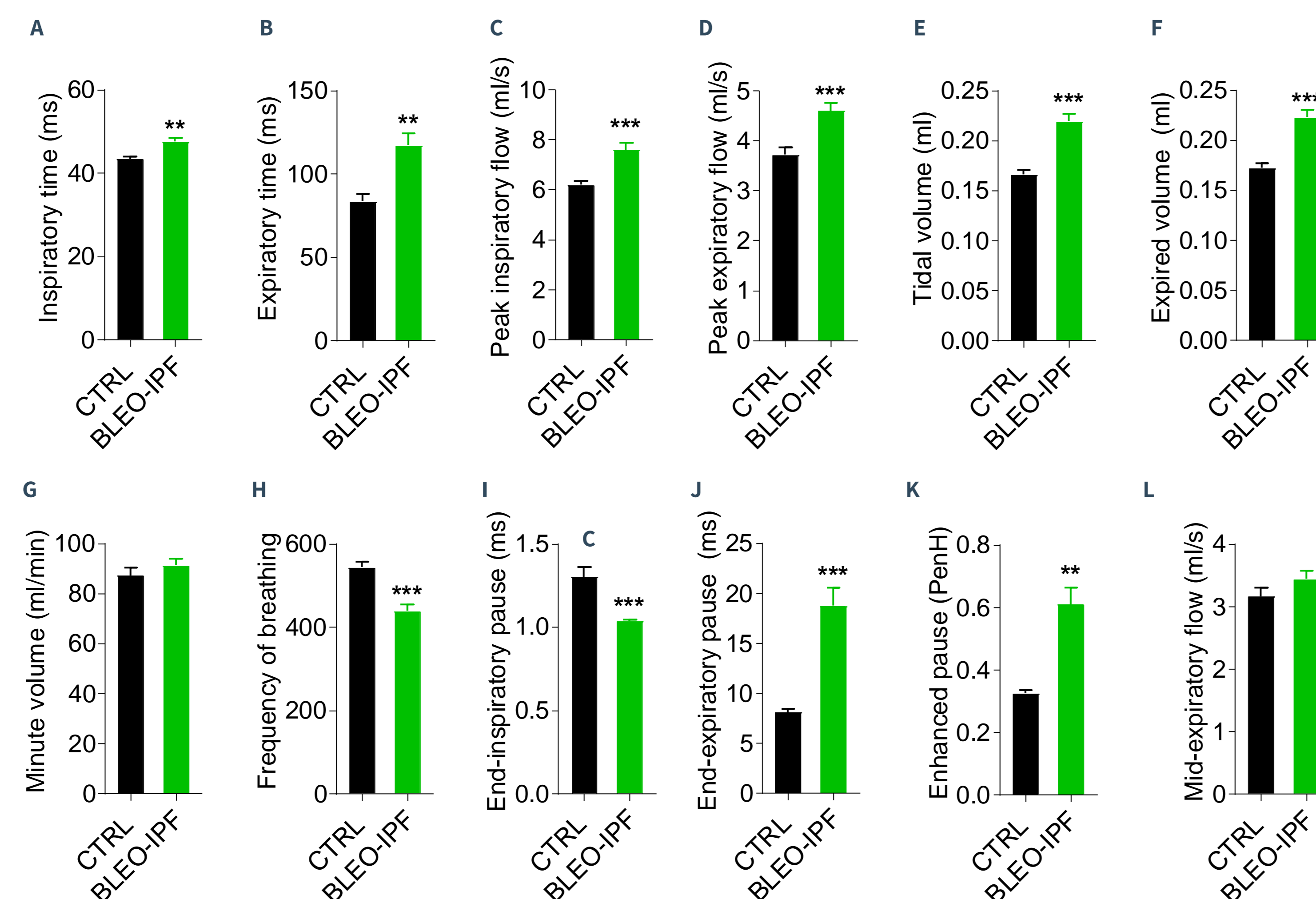


Figure 4. Baseline whole-body plethysmography in CTRL and BLEO-IPF mice.

(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

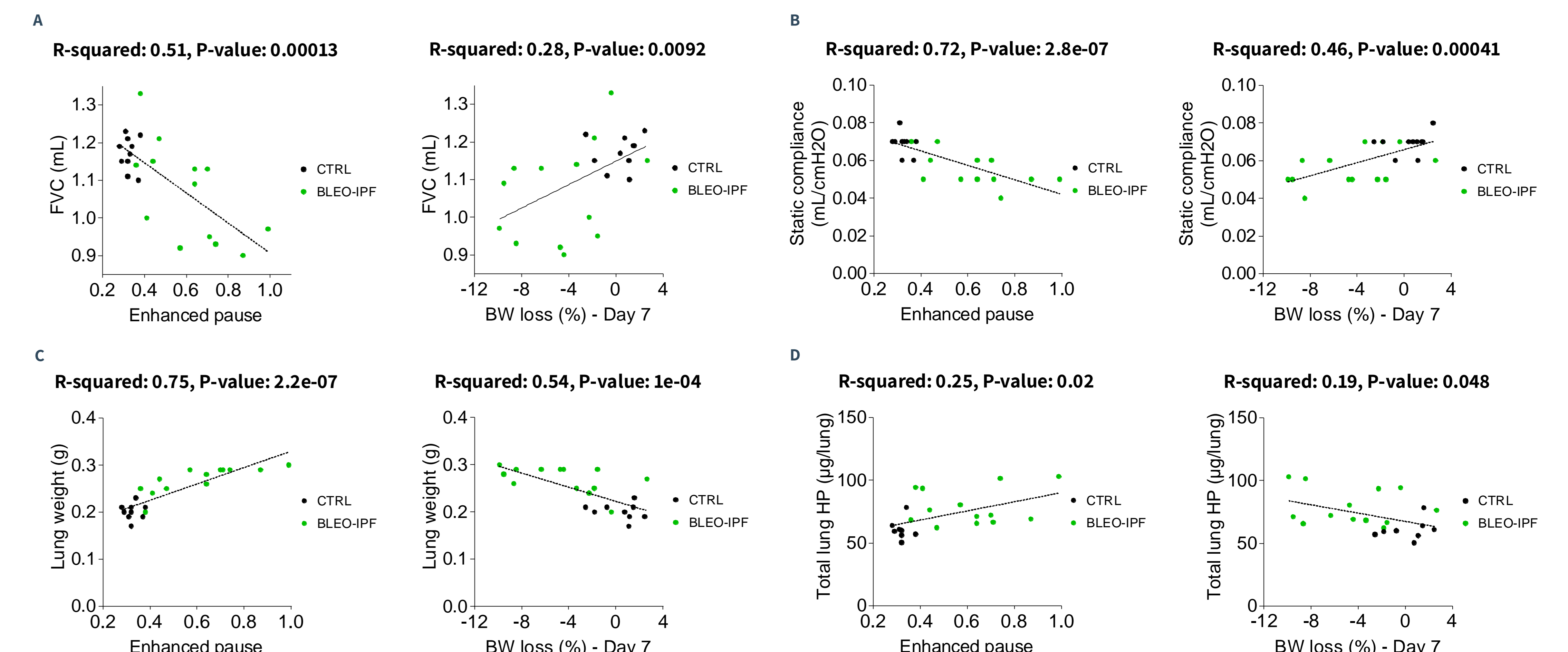


Figure 5. Correlations of enhanced pause and relative body weight loss at day 7 post-BLEO administration to spirometry, metabolic and biochemical parameters.

(A) Forced vital capacity (FVC) plotted against either enhanced pause or body weight loss at day 7. (B) Static compliance plotted against either enhanced pause or body weight loss at day 7. (C) Lung weight plotted against either enhanced pause or body weight loss at day 7. (D) Total lung HP plotted against either enhanced pause or body weight loss at day 7.