

Mechanisms of Fe_{NO} Non-Suppression in Severe Asthma: Analysis of Sputum Type 2 Cytokines and Chemokines

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Background: Non-suppression of fractional exhaled nitric oxide (Fe_{NO}) during remotely monitored inhaled corticosteroid (ICS) therapy is associated with persistent symptoms and blood eosinophilia. To provide mechanistic insight, we assessed sputum type 2 cytokines and chemokines before and after a Fe_{NO} suppression test.

Methods: Fe_{NO} suppression was performed in 44 patients with severe asthma and Fe_{NO} > 40 ppb. Fe_{NO} was monitored for 7 days of 1000µg of fluticasone propionate delivered via an INCA™ device, with clinical and sputum sampling on days 0 and 7. Fe_{NO} suppression was defined as a 42% reduction in Fe_{NO}. Sputum supernatant was analyzed in 15 paired samples by ELISA (Prostaglandin D2, Leukotriene E4) and MSD assays (IL-4,-5,-13,-25,-33, CCL26, TSLP).

Results: Suppressors (n=20) vs non-suppressors had a greater drop in ACQ-5 (meanΔ: -1.2 vs -0.3, p<0.003). Only suppressors significantly (p=0.008) decreased their blood eosinophils (geomeanΔ: -0.27 vs -0.08x10⁹/L, ns). There was a greater reduction in sputum PGD2 in suppressors (2.4-fold) vs non-suppressors (-241 vs 3 pg/mL, p=0.04; Fig.1A). There was a significant 4.7-fold reduction in LTE4 in suppressors (-298 pg/mL, p=0.049; Fig.1B). No significant change was observed for other type 2 sputum proteins or sputum eosinophils.

Conclusion: Failure to suppress Fe_{NO} during ICS treatment was associated with steroid-unresponsive sputum PGD2 and LTE4 levels.

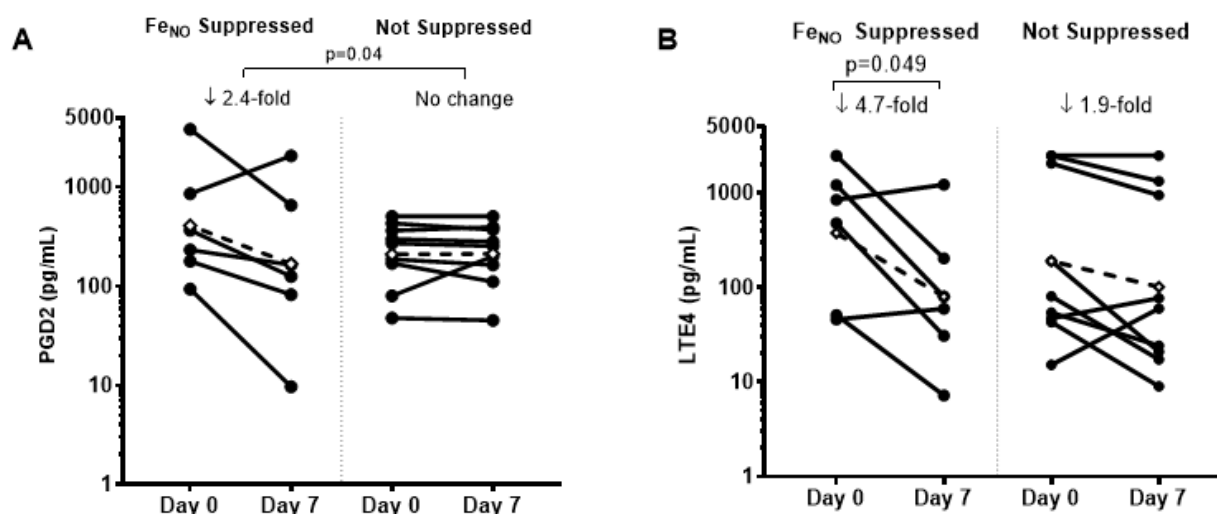


Figure 1. Individual before/after sputum protein levels during Fractional exhaled Nitric Oxide (Fe_{NO}) suppression tests for **A)** Prostaglandin D2 (PGD2) and **B)** Leukotriene E4 (LTE4).
-◇- indicate geometric means