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Title: Increased exhaled nitric oxide precedes lung fibrosis in a murine model of systemic sclerosis

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Body: Background: Exhaled nitric oxide (eNO) increased in patients with systemic sclerosis (SSc) and interstitial lung disease. Reactive oxygen species (ROS) and bleomycin induced skin and lung fibrosis in mice, mimicking the SSc in humans. Objectives: This study aimed to validate eNO measurement method in mice and to study the evolution of lung inflammatory and fibrotic processes in mice injected with HOCl or bleomycin. Methods: C57BL/6 mice were randomized into 3 groups receiving subcutaneous injections of HOCl, bleomycin, or PBS for 2, 4, or 6 weeks. Exhaled NO was measured at the end of each injection period and after 2 resting weeks without injection (8 weeks). Mice were then sacrificed to obtain skin and lung tissues for NO synthases (NOS) expression analysis. Results: Increased exhaled NO, inducible NOS and 3-nitrotyrosine expression in bronchial epithelium, lung neutrophils and macrophages were observed at early phases (2 and 4 weeks) in HOCl- and bleomycin-treated mice. Inversely, lung vascular endothelial NOS expression decreased significantly at 6th and 8th week. Skin fibrosis was significantly increased from the 4th week and lung fibrosis from 6th week. Conclusions: Exhaled NO can be used as a sensitive biomarker of lung inflammation in these murine models in which inflammation precedes fibrotic processes in skin and lungs. Mechanisms linking inflammation and fibrosis remain to be clarified.