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Title: Small moleculae ACE2 activator, diminazene aceturate attenuates bleomycin-induced pulmonary fibrosis

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Body: INTRODUCTION: Angiotensin Converting Enzyme2 (ACE2), a member of the renin angiotensin system has been shown to render protection against lung diseases, particularly pulmonary fibrosis (PF). In this study, we investigated the effects of a recently identified synthetic activator of ACE2, Diminazene aceturate (DIZE) against bleomycin-induced PF. METHODS: A single intratracheal instillation of bleomycin (Bleo, 5U/Kg) in 8-week old male rats induced PF. Animals were randomized into Control, Bleo and Bleo+DIZE groups. DIZE treatment (15mg/Kg, sc) was commenced soon after bleomycin administration. Following 14 days of bleomycin instillation, right ventricular systolic pressure (RVSP) was measured, followed by heart and lung excision to examine cardiopulmonary remodeling. RESULTS: Control rats exhibited a weight gain of 35%, while bleomycin-challenged animals lost 10% of their initial body weight by the end of the study period. Conversely, Bleo+DIZE group demonstrated 16% weight gain. Furthermore, Bleo animals displayed marked elevation in RVSP (Control: 27±1; Bleo: 40±2 mmHg; $p<0.05$, n=5-6), with subsequent development of right ventricular hypertrophy (RVH; Control: 0.26±0.007; Bleo: 0.36±0.03; $p<0.05$). However, DIZE treatment prevented bleomycin-induced increases in RVSP (32±0.5 mmHg; $p<0.05$) and RVH (0.30±0.01; $p<0.05$). Also, DIZE attenuated both the development of PF and the ensuing increase in lung weight/tibial length ratio associated with bleomycin injury. CONCLUSION: Collectively, our results suggest that DIZE prevents bleomycin-induced lung fibrosis and improves cardiopulmonary hemodynamics. Thus, DIZE treatment may represent a promising therapeutic strategy for treating PF.