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**Title:** The effect of airway alkalization by nebulized sodium bicarbonate on airway blood flow

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**Body:** Background: The airway acidifies in a variety of inflammatory lung diseases as measured by exhaled breath condensate (EBC). We have demonstrated in vitro that alkalization improves absorption of cationic bronchodilators, such as albuterol and tiotropium, both in airway epithelia and smooth muscle cells; however, the rationale of airway alkalization therapy is not fully understood. Objective: The purpose of the study was to determine the effect of nebulized sodium bicarbonate (NaHCO<sub>3</sub>) solution on airway vascular smooth muscle function. Methods: Ten healthy non-smoker volunteers participated in the study. To assay airway pH, EBC was collected pre- and post-administration of 4.2% NaHCO<sub>3</sub> (pH=8.4). NaHCO<sub>3</sub> induced CO<sub>2</sub> production was evaluated with a real-time mass spectrometer gas analyzer by measuring Phase 1 and end-tidal CO<sub>2</sub> levels during normal breathing, and breath-hold maneuvers for 5 and 15 sec. Airway vascular smooth muscle responses were assessed by measuring airway blood flow (Q<sub>aw</sub>). Results: After NaHCO<sub>3</sub> administration for 15 min using a heated ultrasonic nebulizer, EBC pH increased from 7.54±0.2 to 8.07±0.09 units (p<0.05). Pre- and post-treatment exhaled CO<sub>2</sub> levels during normal breathing, and breath-hold maneuvers for 5 and 15 sec were not significantly different, suggesting no excessive CO<sub>2</sub> generation from the breakdown of inhaled NaHCO<sub>3</sub>. NaHCO<sub>3</sub> nebulization resulted in an increase of mean Q<sub>aw</sub> from 33.9±3.8 to 48.7±5.5 µl/min/ml (p<0.05). Conclusion: Nebulized NaHCO<sub>3</sub> can increase airway pH without significant effects on exhaled CO<sub>2</sub> levels in healthy subjects. NaHCO<sub>3</sub> induced increase in Q<sub>aw</sub>, together with elevated airway pH, could improve absorption of inhaled cationic bronchodilators.