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**Title:** Assessment of ventilation heterogeneity by impulse oscillometry in patients with mild asthma

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**Body:** Ventilation heterogeneity is an independent determinant of airway hyperresponsiveness (AHR) in asthma, and its measurement is complex and technically difficult. Impulse oscillometry (IOS) is increasingly used to obtain information on the state of the respiratory system. In this study, we determined the clinical validity of IOS as a novel and simple method for the assessment of ventilation heterogeneity in asthma. Serial measurement of resistance at 5 Hz (R5) or 20 Hz (R20) by IOS was performed in 23 mild asthmatic patients and 28 normal control subjects; the measurements were made at baseline, after methacholine (maximal dose) provocation test for asthma and subsequent salbutamol administration. Further, exhaled nitric oxide (eNO) levels were examined and pulmonary function test was also performed. The baseline R5, but not R20, was significantly higher in asthmatic patients than in controls. Both R5 and R20 were not significantly correlated with the degree of airway obstruction and eNO levels. However, R5 was significantly correlated with the severity of AHR ( $r = -0.55$ ,  $P = 0.01$ ), whereas R20 was not. The change in forced expiratory volume in 1 s (FEV<sub>1</sub>) (mean, 30%) after methacholine challenge was almost similar to the change in R20 (20%). However, the change in R5 (77%) after methacholine challenge was significantly greater than the change in FEV<sub>1</sub>, and this finding is consistent with its greater sensitivity to airway dilated responses after salbutamol administration. The proportional change in R5 after methacholine and salbutamol administration is attributable to variable small airway functions, suggesting that R5 may potentially represent ventilation heterogeneity in asthma patients.