Volume history and effect on airway reactivity in infants and adults

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Weiss, A., T. Williams, J. Kisling, C. Clem, and R. S. Tepper. Volume history and effect on airway reactivity in infants and adults. J. Appl. Physiol. 93: 1069–1074, 2002. First published May 17, 2002; 10.1152/japplphysiol.00986.2001.—Volume history is an important determinant of airway responsiveness. In healthy adults undergoing airway challenge, deep inspiration (DI) provides bronchodilating and bronchoprotective effects; however, the effectiveness of DI is limited in asthmatic adults. We hypothesized that, when assessed under similar conditions, healthy infants have heightened airway reactivity compared with healthy adults and that the effectiveness of DI is limited in infants. We compared the effect of DI on reactivity by using full (DI) vs. partial (no DI) forced-expiratory maneuvers on 2 days in supine, healthy nonasthmatic infants (21) and adults (10). Reactivity was assessed by methacholine doses that decreased forced expiratory flow after exhalation of 75% forced vital capacity during a full maneuver and maximal expiratory flow at functional residual capacity during a partial maneuver by 30% from baseline. Reactivity in adults increased when DI was absent, whereas infants’ reactivity was unchanged. Infants were more reactive than adults in the presence of DI; however, adult and infant reactivity was similar in its absence. Our findings indicate that healthy infants are more reactive than adults and, like asthmatic adults, do not benefit from DI; this difference may be an important characteristic of airway hyperreactivity.

Deep inspirations; infant pulmonary function; maturation; forced expiration

Volume history maneuvers, such as deep inspirations, are important determinants of airway reactivity in healthy adults. Deep inspirations have been shown to have a bronchodilating effect, by decreasing the degree of airway obstruction after induced bronchoconstriction (5, 16). In addition, deep inspirations immediately before the administration of the bronchoconstricting agent can diminish the subsequent degree of bronchoconstriction, a bronchoprotective effect (10–12, 17, 20). The mechanisms for the bronchodilating and bronchoprotective effects of deep inspirations in vivo have not been clearly identified; however, it has been suggested that these effects are related to the decreased force generation that results from stretching airway smooth muscle or NO release from nonadrenergic noncholinergic nerves (6–8, 13, 25).

Heightened airway reactivity is a characteristic finding of asthmatic adults, manifested by both greater sensitivity and greater maximal airway narrowing to induced bronchoconstriction compared with healthy adults (26). Asthmatic adults also differ from healthy adults in their response to deep inspirations, demonstrating both smaller bronchodilating and smaller bronchoprotective effects (1, 10, 20). The absence of a significant effect of deep inspiration on airway reactivity may be an important phenotypic expression of airway hyperresponsiveness and may contribute to the greater airway obstruction that occurs in asthmatic subjects.

Our laboratory has previously reported that healthy children have heightened airway reactivity compared with healthy adults matched for somatic size and lung volume (23). We have also found that healthy infants demonstrate a significant reduction in forced expiratory flows after inhalation of relatively low concentrations of methacholine (MCh), suggesting heightened airway reactivity in healthy infants compared with healthy children and adults (14, 21). Airway reactivity in infants has primarily been assessed by using partial forced expiratory maneuvers, a methodology that avoids deep inspirations. The absence of deep inspirations when testing infants may have contributed to their heightened airway responsiveness. In addition, infants are tested in the supine position whereas adults are routinely assessed in the upright position. The supine position has been shown in adults to heighten airway responsiveness secondary to a decrease in lung volume and the elastic load that limits airway narrowing (18).

We hypothesized that infants are more reactive than healthy adults when assessed under comparable conditions. In addition, we hypothesized that heightened airway responsiveness in infants is associated with a smaller effect of deep inspirations on airway responsiveness compared with healthy adults. We therefore compared airway responsiveness of healthy infants and adults in the supine position on 2 different days.

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Changes in airway function during bronchial challenge were assessed with partial flow-volume maneuvers on 1 day (no deep inspirations) and full flow-volume maneuvers on the other day (deep inspirations).

METHODS

Subjects

Twenty-one infants and 10 adults were studied. All were healthy, and the adults were all nonsmokers. None of the subjects had a history of respiratory disease or any upper respiratory symptoms for at least 3 wk before testing. In the infant group, there were 13 boys and 8 girls who ranged in age from 2 to 34 mo and length from 58 to 93 cm. In the adult group, four men and six women were tested, who ranged in age from 24 to 49 yr and height from 165 to 181 cm.

Protocol

Both adults and infants were evaluated in the supine position. The adults were awake, and the infants were sleeping after sedation with chloral hydrate (50–75 mg/kg). MCh challenges were performed on 2 separate days, no more than 7 days apart. Airway function during the MCh challenge was assessed using full expiratory flow-volume (FEFV) maneuvers and partial expiratory flow-volume (PEFV) maneuvers, with the sequence randomized between the 2 days. For the infants, partial and full forced expiratory maneuvers were quantified by the forced expiratory flow at 75% expired vital capacity (FEF75) and maximal expiratory flow at functional residual capacity (VmaxFRC), respectively.

Three reproducible baseline flow-volume curves were obtained. After completion of the baseline flow-volume curves, 2 ml of MCh solution were placed in a nebulizer (Hudson Micromist, no. 1882; Temecula, CA), and an aerosol was generated with 10 l/min flow of compressed air. The MCh aerosol was combined with another source of air at 10 l/min to produce a total flow of 20 l/min, from which subjects inspired for 2 min of tidal breathing. This high flow ensured that the MCh aerosol produced by the nebulizer was contained in a total airflow that exceeded the inspiratory flow of the infant and the adult; thus both age groups inhaled the same aerosol concentration and received an aerosol dose proportional to minute ventilation. Airway function was measured 2 min after inhalation of the MCh. MCh concentrations included 0.075, 0.15, 0.31, 0.62, 1.25, 2.5, 5.0, and 10 mg/ml. The challenge was stopped before the highest MCh dose if FEF75 or VmaxFRC decreased by >40% from baseline, a degree of airway obstruction associated with a change in the shape of the flow-volume curve. After the last MCh dose, 5 mg of albuterol solution was nebulized and inhaled by the subjects.

Equipment and Techniques

Infants. PEFV maneuvers were produced by the rapid thoracic-compression technique. Tidal breathing was observed on the computer screen until a stable end-expiratory level (FRC) was observed; then, at end-tidal inspiration, an inflatable jacket encircling the infant’s chest and abdomen was rapidly inflated to generate PEFV curves. The jacket consisted of an expandable inner compartment surrounded by a stiff outer fabric, inflated from a 40-gallon pressurized reservoir (range 0–150 cmH2O). The compression pressure was progressively increased until there was no further increase in VmaxFRC. Flow was measured by a screen pneumotachometer (Hans Rudolph model 3700, Kansas City, MO) attached to a face mask, which covered the nose and the mouth. The pneumotachometer was connected to a +2 cmH2O differential pressure transducer (Validyne MP-45-871, Northridge, CA). The flow signal was amplified and filtered above 60 Hz (Validyne CD-19A-871 carrier demodulator amplifiers). Analog signals were digitized at 150 Hz (data translation DT2801-A, Marlboro, MA) and stored on an IBM-compatible microcomputer. Volume was obtained by digital integration of the flow signal.

FEFV maneuvers were performed with the raised volume/rapid thoracic-compression technique. The equipment was the same as that used for the partial maneuvers; however, forced expiratory flows were initiated from a lung volume at which the airway pressure was 30 cmH2O (V30). Immediately before the forced expiratory maneuver, several inflations of the respiratory system to V30 produced a brief respiratory pause, which enabled forced expiration to proceed from V30 to residual volume without respiratory effort. Lung inflations were produced by briefly occluding the expiratory side of a bias flow circuit attached to the face mask. During expiratory occlusion, the 20 l/min flow inflated the respiratory system to 30 cmH2O, which was determined by a pressure-relief valve (Sechrist IV-317, Anaheim, CA). Forced expiratory maneuvers were repeated with increasing jacket compression pressures between 40 and 120 cmH2O until the highest expired volume and flows were obtained.

Adults. Adults were supine on a gurney and breathed either through a face mask that covered the nose and mouth or a mouthpiece with clips to close the nares. Flow was measured with a screen pneumotachometer (Hans Rudolph model 3813). The flow signal was amplified, filtered, and processed with the same equipment used for the infants. For the partial flow-volume maneuver, the subject took tidal breaths until a stable end-expiratory level (FRC) was observed on the computer screen; then subjects voluntarily performed a forced expiratory maneuver from end-tidal inspiratory lung volume. Full expiratory flow-volume maneuvers were performed after deep inspiration to total lung capacity.

Analysis

From the PEFV curve, VmaxFRC was measured as the flow referenced to FRC, the end-expiratory level immediately before the maneuver. From the FEFV curve, FEF75 was calculated as the flow at 75% of the expired FVC. The mean baseline values for FEF75 and VmaxFRC were calculated from the three best baseline curves obtained immediately before the bronchial challenge. The values obtained after each MCh dose were expressed as the percent change from baseline, and a dose response curve was then constructed. The MCh concentrations that produced at least a 30% decrease in FEF75 and VmaxFRC were defined as PC30FEF75 and PC30VmaxFRC, respectively. The values of PC30 were log-transformed for statistical analysis. If the subject did not achieve a 30% decrease after inhalation of a nebulized MCh concentration of 10 mg/ml, a logPC30 value of 1.4 was assigned (the log of what would have been the next standard concentration of MCh, 25 mg/ml). Nonparametric analysis
was performed for within-group and between-group comparisons of PC₃₀.

RESULTS

FEFV and PEFV curves obtained during MCh challenges for a representative adult and infant are illustrated in Figs. 1 and 2; full maneuvers (deep inspirations) are shown in A and partial maneuvers (no deep inspirations) in B. A baseline flow-volume curve, before any MCh, is overlaid with flow-volume curves after increasing doses of MCh; only a few flow-volume curves are included for clarity. The calculated dose-response curve for all doses is also included to illustrate the overall sequential nature of the responses. During the full maneuver (FEFV), the adult inhaled MCh doses up to the maximum of 10 mg/ml, with only a minimal decrease in forced expiratory flow and no change in the shape of the curve. However, when not allowed to take any deep inspirations during the partial (PEFV) maneuvers, the same adult subject demonstrated a significant decrease in forced expiratory flows and developed a concave shape to the PEFV curve after only receiving the third dose of MCh (0.31 mg/ml).

The two MCh challenges for a healthy infant are illustrated in Fig. 2. For the FEFV there is a significant decrease in flow and a development of a concave shape to the flow-volume curve at a MCh dose of 5.0 mg/ml. For the PEFV maneuvers there is also a significant decrease in forced expiratory flow and a concomitant shape change at a MCh dose of 2.5 mg/ml.

The individual paired values of PC₃₀ from the full and partial maneuvers are illustrated in Fig. 3 for the adults and infants. The adults were significantly less reactive to MCh (higher PC₃₀) during full maneuvers compared with partial maneuvers (geometric mean: 17.1 vs. 0.75 mg/ml, P = 0.002). In contrast to the adults, there was no significant difference in PC₃₀ when infants were assessed with full compared with partial maneuvers (geometric mean: 1.27 vs. 1.26 mg/ml, P = 0.60). In comparing infants to adults during full maneuvers, the infants were more reactive to MCh (lower PC₃₀) than the adults (geometric mean: 1.27 vs. 17.1 mg/ml, P = <0.001). However, in comparing infants to adults during partial maneuvers, there was not a significant difference between the two groups (geometric mean: 1.26 vs. 0.75 mg/ml, P = 0.27).

Fig. 1. Flow-volume curves from an adult subject who underwent methacholine (MCh) challenges with full (A) and partial (B) forced expiratory maneuvers; selected MCh doses are illustrated. C: corresponding dose-response curve with all MCh doses. During the full maneuvers (with deep inspirations), the challenge proceeded to the maximum dose of MCh (10 mg/ml) with only a small reduction in forced expiratory flow. However, during the partial maneuvers (no deep inspirations), the same subject displayed significant decrease in forced expiratory flow at a MCh dose of 0.31 mg/ml.
DISCUSSION

Our study demonstrates that healthy infants have greater airway reactivity than healthy adults when assessed under comparable conditions with full forced expiratory maneuvers. In addition, the absence of deep inspirations during bronchial challenge testing increased airway reactivity among healthy adults but not among healthy infants. The differences between

Fig. 2. Flow-volume curves from an infant subject who underwent MCh challenges with full (A) and partial (B) forced expiratory flow maneuvers; selected MCh doses are illustrated. C: corresponding dose-response curve with all MCh doses is illustrated below the flow-volume curves. During both the full (with deep inspirations) and partial (no deep inspirations) maneuvers, there was a significant decrease in forced expiratory flow. The presence or absence of deep inspirations had no effect on the airway reactivity.

![Flow-volume curves](image)

Fig. 3. Individual subjects' paired log-transformed values of MCh concentration that produced at least 30% decrease (logPC_{30}) for forced expiratory flow at 75% expired vital capacity (FEF_{75}) and maximal expiratory flow at functional residual capacity (V_{max-FRC}) measured from full (DI, deep inspiration) and partial (no DI) maneuvers for adults (A) and infants (B). The adults had significantly lower logPC_{30} when assessed by partial maneuvers (V_{max-FRC}) compared with full maneuvers (FEF_{75}). For the infants, there was no significant difference in logPC_{30} assessed by partial maneuvers (V_{max-FRC}) compared with full maneuvers (FEF_{75}).

![Individual subjects' paired log-transformed values](image)
healthy infants and healthy adults parallel the previously reported differences between asthmatic and healthy adults (1, 10, 20). Our findings suggest that the absence of an effect of deep inspirations on airway reactivity is characteristic of subjects with airway hyperreactivity and that there may be common mechanisms for these findings in infants and asthmatic subjects.

Greater airway reactivity in infants than in adults when assessed with full forced expiratory maneuvers is consistent with our laboratory’s (23) previous study demonstrating heightened airway reactivity in children compared with adults matched for body size and assessed with full forced expiratory maneuvers. Differences in aerosol dose and body position for an infant compared with an adult have been suggested as the explanation for the heightened airway reactivity previously reported for healthy infants (2). Nebulizers used for bronchial challenges are often driven with a flow of 6 l/min, which may exceed the infant’s inspiratory flow but may be less than that of the adult, which may exceed 10 l/min. This may result in adult subjects entraining room air and thus receiving a relatively dilute dose of MCh compared with infants. This mechanism has been proposed as a reason why adults compared with infants respond at higher agonist concentrations in the nebulizer chamber (2). Therefore, in this study we delivered the nebulized MCh aerosol with a flow of 20 l/min, which exceeds the inspiratory flow for both infants and adults.

Airway reactivity is also dependent on lung volume; changing position from a sitting to a recumbent posture increases airway reactivity in adults (18). For that reason, we assessed both infants and adults in the supine position, which is required for testing infants. Our laboratory has previously demonstrated that flow limitation is achieved during full forced expiratory maneuvers in infants using the methodology that we employed in this study (4). In our study, adults voluntarily inspired to total lung capacity whereas infants were passively inflated to 30 cmH$_2$O; voluntary inspiration may have produced a better stretch of the airway. We did not measure the transpulmonary pressure generated during the deep inspiration for the adults or infants; however, in healthy infants the inflation to 30 cmH$_2$O does approach total lung capacity (24). Another methodological difference in this study between infants and adults was the number of deep inspirations performed before forced expiration during the full forced expiratory maneuvers. Three to four inflations are used in the infant to inhibit respiratory effort before the jacket-assisted forced expiration. In contrast, the adult took a single deep inspiration before each forced maneuver. Because increasing the number of deep inspirations from 1 to 5 produces a progressively greater bronchoprotective effect in healthy adults (10), we may have actually underestimated the true difference in airway reactivity between the infants and the adults. Therefore, we believe that our present results demonstrate that healthy infants have heightened airway reactivity compared with healthy adults when assessed under comparable conditions with deep inspirations.

In our study, healthy adults in the supine position were less reactive with full maneuvers than with partial maneuvers. This finding is consistent with previous reports that deep inspirations decrease airway reactivity in healthy adults assessed in the upright position (10, 12, 17, 20). In contrast to the adults, the infants did not demonstrate a significant increase in airway reactivity when assessed with partial compared with full maneuvers. We chose to compare the effects of deep inspiration on airway reactivity measured with full and partial maneuvers by using FEF$_{75}$ and $V_{\text{max}}$FRC, respectively. These flows are at similar lung volumes, and the alternative of tracking flows at the same absolute lung volume would have required a body plethysmograph that could be used in the supine position for both infants and adults. One difficulty in using partial maneuvers is that FRC, the volume reference for flow, may increase during bronchoconstriction and thus underestimate the magnitude of airway narrowing assessed with $V_{\text{max}}$FRC. We did not measure changes in FRC; however, both infants and adults demonstrated the same percent decrease in FVC measured with full maneuvers, even though the infants were more reactive with the full maneuvers. We expect that the effects of bronchoconstriction on FRC were thus similar for the infants and adults. Our findings that deep inspirations did not alter airway reactivity in infants assessed on 2 different days with two different maneuvers is consistent with a previous report that transiently increasing lung volume during bronchial challenge testing did not alter $V_{\text{max}}$FRC in infants (9). Therefore, we believe our results demonstrate that deep inspiration during bronchial challenge decreases airway reactivity for adults but not infants. In addition, in the absence of deep inspirations, airway reactivity of healthy adults is similar to that for healthy infants, not unlike the comparison between asthmatic and healthy adults.

In our study, we were not able to distinguish between the bronchoprotective and the bronchodilating effects of deep inspirations on airway reactivity because deep inspirations were delivered both before and during the bronchial challenge. In adults, the bronchoprotective effect is reported to be stronger than the bronchodilating effect (17). The effect of deep inspirations on airway reactivity has been attributed to the effects of stretch on the contractile properties of airway smooth muscle (6–8, 13, 25); however, the mechanisms for the bronchodilating and the bronchoprotective effects may differ. It has also been suggested that deep inspirations may release a local bronchodilator such as nitric oxide from nonadrenergic noncholinergic nerves (15, 19). The relationship of heightened airway responsiveness and the absence of an effect of deep inspirations on airway reactivity for infants and asthmatic subjects suggest the possibility of a common mechanism in these two populations.
In conclusion, our study has demonstrated that healthy infants, compared with healthy adults, have heightened airway reactivity when assessed with full forced expiratory maneuvers. In addition, the absence of deep inspirations during bronchial challenge increases airway reactivity in healthy adults but not in healthy infants. In the absence of deep inspirations, the heightened airway reactivity in healthy adults is similar to that of healthy infants.

REFERENCES


