Airway response to deep inspiration: role of inflation pressure

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Brown, Robert H., and Wayne Mitzner. Airway response to deep inspiration: role of inflation pressure. J Appl Physiol 91: 2574–2578, 2001.—Deep inspirations (DIs) have been shown to have both bronchoprotective and bronchodilator effects in healthy subjects. However, the bronchodilator effects of a DI appear to be impaired in asthmatic compared with healthy subjects. Because the ability to generate high transpulmonary pressures at total lung capacity depends on both the lung properties and voluntary effort, we wondered how the response of airways to DI might be altered if the maneuver were done with less than maximal inflation. The present work was undertaken to examine the effects of varying the magnitude of lung inflation during the DI maneuver on subsequent airway caliber. In five anesthetized and ventilated dogs during methacholine infusion, changes in airway size after DIs of increasing magnitude were measured over the subsequent 5-min period using high-resolution computed tomography. Results show that the magnitude of lung inflation is extremely important, leading to a qualitative change in the airway response. A large DI (45 cm H2O airway pressure) caused subsequent airway dilation, whereas smaller DIs (≤35 cm H2O) caused bronchoconstriction. The precise mechanism underlying these observations is uncertain, but it seems to be related to an interaction between intrinsic properties of the contracted airway smooth muscle and the response to mild stretch.

asthma; bronchoconstriction; high-resolution computed tomography; lung inflation; smooth muscle

DEEP INSPIRATIONS (DIs) have been shown to have both bronchoprotective and bronchodilator effects in healthy subjects (22, 23). However, the bronchodilator effects of a DI appear to be impaired in asthmatic compared with healthy subjects (23). In addition, separate experiments by Brusasco et al. (11) and Brown et al. (9) also suggest that there are intrinsic differences between the responses to lung inflation in airways of asthmatic and normal subjects. Healthy normal subjects demonstrated bronchodilation after the DI, whereas asthmatic subjects showed further bronchoconstriction after the DI maneuver (9).

When considering the effects of a DI, an implicit assumption is that all of the airways are distending to their maximal size at total lung capacity (TLC). However, we have previously shown in a canine model that static distension of both relaxed and contracted airways is not directly proportional to lung inflation (3). Fully relaxed airways are quite distensible at low lung volume, but they quickly reach a maximal size with no further distension up to TLC. With smooth muscle tone, the airways show variable degrees of dilation with lung inflation, but maximal distension of moderately constricted airways is generally not achieved even at TLC (3).

In assessing the response of airways to DI, it would thus seem important to use a consistent and well-defined lung volume history. In human subjects, however, it is not routine to measure transpulmonary pressure (Ptp), and often even the duration of the DI is not well characterized. In a recent study, we demonstrated that the length of time at TLC can alter the qualitative response of the airways after the DI (19a). However, because the ability to generate high Ptp at TLC depends on both the lung properties and voluntary effort, we wondered how the response of airways to DI might be altered if the maneuver were done with less than maximal inflation. Therefore, the present work was undertaken to examine the effects of varying Ptp during the DI maneuver on subsequent airway caliber. Results show that decreasing the magnitude of the peak airway pressure can cause a qualitative change in the response, with a large DI (45 cm H2O airway pressure) causing subsequent airway dilation and a smaller DI (≤35 cm H2O) causing bronchoconstriction.

METHODS

Our study protocol was approved by The Johns Hopkins Animal Care and Use Committee. Five dogs weighing ~20 kg were anesthetized with thiopental (15 mg/kg induction dose followed by 10 mg·kg−1·h−1 intravenous maintenance dose). After induction of anesthesia, the dogs were paralyzed with 0.5 mg/kg of succinylcholine with occasional supplemental doses as required to ensure no respiratory motion during imaging. After endotracheal intubation with an 8.0-mm-ID endotracheal tube, the dogs were placed supine and their lungs were ventilated with room air with a volume-cycled ventilator (Harvard Apparatus, Millus, MA) at a tidal volume of 15 ml/kg and a rate of 18 breaths/min. A stable depth of anesthesia was maintained by monitoring heart rate changes and eyelash reflex.

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Imaging and analysis of airways. High-resolution computed tomography (HRCT) scans were obtained with a Somatom Volume Zoom scanner (Siemens, Iselin, NJ) using a spiral mode to acquire 50 contiguous images during an 8-s breath hold (apnea) at 137 kVp and 165 mA. The images were reconstructed as 1-mm slice thickness and a 512 x 512 matrix using a 125-cm field of view and a high-spatial-frequency (resolution) algorithm that enhanced edge detection, at a window level of -450 Hounsfield units (HU) and a window width of 1,350 HU. These settings have been shown to provide accurate measurement of luminal size as small as 0.5 mm in diameter (18, 27). For repeated airway measurements in a given dog within each experimental protocol, adjacent anatomic landmarks, such as airway or vascular branching points, were defined and used to measure the airway size at the same anatomic cross sections.

The HRCT images were analyzed using the airway analysis module of the Volumetric Image and Display Analysis image-analysis software package (Div. of Physiologic Imaging, Dept. of Radiology, Univ. of Iowa, Iowa City, IA) as previously described and validated (1, 3). The HRCT images were transferred to a UNIX-based Sun workstation. An initial isocontour was drawn within each airway lumen, and the software program then automatically located the perimeter of the airway lumen by sending out rays in a spoke-wheel fashion to a predesignated pixel intensity level that defines the luminal edge of the airway wall. Intra- and interobserver accuracy and variability of the software program using this HRCT technique in phantoms, consisting of rigid tubes to measure known areas, has been previously shown by our laboratory (18) and by others (1) to be highly resistant to operator bias.

Protocol. Dogs were anesthetized and ventilated as described above. To standardize lung volume history, the dogs were initially given a deep inspiration of both lungs to 35 cmH2O airway pressure for 5 s. A stable state of airway tone was induced with a continuous intravenous infusion of 67 μg/min methacholine (MCh; Sigma Chemical, St. Louis, MO). The tubing from the ventilator to the endotracheal tube of the animals had an added large-bore Y connector. One branch of the Y went to the ventilator, and the other branch was connected to a constant-pressure source set at one of three different pressures: 25, 35, and 45 cmH2O. This source consisted of an underwater overflow fed by a line from a high-flow oxygen supply. At the start of scanning, the ventilator was simultaneously shut off, a solenoid valve to the ventilator was closed, and another solenoid to the pressure source was opened to the dog for 10 s. Then solenoids were switched to suddenly expose the trachea to atmospheric pressure, and the scans were acquired. Scanning was performed immediately after the DI (~4 s) and at 30, 60, 90, 120, 180, 240, and 300 s after the DI. After the scans were acquired, the ventilation was resumed. The maneuver was then repeated with the constant-pressure source set to the next higher pressure. To measure the size of the completely relaxed airways, the dogs received 0.2 mg/kg of atropine at the end of the experimental protocols. Previous work has demonstrated that this dose of atropine abolishes all cholinergic smooth muscle tone in dogs (3).

Analysis. The initial airway area before the DI was defined as 100%. The airway luminal areas were expressed as a percentage of this initial area. Each airway in each dog served as its own control. Analysis of variance was used to compare the airway size among the three DI pressures at the various time points. Scheffé’s correction for multiple pairwise comparisons were used, and P ≤ 0.05 was considered significant.

RESULTS

In each dog, 26–33 airways (range 0.78–7.0 mm in diameter) were matched and measured. MCh infusion at the chosen rate caused a stable airway constriction to 47 ± 0.8% (SE) of their completely relaxed size. All subsequent measurements are referenced to this baseline (pre-DI) size with MCh, which is thus defined as 100%. At the first (4 s) measurement after the DI, the mean airway area as a percentage of baseline area before the DI was 126 ± 3 (SE), 133 ± 4, and 168 ± 4% of pre-DI for the 25-, 35-, and 45-cmH2O DIs, respectively. The airway area after the 45 cmH2O DI was significantly greater than the airway area after either of the other two DIs (P < 0.001; Fig. 1). The initial

![Fig. 1. Percent change in mean airway area immediately after a deep inspiration (DI) to a peak inflation pressure of 25 cmH2O (○), 35 cmH2O (●), and 45 cmH2O (□). For the larger DI (45 cmH2O), the airway size remained above the baseline airway area for the entire measurement period (*P < 0.0001). In contrast, for the smaller (35 and 25 cmH2O) DIs, the airways actively contracted to a smaller area than at the pre-DI baseline. At 5 min, the airway area was 91 ± 3% for the 35-cmH2O DI (P < 0.0001) and 73 ± 1% for the 25-cmH2O DI (*P < 0.0001) of pre-DI airway area.](http://jap.physiology.org/doi/10.1152/jappl.01227.2001)
airway area at the first measurement after the 35-cmH2O DI was not different from the 25-cmH2O DI ($P = 0.36$). During the 5-min interval after the DI, the airway size decreased in a quasi-exponential manner (Fig. 1). However, there was a qualitative difference in the response of the airways to the DI depending on the size of the DI. For the largest DI (45 cmH2O), the airway size remained above the baseline airway area for the entire measurement period. At 5 min, the airway area was $111 \pm 2\%$ of pre-DI ($P < 0.0001$; Fig. 1). In contrast, for the smaller (35 and 25 cmH2O) DIs, the airways actively contracted to a smaller area than at the pre-DI baseline. At 5 min, the airway area was $91 \pm 3\%$ for the 35-cmH2O DI ($P < 0.0001$) and $73 \pm 1\%$ for the 25-cmH2O DI ($P < 0.0001$) of pre-DI airway area (Fig. 1). The airway size at 5 min was also significantly different between all three pressures ($P < 0.0001$).

DISCUSSION

Our results clearly show that the extent of lung inflation during a DI has a major effect on the subsequent airway size. A small DI causes initial airway distension but subsequent airway constriction, whereas a large DI also causes initial airway distension but subsequent airway dilation. The levels of peak inflation used in this study were within the range that can be obtained in vivo. Although we did not measure the pleural pressure, we can estimate the approximate Ptp from a previous study in which such measurements were done (3). In that work, when the airway pressure was 36 cmH2O, the Ptp was 23 cmH2O. With a simple linear extrapolation, we thus estimate that the Ptp at each of the three airway pressures were 17, 23, and 30 cmH2O.

Mechanisms underlying the observation in this study may have important implications regarding its potential manifestation in human asthma. It is generally accepted that lung inflation distends the airways of animals and humans (3, 7–9). In airways with little smooth muscle tone, even moderate lung inflation readily distends airways to their maximal size, and this was shown true in experimental animal models even when airways were made edematous (8, 10). In normal healthy human volunteers and mildly asthmatic subjects, there were similar degrees of airway distension at TLC either at baseline or after mildly increased airway tone with aerosol MCh challenges (9).

In animal models, we have previously shown that static distension of the airways is not directly proportional to the inflation of the lung either in relaxed or contracted airways (3). Fully relaxed airways are quite distensible at low lung volume but quickly reach a maximal size with no further distension up to TLC. With smooth muscle tone, the airways do distend with increasing lung inflation, but maximal distension of moderately constricted airways was not achieved even at TLC (3). In the present study, distension of MCh-contracted individual airways with tone would be expected to increase with increasing peak inflation pressure but would not necessarily achieve maximum even at the largest DI examined. These previous observations likely explain the smaller initial airway size at the first time point after the inflation to TLC in Fig. 1. However, the subsequent bronchodilation or bronchoconstriction after the DI could not be predicted from this previous work. With a DI to 25–35 cmH2O, the airways showed a paradoxical constriction after release of the DI. Although we do not yet have a clear mechanistic picture, several possibilities that could play a role are discussed below.

One consideration relates to changes in recoil pressures of the airway smooth muscle and lung parenchyma after the DI. We know that, at the lower inflation pressures, the airways are less dilated. When the lung recoil pressure is decreased after the DI maneuver, this loss of lung recoil may then lead to a further decrease in airway luminal size. It is not entirely clear, however, why the paradoxical narrowing should take so long to develop. This delay suggests perhaps that some intrinsic properties of the smooth muscle contractile proteins might also be important. Previous in vitro work with canine bronchial segments by Gunst and Mitzner (17) clearly demonstrated that contraction can occur in response to airway distension. In that study, the contraction only occurred at a midrange of pressures, with dilation occurring and both low and high pressures. The protocol in that in vitro study was not the same as that in the present in vivo work, so, other than noting this intrinsic ability of airways to contract in response to stretch, further comparison is limited. Regarding the dynamic aspects of these in vivo observations, mechanical plasticity (24) would surely limit the ability of the muscle to be dynamically stretched, but how or why this would lead to delayed contraction is similarly not clear. Dynamic constraints are also imposed in a model of tonically contracted muscle presented by Fredberg and colleagues (14). This model involves the physical manifestation of the different chemical dynamics of slowly cycling latch bridges and rapidly cycling cross bridges in the airway smooth muscle. The model predicts that, in the latch state, airway muscle will be very stiff with little hysteresis in recoil pressure. Such a stiff airway could achieve a smaller size if the outward recoil of the parenchyma were diminished at the new lung volume after the DI (15). We did not measure lung volume in the present study, but, in a previous study where this was done (4), it was observed that, when a DI led to a further narrowing, the lung volume also decreased. If this also occurred in the present study with the DIs to lower inflation pressures, then the decreased lung recoil at the new functional residual capacity would contribute to a smaller airway size.

In a closely related recent study (19a), we found that shortening the time spent at maximal lung volume during a DI maneuver also led to a subsequent paradoxical contraction of airways. In the present work, we held the peak pressure for 10 s, which should have been long enough to reach a steady-state airway size (5), but, because the peak pressure was lower, the
airway size at peak inflation during the inspiratory part of the maneuver was likely smaller. Thus it appears that, to obtain a normal airflow dilation after a DI, one must effectively dilate the airways to some minimal size, either by increasing the peak inflation pressure or by lengthening the time at peak pressure. The details of this pressure-time interaction are not yet clear. For example, we do not yet know whether we would have observed a post-DI dilation with a peak pressure of 25 cmH2O if we had held this pressure for a longer period of time.

Other potentially important mechanisms for the post-DI contraction include release of some intrinsic contractile agonist or an increase in vagal tone. There are myelinated afferent fibers in the vagi that have both slowly adapting (SAR) and rapidly adapting pulmonary stretch receptors in the lung. Many SARs are known to be active at functional residual capacity (21), and, because increased SAR activity with lung inflation causes bronchodilation, any decrease in SAR activity will lead to bronchoconstriction. The effect of a deep inspiration thus would be to greatly increase the SAR firing during the large inflation. Recovery from the inflation would in turn lead to a prolonged decrease in the SAR firing rate and hence to augmented constriction superimposed on the exogenous MCh-induced constriction. Although the effect of large distension of the airways on the firing of the SARs is not known, if this decreased firing from SARs and subsequent increased vagal tone only occurs with small stretching of the lung, then it might only be apparent with the small DIs <35 cmH2O. With large DIs, the increased neural signals associated with lung stretch may fade, leaving the airways dilated. Our results also could be explained if small stretches released a local contractile mediator. Such a substance would surely be present with large stretches, but the large stretch would also cause a muscle dilation that might be slow to recover.

Admittedly, there is a lot of mechanistic speculation here, but unfortunately there is little relevant experimental evidence in the literature that has attempted to address the size of DI on subsequent airway tone. Several current clinical investigations have focused on single or repetitive DIs as a means of preventing or reversing bronchoconstriction (11, 19, 22, 23). In general, the nature of the DIs in most clinical studies is not explicitly specified, but they are usually brief and sigh like, typically on the order of only a few seconds. How these results relate to the paradoxical airway narrowing sometimes seen in asthmatic subjects after a DI (2, 9, 11–13, 16, 20, 25, 26) remains uncertain. Perhaps airways of asthmatic subjects are stretched too little during the maneuver and behave like those of subjects in the low-pressure groups in the present work. A similar study to address this issue could be done in human subjects, with slight modification of protocols that we have used. Brown et al. (9) have studied the ability of a DI to distend the airways of normal healthy volunteers compared with mildly asthmatic subjects at baseline and after increased tone. A DI distended the airways of healthy and asthmatic subjects to a similar extent, suggesting that abnormal interdependence between the lung parenchyma and the airways is unlikely to play a major role in the loss or in the attenuation of the beneficial effect of lung inflation that characterizes asthma. Furthermore, it was observed that, after constriction had already been induced by MCh, deep inspiration resulted in bronchodilation in the healthy subjects but further bronchoconstriction in the asthmatic subjects. These findings suggest that abnormal behavior in the airway smooth muscle of mildly asthmatic subjects to stretch may counteract the bronchodilatory effect of a DI.

In summary, we found that size of the depth of the inspiratory maneuver during a DI determines the qualitative behavior of the airway response. Inflation to relatively high pressure results in airway dilation, whereas one to lower pressure leads to airway constriction. The precise mechanism underlying these observations is uncertain, but it seems to be related to an interaction between intrinsic properties of the contracted airway smooth muscle and the response to mild stretch.

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REFERENCES


