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# Morphometric changes after thermal and methacholine bronchoprovocations

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## ABSTRACT

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To determine whether there are distinctions in the location and pattern of response between different bronchoprovocations, we performed high-resolution computer-assisted tomography in 10 asthmatic subjects before and after isocapnic hyperventilation of frigid air (HV) and methacholine (Meth). The luminal areas of the trachea, main stem, lobar, and segmental bronchi were computed before and after each provocation and blindly compared. Both stimuli reduced the 1-s forced expiratory volume similarly (percent change in 1-s forced expiratory volume HV = 28.1 ± 5.5%, Meth = 25.8 ± 5.2%; $P = 0.69$) but did so in different fashions. Each provocation was associated with the development of both bronchial narrowing and dilation; however, more airways constricted with HV (67.7%) than with Meth (47.0%; $P < 0.001$). Furthermore, there was little concordance between either the magnitude or direction of change between stimuli in any region of the lung ($r = 0.25$). In general, the frequency of narrowing increased with branching. Constriction became more prominent in the lobar regions and increased further in the segmental branches, but a wide range of intensity existed. These data demonstrate

that provocational stimuli evoke complex morphometric changes within the tracheobronchial tree and that different agonists produce different patterns. Thermal stimuli chiefly influence the segmental level, whereas the response to Meth develops more distally. Even within this distribution, the same airway does not respond in an identical fashion to different stimuli, so there does not appear to be a uniform trigger zone.

computer-assisted tomography scans of chest; thermally induced asthma

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IN RECENT YEARS, SIGNIFICANT ADVANCES have been made in understanding the pathophysiology of asthma. Biopsy studies show that characteristic inflammatory features of the disease can be observed from the trachea to the alveoli ([15], [19]), raising the possibility that all of the airways theoretically possess the capability of reacting to stimuli. However, it is unclear whether, or how, they do so, and measurements that deal with the distribution of ventilation ([24]) and frequency-dependent behavior ([25]) made during and after acute episodes suggest that marked differences in involvement exist within the tracheobronchial tree. Furthermore, it is uncertain whether there are regions of the lung that dominate the physiological process. Finally, it is unknown whether the site and pattern of responses are generic phenomena that are common to all types of provocations.

To provide data on these issues, we examined bronchial geometry and the distribution of airway narrowing with high-resolution computer-assisted tomography (HRCT) of the chest before and after airway obstruction was induced with isocapnic hyperventilation and methacholine (Meth). These challenges were chosen because they are in wide clinical use, have dissimilar mechanisms of action, and can be reproducibly and precisely applied ([11], [12], [29]). Our observations form the basis of this report.

# METHODS

Ten nonsmoking individuals [4 men and 6 women; average age $28.6 \pm 2.5$ (mean $\pm$ SE) yr] with asthma (Table 1) underwent bronchoprovocations with isocapnic hyperventilation of frigid air (HV) and Meth using published techniques ([9], [11], [12]). None of the volunteers had symptoms of upper respiratory tract infections or used oral corticosteroids for 3 mo before the start of the investigation. The participants continued their regular asthma medications during the course of the

trial and only stopped them temporarily before challenges. Bronchodilators were withheld for 12 h or more, and long-acting decongestants and leukotriene-modifying agents were not permitted for 5 days before any investigation. Inhaled corticosteroids were continued in patients already using them to prevent destabilization of their disease. The doses were constant for a minimum of 1 mo before the study was initiated and remained so throughout it. The institutional review board for human investigations approved the protocol, and all participants gave informed consent.

**View this table:** Table 1. *Demographic and prechallenge clinical data*
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The trial consisted of two screening and two experimental visits. On one screening day, the individual minute ventilations ($\dot{V}_E$) associated with a reduction in the 1-s forced expiratory volumes ($FEV_1$) of $\geq 20\%$ was determined by having each subject generate stimulus-response curves to HV ([11], [12]). During the challenge, $\dot{V}_E$ was progressively increased in 4-min intervals while the participants inhaled through a heat exchanger

([11](#), [12](#)). The water content of the inspirate was <1 mgH$_2$O/l, which for the purpose of this study was considered zero. The expired air was directed into a reservoir balloon that was being constantly evacuated at a known rate through a calibrated rotameter. The subjects were coached to keep the balloon filled, and, in so doing, their $\dot{V}_E$ could be controlled at any desired value. End-tidal CO$_2$ concentrations were monitored with a Nellcor N-1000 analyzer (Mallinckrodt, Kansas City, KS), and sufficient CO$_2$ was added to the inspiratory port of the exchanger during hyperpnea to maintain end-tidal CO$_2$ at eucapnic levels.

On a second screening day, dose-response relationships to Meth were obtained. Increasing concentrations of Meth were delivered via a DeVilbis nebulizer (Somerset, PA) with a breath-synchronized trigger (Rosenthal Dosimeter, PDS Instrumentation, Louisville, CO) ([9](#)) until a decrease in FEV$_1$ of $\geq$20% developed. The starting concentration was 0.078 mg/ml (0.4 mM). Saline was inhaled first as a control. The solutions of Meth were freshly made before each experiment by dissolving measured concentrations in saline and diluting appropriately. In both the HV and Meth trials, the threshold level of stimulus was obtained by linear interpolation. The resultant $\dot{V}_E$ and Meth values associated with a reduction in FEV$_1$ of $\geq$20% were then employed in the subsequent chest-scan experiments.

Maximum forced exhalations were performed in triplicate with a waterless spirometer before and 5 min after HV and 2 min after Meth ([11](#), [12](#), [29](#)). These time points fall within the maximum response periods for both provocations. The curves with the largest FEV$_1$ were chosen for analysis.

In a second set of experiments, the subjects performed the HV and Meth challenges in conjunction with HRCT scans of the chest. In these trials, baseline values for the FEV$_1$ were obtained, after which the participants underwent a control HRCT. They were then challenged in random order with the previously determined threshold values for each stimulus while seated on the scanner bed and then X-rayed again. Postchallenge scans were undertaken at 5 min post-HV and 2 min post-Meth to duplicate the peak changes in pulmonary mechanics recorded on the screening day. Spirometry was repeated immediately after completion of the HRCT. The two provocations were performed on separate days, $\sim$1 wk apart.

An ultrafast spiral-capable Siemens Somaton Plus 4B computer tomography scanner with a speed of 0.75 s/revolution was used to obtain the chest images. Noncontrasted spiral computer-tomography scans were performed with settings of 3-mm collimation and a pitch of one. The energy settings were 125 keV and 140 mAs. Each HRCT was obtained in four 40-mm contiguous segments that spanned the midthorax. The scan distance was $\sim$150 mm, with $\sim$5 mm of overlap between the segments. External skin markers were placed on the chest so that each scan would involve the same segments. Participants were coached to hold their breath at total lung capacity (TLC) for the duration of the scans for a total time of 11 s per segment. In this fashion, the scans could be standardized for lung volume and completed within $\sim$50 s. With this protocol, we could obtain the HRCT and FEV$_1$ in close proximity to each other at the height of the obstructive response.

The scanned image data were recorded on compact discs for subsequent analysis and reconstructed using standard high-resolution algorithms to provide 0.5-mm slices. The scans were stacked and displayed on a computer monitor using modified Interactive Data Language (IDL) software (IDL 5.3 Visual Data Analysis Research Systems, Boulder, CO). Internal diameters were obtained by visually placing electronic calipers on opposite inside edges of the bronchial wall. The computer software determined the distance between caliper points based on the geometry of the scanner and computed the area. Measurements were obtained in airways that had the same angles in baseline and challenge scans. Regions of interest were visually matched between

control and postchallenge trials on the monitor and enlarged five times, and the luminal area was assessed. Measurements were made in triplicate, averaged, and the coefficient of variation computed. Before the HRCT studies, a phantom was scanned ("Broncho Bob") with the instrument complex employed in the human studies. Measurements were performed with the IDL software and verified with the physical measurements of the phantom.

The data from the pre- and poststudies were encoded and presented to the viewer as a blinded set of side-by-side images for each provocation. The software permitted us to perform a "virtual bronchoscopy" by scrolling through image slices starting from the top of the lungs downward. Thus we could follow the major airways along their branching courses until they disappeared. From a practical standpoint, however, we could only reproducibly examine four generations: the trachea; the 2 main stem bronchi; the 5 lobar bifurcations; and the 18 segmental branches. The internal lumens of bronchi smaller than these could not reliably be studied. Analysis of the inferior lingular segmental bronchus was not included in 7 of the 10 subjects because of cardiac motion artifact.

Data were analyzed by paired $t$-tests, one- and two-factor analyses of variance, and $\chi^2$ test. All statistical tests were two sided, and a $P$ value of $<0.05$ was considered significant.

# RESULTS

The baseline demographic and clinical characteristics of our subjects are provided in Table 1. Their $FEV_1$ on the HV screening day was $3.30 \pm 0.30$ liters ($94.8 \pm 4.3\%$ of predicted). This value was statistically similar to those on the Meth screening visit and on the two HRCT studies trials (Fig. 1). The mean inspired air temperature during the HV challenge was $-9.4 \pm 1.2°C$. The values of HV and Meth associated with reductions in $FEV_1$ of $\geq 20\%$ averaged $53.8 \pm 6.0$ l/min and $0.81 \pm 0.39$ mg/ml for HV and Meth, respectively. Nine participants used inhaled sympathomimetics. Five subjects also took inhaled steroids, two subjects were prescribed antihistamines, and one subject took antileukotrienes and cromolyn sodium.



Fig. 1. The impact of hyperventilation (HV) and methacholine (Meth) provocations on the 1-s forced expiratory volume ($FEV_1$) on the screening and high-resolution computer-assisted tomography (HRCT) challenge days. The heights of the bars are mean values, and the brackets designate 1 SE. Numbers below the graphs are $P$ values for the listed comparisons.

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A comparison of the baseline $FEV_1$ data for each study, as well as the magnitude of the airway responses after the provocations, are shown in Fig. 1. The prechallenge $FEV_1$ values were similar for all experiments

and ranged between $3.22 \pm 0.32$ and $3.41 \pm 0.31$ liters ($P = 0.60$). Significant airway obstruction was induced with each challenge (change in $FEV_1$ HV screening $= 31.9 \pm 2.9\%$, $P < 0.001$; Meth screening $= 31.8 \pm 2.0\%$, $P < 0.001$; change in $FEV_1$ HV HRCT $= 28.1 \pm 5.5\%$, $P = 0.001$; Meth HRCT $= 25.8 \pm 5.2\%$, $P = 0.001$). There were no significant differences between the obstructive responses found on the screening and experimental days ($P = 0.76$), and there were no significant differences between challenges on the HRCT days ($P = 0.69$).

Representative examples of the caliper placement and luminal area analysis are shown for a single subject in Fig. 2. The pre- and post-HV and -Meth data were taken from the lung slice identified in Fig. 2A. The images in Fig. 2B are an unzoomed presentation of the electronic calipers outlining the inner walls of longitudinally and cross-sectionally cut airways before and after Meth. The sites marking the diameters used for the calculation of the respective areas are also shown. Figure 2C presents a zoomed version of a longitudinal measurement with HV. The inner edges of the walls of the airways could be readily outlined, and their diameters identified. As is apparent in this subject, luminal areas decreased with both challenges.



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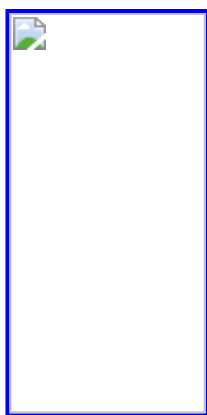
Fig. 2. *A*: section of lung chosen from a representative subject to demonstrate electronic caliper placement and measurement of airway diameter and area. *B*: unzoomed HRCT image showing longitudinal and cross-sectional measurements before and after Meth. The lines represent the electronic calipers marking the lumens and diameters. Numeric data are the area calculations. Placement of the calipers was assisted by the computer software and verified. The small discrepancies between the edges of the walls and the calipers in this figure are distortion artifacts created by enhancement and conversion of the computer image to a photograph. *C*: zoomed HRCT image showing longitudinal measurements before and after HV. The numbers are area values. The placement of the calipers was assisted by the computer software and verified. The small discrepancies between the edges of the walls and the calipers in this figure are distortion artifacts created by enhancement and conversion of the computer image to a photograph.

Paired HV and Meth data were available from 248 airways (10 trachea, 20 main stem bronchi, 50 lobar bronchi, and 168 segmental bronchi) before and after exposure to each stimulus (total challenge $= 496$). The unchallenged airway diameters for the right lung and composite regional luminal areas from both lungs before and after HV and Meth are presented in Fig. 3. Diameters decreased with increasing branching from $16.6 \pm 0.6$ mm in the trachea to $3.6 \pm 0.3$ mm in the right apical segment before HV and $16.5 \pm 0.8$ and $3.8 \pm 0.3$ mm before Meth. There were no significant differences in the measurements made with each trial by analysis of variance ($P = 0.92$). HV and Meth data from the left lung match those of the right lung and are omitted for brevity.

Fig. 3. Comparisons of the diameters of the airways in the right lung (*left*) and the luminal areas of all of the regions in both lungs (*right*) before HV and Meth challenges. Heights of the bars are mean values, and the brackets are 1 SE. RM, right mainstem; RUL, right-upper lobe; R Apical, right apical segment. *Right*: comparisons of the aggregate luminal areas in different regions of the tracheobronchial tree.

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The luminal areas of the trachea were $217.9 \pm 14.9$ and $219.0 \pm 21.4$ mm$^2$ for HV and Meth, respectively, whereas those of the segmental bronchi were $168.2 \pm 11.9$ (HV) and $159.9 \pm 12.0$ mm$^2$ (Meth) (Fig. 3). The coefficients of variation for repeat measures for HV ranged between 3.8 and 5.9% and 3.8 and 6.5% for Meth. The more distal regions showed greater variation. There were no significant differences between HV and Meth ($P = 0.56$). As shown below the graph, the data on luminal areas are sectional aggregates, and for this reason the summed areas of the main stem bronchi are larger than the trachea, even though the diameters are smaller.

Regressing the individual prechallenge areas of all airways for HV against those for Meth showed an extremely tight fit. The correlation coefficient was 0.99 with a slope of 1.00.

Postchallenge, there was considerable heterogeneity in the type, magnitude, and location of the effects observed between stimuli, among subjects, and within the different areas of the lungs. Even though significant decrements in the FEV$_1$ were produced, only 60.3% of the aggregate airways in both challenges narrowed. The remainder either dilated (39.1%) or were unchanged (0.6%) (frequency of constriction vs. dilation, $P < 0.001$). More of the airways examined tended to constrict with HV (67.7%) than with Meth (47.0%) ($P < 0.001$). The frequency distribution of the changes in area is presented in Fig. 4. In the main stem, the majority of the dilatory and constrictor effects was small. Of the 299 airways that dilated, 285 of them (95.3%) changed $\leq$50% and 58.9% of them changed $\leq$20%. Of the 194 bronchi that constricted, 95.4% had a decrease in area of $\leq$50% and 158 (81.4%) showed $\leq$20% effect.



Fig. 4. Frequency distribution of the changes in airway areas with HV and Meth. *Top* and *bottom* show dilatory and constrictor effects, respectively. The number of airways involved is presented on the *y*-axis and the magnitude of change on the *x*-axis.

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The concordance between the effects of HV and Meth is shown in Fig. 5. The correlation between the changes in luminal area was poor ($r = 0.25$), and all patterns were observed. Only 41% of the airways that constricted did so with both stimuli, and even then the variance was high ($r = 0.25$).
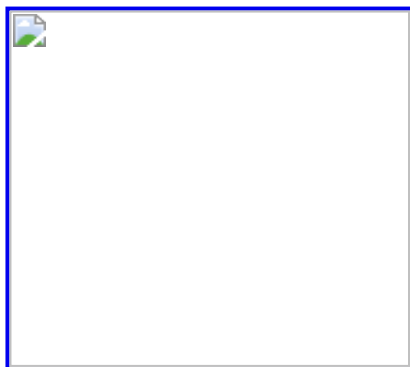


Fig. 5. Comparison of the individual changes in luminal area induced by HV and Meth. Data points in at *top right* and *bottom left* quadrants represent concordant bronchoconstriction and bronchodilation, respectively, by both stimuli. The other quadrants show the mixture of effects. Concordance in any quadrant would fall along a line of identity.

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The combined and challenge-specific distribution of bronchoconstriction throughout the airway segments is displayed in Fig. 6. In general, the frequency of induced narrowing increased with branching. Thirty-two percent of the extrapulmonic airways, 56% of the lobar branches, and 67% of the segmental bronchi narrowed ($P < 0.001$). Of the airways that constricted, the decrement in luminal area averaged $22.5 + 1.3\%$ for HV and $17.3 + 1.3\%$ for Meth ($P < 0.005$). Conversely, for those that dilated, the mean increase was $13.0 \pm 1.8\%$ for HV and $15.0 \pm 2.1\%$ for Meth ($P = 0.48$).
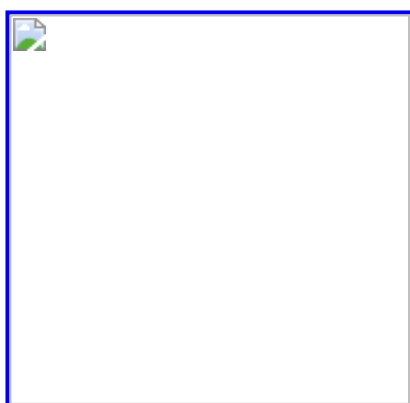


Fig. 6. Anatomic distribution of airway constriction after HV and Meth challenges. Overall mean changes are depicted by {bullet} and the line.

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The changes in airway geometry at different segments are shown in Fig. 7. On average, the trachea and main stem bronchi distended a small amount (3.3 and 2.8%, respectively), whereas the lobar and segmental branches constricted (lobar decrement = 1.9%; segmental = 9.8%). Hyperpnea was associated with less dilatation in the extrapulmonic airways and more constriction in the intrapulmonic regions ($P < 0.001$). The greatest change for both challenges occurred in the segmental branches (HV = $15.7 \pm 2.1\%$; Meth = $3.9 \pm 2.2\%$; $P = 0.006$).
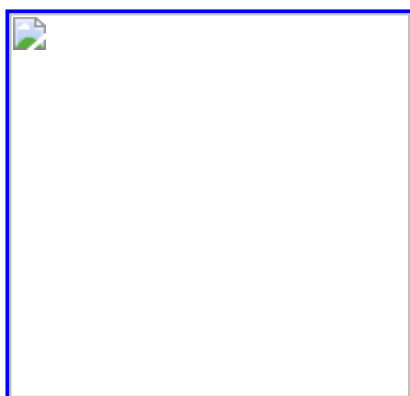
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Fig. 7. Quantitative effect of HV and Meth on airway areas in different generations of the tracheobronchial tree. Overall mean changes are shown by {bullet} and the line. Heights of the bars are the mean values in each region sample, and the brackets indicate 1 SE. Positive values represent bronchodilatation, and negative values indicate bronchoconstriction. N, number of airways examined in each anatomic site; {Delta}, change.

A more detailed analysis of the responses in the lobar and segmental branches is provided in Figs. 8 and 9. There was a more consistent distribution of effects of HV at the lobar level. Although there was considerable variability in magnitude in each region, the overall effect was one of constriction. In contrast, Meth reduced the luminal areas of the right-middle and right-lower lobes only. The other regions dilated (Fig. 8).



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Fig. 8. Effects of HV and Meth on the luminal areas of the lobar branches. RUL, RML, and RLL indicate the right-upper, -middle, and -lower lobes, respectively, whereas LUL and LLL represent the left-upper and -lower lobes, respectively. The format is similar to Fig. 7. $N = 10$ for each region for each challenge.
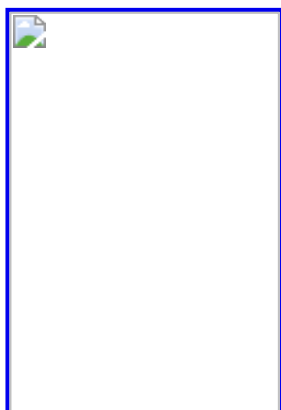


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Fig. 9. Effects of HV and Meth on the segmental branches of the RUL, RML, and RLL (*A*) and the LUL and LLL (*B*). Individual segments are presented above each region. The format is similar to Fig. 7. $N = 10$ for each region for each challenge.

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The qualitative effects of HV became more uniform in the segmental branches, but quantitative heterogeneity still remained (Fig. 9). All of the sampled airways constricted with this challenge with a wide variation in intensity. Conversely, the areas of 12 of 18 branches fell with Meth.

There were no significant correlations between the decrements in $FEV_1$ and the overall changes in luminal area with either HV ($r = 0.36$, $P = 0.30$) or Meth ($r = 0.30$, $P = 0.41$). Restricting the analysis to only those bronchi with acute reductions in lumen area did not have any major impact (HV, $r = 0.44$, $P = 0.20$; Meth, $r = 0.26$, $P = 0.46$).

# DISCUSSION

The results of the present study demonstrate that the types of bronchoprovocations commonly used in clinical practice produce complex morphometric alterations within the lungs. HV and Meth do not induce uniform or graded changes within the tracheobronchial tree. Rather, they evoke a mixed pattern of bronchial narrowing and dilatation of various intensity that is nonhomogeneously distributed within and among anatomic regions.

Additionally, the measured impairments in airflow that develop with these stimuli do not appear to derive from large decrements in the cross-sectional areas of a few critically located bronchi or widespread airway closure but rather from small alterations in many branches. Although, in a few instances, obstruction began in the extrapulmonic airways, in general the frequency of constriction increased as the tracheobronchial tree branched. Even so, only 60% of the airways examined were involved in the falls in $FEV_1$, and the individual decreases in luminal area were typically $\leq$20%. (Figs. 4, 5, 8, and 9). Last, there does not appear to be a single region in the lungs, or a set of airways, in which an obstructive reaction is initiated. Neither the inherent responsivity of the bronchi nor the site of impact of the stimuli appears to be patient or challenge specific.

Although there are a number of studies using HRCT that have examined how agonists influence airway geometry (1, 4–8, 14, 17, 21, 27, 28), to our knowledge, this is the first to sequentially explore various levels of the tracheobronchial tree and to compare challenges with different mechanisms of action. As can be seen, there are obvious differences in the way that the tracheobronchial tree reacts to different provocations. Even though comparable degrees of obstruction were produced, as measured by standard tests (Fig. 1), HV and Meth do not share similar anatomic profiles of activity. Only 41% of the airways constricted to both challenges, and the concordance between stimuli was poor ($r = 0.25$) (Fig. 4). We appreciate that the lack of significant correlations between the site of obstruction and the alterations in pulmonary mechanics with both challenges suggests the existence of more narrowing beyond our measurements; nonetheless, HV produced larger effects in a greater number of the sampled bronchi than did Meth. It also appeared to have a more proximal impact. In contrast, the major consequence of Meth was in more peripheral regions.

The current findings also raise the possibility that the anatomic-physiological correlates between the site of stimulus contact and the obstructive response may not be as close as imagined. Hyperpnea is believed to induce bronchial narrowing through local thermal stress on the airways (11, 12), whereas Meth is dependent on dispersion throughout the tracheobronchial tree and pharmacologically mediated receptor coupling (26).

Given that the largest intrathoracic impact of HV is in the upper trachea and that its consequences rapidly decrease as the air moves distally ([11], [12]), the expected predominant site of obstruction should have been in the large proximal bronchi. The findings of progressively increasing constriction of three sets of branches distally imply the existence of a heretofore unrecognized propagating mechanism. Whether it is a reflex or the physical delivery of mediators such as prostanoids or leukotrienes peripherally by the bronchial circulation or by diffusion through the surface fluid remains to be determined.

This apparent lack of agreement between anatomy and physiology is further highlighted by the Meth data. Cholinergic receptors are thought to be predominately centrally located ([26]); yet, most HRCT studies ([1], [14], [17], [28]), including ours, have observed the greatest influence to be in the peripheral airways. Amirav et al. ([1]) reported that the 1- to 2-mm-diameter bronchi of pigs were the most sensitive, whereas Okazawa and associates ([28]) and Goldin and colleagues ([14]) found the response to reside in 2- to 5-mm bronchi. Finally, Brown et al. ([7]) noted a predilection for the smallest airways to constrict with this agent in normal subjects. It has not yet been established whether this pattern derives solely from inhalation of small aerosol droplets with their preferential peripheral deposition or from some other cause.

Regional variability in the degree of bronchoconstriction has been previously observed in animals ([1], [5]) and humans ([7], [14], [17], [28]) with Meth and histamine. However, the finding of paradoxical dilatation is unique. Such a phenomenon can be seen in HRCT images in a variety of species, including humans, when sought, but its potential significance has not been specifically commented on. Brown et al. ([5]) noted the luminal areas of dogs to increase after aerosolized histamine, but the frequency of occurrence was not described. Similar findings have been observed in normal subjects with Meth ([4]).

We believe that the above information, coupled with our data, allows one to reasonably postulate that a combination of dilatation and variable constriction represents the natural response to airway antagonists, perhaps as a teleological attempt to maintain alveolar ventilation in times of acute pulmonary compromise. Lutchen et al. ([20]), studying the airway constriction pattern in asthmatic subjects using dynamic resistance and elastance, conjectured that a heterogeneous pattern of constriction was a central component of asthma severity. It would be of great interest to combine their functional observations with morphometric studies, such as those reported herein. In any event, mixtures of the type we describe readily provide a visual explanation as to why acute episodes of asthma behave physiologically as they do. The presence of such phenomenon readily leads to frequency-dependent behavior, such as maldistribution of inspired air, ventilation-perfusion mismatching, and falls in resistance and compliance with increased rates of breathing (23–25). We understand that induced episodes of asthma do not, by design, approach the severity of spontaneous attacks; however, because the pathophysiology of both is similar, it is likely that the changes described herein represent quantitative rather than qualitative differences between situations.

Even though more data are required before it is understood how much of the tracheobronchial tree is ultimately involved with provocations, it is important to appreciate that the distribution noted in Fig. 7 has a strategic significance. Obstruction in the third to fifth generation, even if accomplished by the sum of relatively small changes in individual airways, can produce considerable symptoms. These regions function as the neck of a funnel, and minor narrowing produces disproportional effects ([22]). Conversely, obstruction in the lobar and segmental bronchi is also particularly amenable to nebulized therapy, because it is here where changes in local aerodynamics would cause aerosolized particles to preferentially land.

Could the airway dilatation and the differences between stimuli that we observed been an artifact of the protocol employed to obtain the HRCT scans? Traditional HRCT images of the chest are limited to an assessment of the airways that are visible perpendicular to the cross-sectional scan plane irrespective of their

anatomic origin. As such, they present a somewhat narrow or focal view of the events present. In contrast, the "virtual bronchoscopy" technique we used allowed us to precisely document the position in the tracheobronchial tree where the changes were occurring and gain an appreciation of their distributed nature. The data in Fig. 3 coupled with the tight correlations between airway sizes in the HV and Meth control challenges demonstrate that this approach worked well and provided reproducible quantitative analysis of the images. We recognize that starting the scans at TLC may have contributed to, or accentuated, the pattern of differences found. Such a maneuver, although undertaken to attempt to ensure similar starting volumes, could potentially have had two effects. On one hand, the deep inspiration could have increased bronchoconstriction (7) and so worsened the situation in some airways. On the other hand, it could have simultaneously reduced any tendency toward constriction by exposing the bronchi to distending forces. It could also have limited airway closure (13, 19). The net effect we measured would have been the algebraic sum of all events. Although we do not dispute the possible interplay of these influences, we think their practical impact on our images to have been small for several reasons. As above, the prechallenge HRCT airway areas were statistically identical for HV and Meth ($r = 0.99$, slope = 1.00), demonstrating that the complete inspiration used to gather these data either had no effect on the geometry of unstressed airways or produced highly reproducible changes in them. Moreover, the degree of obstruction induced on the screening days with both challenges, as measured by $FEV_1$, was identical to that observed on the HRCT days, indicating the existence of similar underlying geometric components (Fig. 1). Finally, Brown and associates (4) observed that, if normal subjects given Meth are prevented from taking deep breaths, airway dilatation and constriction both occur even though distending and constricting forces are prevented by rigorously controlling lung volume. Thus the pattern we described appears real.

It is well accepted that hyperinflation is part of the acute reaction to asthmogenic stimuli. As a result, the resultant anatomic changes postchallenges are always impacted by this factor in real-world clinical situations. Presumably, this occurs in an effort to stabilize airway size. Residual volume and functional residual capacity invariably increase with induced or spontaneous obstruction, sometimes quite dramatically (2, 3, 10, 15, 22–24). TLC, however, typically remains fairly constant and so is a reasonable starting point. (2, 15, 23, 24). We recognize that TLC has been reported to rise markedly in some patients after histamine and exercise (3, 10), but this phenomenon is inconsistent (2, 15, 23, 24) and has only been found in subjects who developed severe obstruction (3, 10). Such an event was avoided in the present trials by inducing controlled degrees of obstruction. Serial HRCT scans coupled with detailed measures of pulmonary mechanics and lung volumes in patients recovering from acute episodes of asthma will likely be needed before one can appreciate the extent to which the starting lung volume distorts airway anatomy.

# GRANTS

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## ▮ FOOTNOTES

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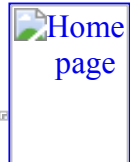
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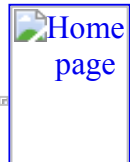
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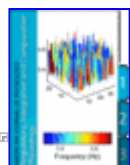Eur. Respir. J., June 1, 2007; 29(6): 1174 - 1181.
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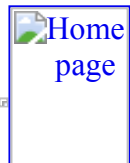
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