Potential role of the airway wall in the asthma of obesity

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Bates JH, Dixon AE. Potential role of the airway wall in the asthma of obesity. J Appl Physiol 118: 36–41, 2015. First published October 23, 2014; doi:10.1152/japplphysiol.00684.2014.—The pathogenesis of late-onset TH2-low asthma in obesity is thought to be related to weight-related decreases in lung volume, but why only a subset of individuals with obesity develop this condition is unknown. We tested the hypothesis that natural variations in both airway wall stiffness and airway wall thickness could lead to a subpopulation of hyperresponsive individuals exhibiting the symptoms of asthma in the setting of obesity. Increases in airway resistance ($R_{aw}$) after airway smooth muscle stimulation were simulated using a computational model of an elastic airway embedded in elastic parenchyma. Using a range of randomly chosen values for both airway wall stiffness and thickness, we determined the resulting probability distributions of $R_{aw}$ for a variety of different levels of transpulmonary pressure ($P_{tp}$). As $P_{tp}$ decreased from 5 to 1 cmH₂O, the resulting distributions of $R_{aw}$ moved toward progressively higher levels of responsiveness. With appropriate choices for the mean and standard deviation of the parameter that controls either airway wall stiffness or thickness, the model predicts a relationship between airway hyperresponsiveness and body mass index that is similar to that which has been reported in populations with obesity. We conclude that natural variations in airway wall mechanics and geometry between different individuals can potentially explain why an increasing percentage of the population exhibits the symptoms of asthma as the obesity of the population increases.

ASTHMA IS ONE OF A NUMBER OF COMMON DISEASES BEING NEGATIVELY IMPACTED BY THE CURRENT OBESITY EPIDEMIC. THE REASONS WHY OBESITY INCREASES ASTHMA RATES REMAIN TO BE FULLY ELUCIDATED, BUT IT HAS BEEN SHOWN THAT THE ASTHMA OF OBESITY APPEARS IN TWO PRINCIPLE FORMS. ONE IS AN EARLY-ONSET TH2-HIGH PHENOTYPE THAT IS REMINISCENT OF MOST CONVENTIONAL ASTHMA AND THAT IS EXACERBATED BY THE OBESE STATE. THE OTHER IS A DISTINCT OBESITY-RELATED PHENOTYPE THAT FREQUENTLY RESOLVES WITH SUFFICIENT WEIGHT LOSS (18, 36). IT SEEMS LOGICAL TO SUPPOSE THAT THE LATTER PHENOTYPE IS RELATED TO THE CHRONIC DEPRESSIONS IN LUNG VOLUME THAT INVARIABLY OCCUR IN MORBID OBESITY DUE TO THE WEIGHT OF EXCESS ADIPOSE TISSUE AROUND THE CHEST WALL (30). THIS CAUSES REDUCTIONS IN TRANSPULMONARY PRESSURE, SOMETHING THAT IS WELL KNOWN TO BE A POTENT MECHANISM LEADING TO AIRWAYS HYPERRESPONSIVENESS (17). CURIOUSLY, ONLY A SUBSET OF PEOPLE WITH SEVERE OBESITY DEVELOP ASTHMA (38), YET PRESUMABLY ALL SUCH INDIVIDUALS ARE AT RISK FOR HAVING THEIR LUNG VOLUMES DEPRESSED. THIS WOULD SEEM TO INDICATE THAT SOME PREDISPOSING FACTOR IS OPERATIVE IN THOSE INDIVIDUALS WHO DEVELOP THE LATE-ONSET TH2-LOW FORM OF OBESITE ASTHMA.

We recently obtained evidence that this predisposing factor is related to an increased propensity for the lung periphery to become derecruited at reduced transpulmonary pressures in subjects with obesity and asthma compared with their counterparts without asthma (2). Specifically, we used a simple mathematical model of lung impedance to show that weight loss in a group of subjects with obesity and asthma led to a greater increase in lung compliance compared with controls, which can be explained by excess weight having caused greater collapse of the lung periphery in the subjects with asthma. To explain how this difference might arise, we first note that the reason why peripheral airways become more easily collapsed as lung volume is reduced is because of the associated reductions in the outward tethering forces exerted on the airway walls by their alveolar parenchymal attachments (32). These attachments mediate the transmission of transpulmonary pressure across the airway wall, so a given reduction in transpulmonary pressure would be expected to have an essentially equal effect on airway collapsibility for all subjects. However, the compressive stiffness of the airway wall itself also plays a substantial role in the collapsibility of airways (1, 4), and there is no a priori reason to suppose that wall stiffness should be the same in all individuals. Similarly, the thickness of the epithelial and submucosal layers inside the airway smooth muscle (ASM) exerts a powerful influence on both airway responsiveness and closure and again we might expect thickness to exhibit a natural variation within the population. This raises the possibility that nonatopic asthma may arise in individuals with obesity with airways that are either more compliant or thicker than average, something that would require novel therapies and is thus an important matter to understand.

Accordingly, the goal of the present study was to investigate, with the use of a computational model, the possibility that natural variations in the mechanical and geometric properties of the airway wall might explain how modest reductions in lung volume could give rise to a distinct population of individuals who develop the symptoms of asthma when they become obese.

METHODS

The calculations performed for this study were made using a computational model that we described in detail previously (4) and used in several other studies (3, 5, 14, 26). The model consists of a circular airway wall embedded in elastic parenchyma. The airway itself consists of a ring of ASM wrapped around an elastic airway wall. ASM contraction decreases airway radius by compressing the airway wall and by pulling against the parenchyma that is attached to the outside of the wall. The opposing force exerted by the parenchyma comes from transpulmonary pressure ($P_{tp}$) and from the local parenchymal distortions caused by the narrowing of the airway. The latter are assumed to follow the relationship identified by Lai-Fook (27).

The inward recoil of the airway wall is determined by its stiffness, which is assumed to arise from a fraction (1 – $k$) of the airway circumference that expands according to the one-third power of $P_{tp}$.

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After ASM activation the model airway narrows dynamically according to the Hill hyperbolic force-velocity relationship (4, 21)
given by
\[
-2\pi \frac{dr}{dt} = \frac{b(F_0 - F_A)}{a - F_A} \quad \text{when } F_A < F_0
\]
\[
= \frac{bF_0}{a + F_0} - \frac{bF_A}{a + F_0} \quad \text{when } F_A \geq F_0
\]
where \( r \) is airway radius, \( F_A \) is active force generated by the ASM, and \( a \) and \( b \) are constants. After experimental findings reported in rats (7), we set \( a = F_0/4 \).

This model thus has four free parameters (\( k, P_0, b, \) and \( F_0 \)) that can be evaluated by fitting it to experimentally measured profiles of \( R_{in} \), obtained immediately after injections of bronchial agonist repeated at different levels of lung inflation (4). Such data have not been collected in humans and indeed are unlikely to be for practical and ethical reasons. Accordingly, for the purposes of the present study we based our simulations on model parameter values previously identified for the mouse (14), namely \( P_0 = 10 \text{ cmH}_2\text{O}, F_0 = 4.8 \text{ cmH}_2\text{O}, \) and \( b = 0.042 \text{ cm/s}. \)

The values of \( k \) were chosen as follows. We assume that there exists within the normal human population a natural variation in airway wall stiffness. We represented this variation by drawing \( k \) from a Gaussian distribution with mean \( k_{mean} \) and standard deviation \( k_{SD} \). We do not have data from human subjects to guide the choice of \( k_{mean} \) and \( k_{SD} \), so in the present study we based \( k_{mean} \) on values we previously determined for mice (14) and chose \( k_{SD} \) to give a realistic variation in responsiveness within the simulated population (see RESULTS).

To calculate how variations in airway wall stiffness translate into variations in airway responsiveness we performed a series of Monte-Carlo simulations. For each such simulation the model was run 10,000 times at a fixed value of \( P_{tp} \) with \( k \) being drawn randomly for each run from the specified Gaussian distribution. The model airway was relaxed at the beginning of each run, but reached different levels of steady-state contraction (achieved by 200 s) depending on the value of \( k \). During each run the model was assumed to be at a constant lung volume determined by the specified value of \( P_{tp} \) (i.e., ventilation was at a sufficiently low level that changes in lung volume did not influence the capacity of the ASM to shorten). We characterized airway responsiveness in each run as the final value of airway resistance, \( R_{in} \), at the end of each 200-s model run, where \( R_{in} \) was taken as proportional to the fourth power of the radius of the airway lumen (i.e., assuming Poiseuille airflow in the airways). The histogram of the 10,000 values of \( R_{in} \) obtained in this manner then yielded the responsiveness probability distribution for the simulated population. This procedure was repeated for different values of \( P_{tp} \).

We then repeated these simulations, keeping \( P_{tp} \) fixed while varying the thickness of the epithelial and other tissues on the luminal side of the ASM. These tissues are represented in the model by an annular lining between the ring of ASM and airway lumen. The thickness of the lining is a fraction, \( \alpha \), of the ASM radius under baseline conditions defined as when the ASM is relaxed and functional residual capacity (FRC) is at its nominal normal value when PEEP = 5 cmH\(_2\)O. The lining retains its annular shape and its area is preserved as the ASM shortens, which leads to a geometric accentuation of the narrowing of the airway lumen. The calculations involved are detailed in the appendix of Ref. 5. Of course, the thickness of the tissue lying to the luminal side of the ASM in a real lung does not scale with airway size, so there is no single anatomically defined value of \( \alpha \) that can be used to guide its choice for the model. Accordingly, we chose its value empirically in the present study.

**RESULTS**

Figure 1 illustrates how airway responsiveness predicted by the model is affected by variations in the level of lung inflation, airway wall stiffness, and airway wall thickness. Figure 1A shows \( R_{in} \) vs. time for \( P_{tp} = 5, 3, \) and 1 cmH\(_2\)O with \( k = 0.73 \) (\( R_{in} \) in Fig. 1A has been normalized to its initial value at \( P_{tp} = 5 \text{ cmH}_2\text{O} \)). As one would expect, the responsiveness of the model is inversely related to the degree of lung inflation. Figure 1B gives corresponding plots for \( k = 0.68, 0.73, \) and 0.78 with \( P_{tp} = 5 \text{ cmH}_2\text{O} \) and \( \alpha = 0 \) (\( R_{in} \) in Fig. 1B has been normalized to its initial value at \( k = 0.73 \text{ cmH}_2\text{O} \)), which shows that responsiveness is also highly sensitive to wall stiffness; a relatively stiff airway wall (\( k = 0.78 \)) leads to an increase in \( R_{in} \) that is much smaller than when the airway wall...
Figure 2A shows histograms of $R_{aw}$ obtained with 3 different values of $P_{tp}$ while $k$ was drawn randomly from a Gaussian distribution with $k_{\text{mean}} = 0.73$ and $k_{SD} = 0.04$. Figure 2B: corresponding histograms obtained with 3 different values of $P_{tp}$ while $\alpha$ was drawn randomly from a Gaussian distribution with mean $= 0.08$ and standard deviation $= 0.03$. Horizontal axis has been transformed from $P_{tp}$ to body mass index (BMI) using a published relationship between BMI and reduction in functional residual capacity (FRC), as described in the text.

is more compliant ($k = 0.68$). Figure 1C gives corresponding plots for $\alpha = 0.05, 0.08$, and $0.11$ with $P_{tp} = 5$ cmH$_2$O and $k = 0.73$ ($R_{aw}$ in Fig. 1C has been normalized to its initial value at $\alpha = 0.08$), which shows that responsiveness is at least as sensitive to wall thickness as to either $P_{tp}$ or $k$.

Figure 2A shows histograms of $R_{aw}$ for $P_{tp} = 5, 3$, and $1$ cmH$_2$O obtained with $k$ selected from a Gaussian probability distribution with $k_{\text{mean}} = 0.73$, corresponding our previous findings in mice (14), and $k_{SD} = 0.04$. (Note that $R_{aw}$ in this plot has been normalized to the value defining the upper 5% of the distribution obtained with $P_{tp} = 5$ cmH$_2$O.) The histograms have extended tails that spread to the right as $P_{tp}$ decreases. These results show, first of all, that a naturally occurring variation in airway wall stiffness within the population is predicted to lead to a substantial variation in airway responsiveness. Most importantly, however, a decrease in $P_{tp}$, as tends to occur with obesity due to a decrease in lung volume, causes a substantial shift in the responsiveness distribution in the direction of hyperresponsiveness.

Figure 2B shows a corresponding plot obtained when $k_{SD}$ is set to zero (i.e., no variation in airway wall stiffness) and the lining of the airway wall is given a finite and varying thickness such that the mean value of $\alpha$ is 0.08 and its standard deviation is 0.03. The histograms for $R_{aw}$ are very similar to those obtained when $\alpha = 0$ and $k$ is allowed to vary (Fig. 2A).

We next use the model to predict how responsiveness in the population increases with increasing obesity. The $R_{aw}$ histogram obtained with $P_{tp} = 5$ cmH$_2$O defines the distribution of responsiveness within the normal weight population at normal FRC. The value of $R_{aw}$ below which 95% of this distribution lies then defines the upper limit of normal responsiveness (hence the normalization of $R_{aw}$ to this value in the distributions shown in Fig. 2). As we decrease $P_{tp}$, progressively more of the population surpasses this limit and thus becomes hyperresponsive, as shown by the rightward movement of the distributions in Fig. 2. The increasing % of hyperresponsive individuals is shown in Fig. 3 as a function of body mass index (BMI) for both variations in $k$ and variations in $\alpha$. The transformation of the horizontal axis in this plot from $P_{tp}$ to BMI was made as follows. First, increasing BMI reduces the volume of the thoracic cavity, which reduces $P_{tp}$ and thus reduces FRC correspondingly. We assume that FRC at normal weight is 100% of its predicted value when $P_{tp} = 5$ cmH$_2$O. As BMI increases, FRC approaches residual volume at $P_{tp} = 0$ cmH$_2$O. Assuming a nominal value for residual volume at normal weight of 50% FRC, this gives FRC (% predicted) = $(50 \times P_{tp}/5) + 50$. Finally, using the equation FRC (% predicted) = 231.9e$^{-0.07/BMI}$ + 55.2, derived by Jones et al. (23), we convert a particular value of FRC to its corresponding value of BMI. Also shown on Fig. 3 are incidences of asthma as a function of the midpoints of different BMI ranges from (26a) for patients with obesity, as well as the midpoint of the incidence range in the general population placed at a healthy BMI (although it should be noted that the general population contains a significant number of individuals with obesity, so this point should perhaps be moved somewhat to the right). Figure 3 thus demonstrates that by judicious choice of its parameters the model predicts an increase in hyperresponsiveness with BMI that resembles the observed increasing inci-

Fig. 3. Percentage of the population that is hyperresponsive as a function of BMI predicted by the computational model for $k_{\text{mean}} = 0.73$ and $k_{SD} = 0.04$ (solid line) (A) and for $\alpha$ having a mean value of 0.08 and a standard deviation of 0.03 (dashed line) (B). ★ indicate the mid regions of BMI for corresponding incidence of asthma from (26a). Right most ★ is BMI > 60; left-most ★ corresponds to the general population.
idence of asthma with obesity. However, this prediction can be made equally on the basis of variations in airway wall stiffness and wall thickness.

**DISCUSSION**

The present study was motivated by our recent observations that individuals with obesity who develop late-onset T2low asthma appear to suffer from a greater degree of peripheral lung derecruitment under baseline conditions (2) and by findings from other laboratories indicative of a similar phenomenon during induced bronchoconstriction in subjects with obesity (11, 16, 35, 37). Having airways that are on the more compliant side of the distribution found in the normal population is one possible explanation for increased peripheral lung collapse in a subset of subjects with obesity. Furthermore, anecdotal experience from the bronchoscopy suite indicates that the airway walls of subjects with obesity and asthma are visually more labile during breathing compared with subjects who are lean, and there are some recent reports of central airway instability associated with obesity (8, 25). Accordingly, we hypothesized that the late-onset T2low asthma of obesity could be explained by the appearance of a hyperresponsive phenotype after weight gain in those individuals who find themselves at the more compliant end of the airway stiffness spectrum. This hypothesis derives from the known sensitivity of airway responsiveness to decreases in both $P_{\text{eq}}$ (17) and airway wall stiffness (26). We chose to test the plausibility of this hypothesis in a simple computational model of an elastic airway embedded in elastic parenchyma that we previously showed can recapitulate both effects (3, 4, 26), as illustrated in Fig. 1, A and B, respectively.

What came as a surprise was the finding that, for a given variation in wall stiffness, the hyperresponsive (righthand) end of responsiveness distribution is affected by a decrease in $P_{\text{eq}}$ much more than is the less responsive (lefthand) end, as illustrated in Fig. 2. We must remember that the computational results of the present study were based on data from mice, so extrapolating these results to humans assumes that the basic behavior of the airway smooth muscle and the airway wall is similar. That caveat aside, the results presented in Fig. 2 show how, in principle, a range of airway wall stiffness that is physiologically unproblematic in individuals of normal weight can yield a subpopulation of hyperresponsive individuals in the setting of obesity (16, 34). Figure 3 shows that the rates of asthma predicted by our model are actually quite similar to those rates reported in individuals with obesity (26a): in patients undergoing bariatric surgery, the prevalence of asthma increases from 21% in those with a BMI of 40–50 kg/m² to 33% in those with a BMI of 60 kg/m² or more. These results also offer an explanation for the puzzling question of why only some individuals with obesity have asthma when all such individuals are presumably at risk for the reduced lung volumes that come from being severely overweight; the individuals with asthma may be those who have the more compliant airways. It also suggests that those individuals on the compliant end of the airway stiffness spectrum should be specifically targeted for therapies that elevate lung volume, such as continuous positive airway pressure (20, 33).

On the other hand, our study also shows that one can arrive at essentially identical conclusions on the basis of variations in the thickness of the airway wall material lying to the luminal side of the ASM (Figs. 2 and 3). We previously found wall thickness to play a very strong role in airway responsiveness both from modeling and experimentally (5, 39). In the present study, we chose values for the mean and standard deviation of $\alpha$ purely on the grounds that they gave appropriate distributions for $R_{\text{eq}}$ (Figs. 2 and 3), although how these values related to wall thickness in a real lung is difficult to say given that the effect of thickness is very much a function of airway size. In any case, our results would appear to demonstrate that, in principle, variations in either wall stiffness or thickness could serve as a mechanism for the appearance of a hyperresponsive phenotype with increasing obesity in the population. However, we previously showed evidence that weight loss reduces the tendency for peripheral airways to close after methacholine challenge in subjects with T1low but not T1high asthma and obesity (12). Because one would expect airway inflammation and its attendant epithelial hypertrophy to be more pronounced in the latter group, this would seem to mitigate against airway wall thickening as the mechanism behind nonatopic obese asthma.

Of course, the physical properties of the airway wall are not the only phenomena that may be behind the increased peripheral lung collapse seen in subjects with late-onset T1low asthma and obesity. Perhaps an even more obvious candidate is variations in the way that adipose tissue is distributed around the body. Those who store fat centrally (in or around the abdomen and mediastinum) might be expected to suffer from greater lung compression and thus increased airway responsiveness compared with those who store it more peripherally on the thighs and buttocks. Exactly how different fat deposition patterns vary in their degrees of lung compression is not known, and we have thus far assumed that this deposition pattern, and hence the degree of consequent reduction in $P_{\text{eq}}$, is the same for subjects with and without asthma. Nevertheless, central obesity is a risk factor for asthma even after adjusting for BMI (9, 29), and the incidence of T1low obese asthma is more likely due to a constellation of factors that act synergistically rather than to any one factor alone.

Another issue that has relevance for the extrapolation of our model findings to human patients is that a change in lung volume due to excess weight in and around the thoracic cavity is not the only factor at play in subjects with late-onset T1low obesity and asthma. Adipose tissue is highly metabolically active (36), creating a biological milieu that differs substantially from that in normal weight individuals. Thus far, we have been working on the assumption that airway wall stiffness and thickness both exhibit normal variations in the population that carry over unchanged to the obese state. Alternatively, the altered milieu of the obese state might lead to airway remodeling that manifests as decreased wall stiffness, and this could be the phenomenon that varies between individuals. Equally, an inflammatory state in obesity could increase the thickness of the airway wall as has been demonstrated in allergic mice (39). We cannot distinguish between these various possibilities on the basis of their predicted responsiveness distributions (Fig. 2).

A limitation of our study is that it is based on a computational model that has been fit to data from mice rather than human subjects (14). Our interest in the present study is, of course, in the human lung, but collecting the data necessary to
estimate human parameters would probably be impossible for practical and ethical reasons, so there is no way of knowing for sure how the parameter values in the model should be adjusted to represent the human condition. On the other hand, there is also no reason to suppose that the relative dependencies of airway responsiveness on positive end-expiratory pressure would be vastly different in a human compared with a mouse because lung mechanics scale more or less according to body size (6). Also, and of particular relevance for the present study, mouse airways have less cartilage and fewer generations than the human lung (22), which makes the mouse lung mechanically more like a peripheral section of the human lung rather than being simply a version of the entire human on a much smaller scale, and asthma is becoming increasingly recognized as a disease of the lung periphery (19, 24). Thus, although the relationship of our computational results to the condition of human asthma is not entirely clear, this model does account very accurately for the dynamics of airway responsiveness in mice (3, 14) and in rats and rabbits (4), so in an overall sense it appears to capture the essential dependencies of responsiveness on $P_{ep}$ and the physical properties of the airway wall. There is thus no reason at this point to suppose that the same would not also apply to humans.

Other study limitations include the fact that the computational model itself is based on a highly simplified view of lung anatomy that neglects the branching structure of the airway tree and the fact that airway narrowing can be quite heterogeneous (28). Also, and importantly, we equated having asthma with having airways hyperresponsiveness, but this is only one of the factors contributing to the asthma syndrome and there a few data on the direct relationship between BMI and airways responsiveness. For example, individuals who are severely obese may have such reduced lung volumes that they approach limiting flow during expiration, which could contribute significantly to symptoms (34). Also, increased regional heterogeneity that manifests as ventilation defects occurs as lung volume is reduced, which would further exacerbate symptoms (40). Furthermore, we characterized airway responsiveness in terms of the airway narrowing that occurs in response to a single fixed dose of methacholine, whereas it is usual clinical practice to employ sequentially increasing doses to determine the dose at which a specified decrement in lung function occurs. Nevertheless, a link between BMI and airway responsiveness measured by spirometry has been reported (13), so there is no reason to suppose that BMI would not also be related to increased methacholine responsiveness measured by $R_{aw}$.

We also made assumptions about the nature of the variation in airway wall stiffness within the population that are critical to our results. Using a value for $k_{mean}$ of 0.73 derived from our previous study in mice (14), we found by trial and error that a value for $k_{SD}$ of 0.04 gave an increase in the prevalence of hyperresponsiveness with increasing BMI (Fig. 3) that is reminiscent of the way that asthma incidence has been reported to increase with BMI (26a). However, $k_{SD} = 0.04$ also gave rise to a wide range of $R_{aw}$ values for a given $P_{ep}$ (Fig. 3), which raises the question as to whether such variation is actually seen with the human population. There are few reports of how $R_{aw}$ is distributed within the normal population, and in any case the normal population now includes a significant number of individuals with obesity. Nevertheless, there are indications that the natural variation in airway responsiveness measured by methacholine-induced changes in $R_{aw}$ may be rather wide. For example, McLean et al. (31) reported responsiveness to mannitol measured in terms of airway conductance that varied in subjects without asthma by about one order of magnitude, so the widths of the simulated distributions shown in Fig. 2 may not be unreasonable. The same arguments apply to our modeling of variations in airway wall thickness. It should also be pointed out that airway wall stiffness or thickness could be a risk factor for asthma even for individuals of normal weight. In the present study we arbitrarily assigned the most responsive 5% of the normal weight population as hyperresponsiveness in the present study (Fig. 3) simply because this is the conventional cutoff.

Finally, the results of this modeling study have some significant clinical implications for the management of patients with obesity and asthma. First, the hypothesis that the physical properties of the airway wall play a critical role in the asthma of obesity suggests that those at risk for developing this condition could be identified if airway wall compliance and/or thickness could be assessed in some manner. This could provide special motivation for avoiding excessive weight gain, or for losing weight, in such individuals. There are also some potential therapies that might be aimed at patients with these risk factors. For example, in patients with airways that are more compliant than average, stenting the airways with positive applied pressure, such as that provided by continuous positive airway pressure, is an obvious and relatively innocuous treatment. Indeed this has already received significant attention in the asthma community (10). Finally, there remains the unresolved issue of whether having either abnormally thickened or compliant airways in obesity is simply a matter of genetic bad luck or whether it results from some remodeling process associated with the altered metabolic state associated with obesity; the latter case might be responsive, for example, to long-term anti-inflammatory therapy.

In summary, we used a computational model of an airway contracting within the parenchyma to show that variations in both airway wall stiffness and thickness between individuals, coupled with increasing obesity, can potentially lead to an increasing fraction of the population exhibiting the asthmatic symptom of airways hyperresponsiveness. Although we cannot distinguish between these two possibilities at present, together they offer strong evidence that airway wall structure is involved in $T_{H2}$-low late-onset asthma in individuals with obesity. Furthermore, we offer an explanation for why $T_{H2}$-low asthma appears in only a subset of the obese individuals. Indeed, the imposition of a global insult on a distribution of susceptibilities may represent a general mechanism whereby any pathology may appear in only a subset of the entire population.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).
AUTHOR CONTRIBUTIONS

Author contributions: J.H.B. and A.E.D. conception and design of research; J.H.B. performed experiments; J.H.B. analyzed data; J.H.B. and A.E.D. interpreted results of experiments; J.H.B. prepared figures; J.H.B. drafted manuscript; J.H.B. and A.E.D. edited and revised manuscript; J.H.B. and A.E.D. approved final version of manuscript.

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