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Homeokinesis and short-term variability of human airway caliber

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Que, Cheng-Li, C. M. Kenyon, R. Olivenstein, Peter T. Macklem, and Geoffrey N. Maksym. Homeokinesis and short-term variability of human airway caliber. *J Appl Physiol* 91: 1131–1141, 2001.—We hypothesized that short-term variation in airway caliber could be quantified by frequency distributions of respiratory impedance (Zrs) measured at high frequency. We measured Zrs at 6 Hz by forced oscillations during quiet breathing for 15 min in 10 seated asthmatic patients and 6 normal subjects in upright and supine positions before and after methacholine (MCh). We plotted frequency distributions of Zrs and calculated means, skewness, kurtosis, and significance of differences between normal and log-normal frequency distributions. The data were close to, but usually significantly different from, a log-normal frequency distribution. Mean lnZrs in upright and supine positions was significantly less in normal subjects than in asthmatic patients, but not after MCh and MCh in the supine position. The lnZrs SD (a measure of variation), in the upright position and after MCh was significantly less in normal subjects than in asthmatic patients, but not in normal subjects in the supine position and after MCh in the supine position. We conclude that *1*) the configuration of the normal tracheobronchial tree is continuously changing and that this change is exaggerated in asthma, *2*) in normal lungs, control of airway caliber is homeokinetic, maintaining variation within acceptable limits, *3*) normal airway smooth muscle (ASM) when activated and unloaded closely mimics asthmatic ASM, *4*) in asthma, generalized airway narrowing results primarily from ASM activation, whereas ASM unloading by increasing shortening velocity allows faster caliber fluctuations, *5*) activation moves ASM farther from thermodynamic equilibrium, and *6*) asthma may be a low-entropy disease exhibiting not only generalized airway narrowing but also an increased appearance of statistically unlikely airway configurations.

asthma; frequency distributions; respiratory impedance; airway smooth muscle; smooth muscle velocity of shortening; asthma prognosis; homeostasis; entropy; airway obstruction; complexity

HOMEOSTASIS IS DEFINED as the ability of an organism to maintain a constant internal environment by regulating its physiological processes. However, variability of homeostatically controlled parameters is common and appears to be systematic, rather than random (35). This is true for heart rate (17), blood pressure (33), renal blood flow (32), leukocyte counts (11), minute ventilation (12), interbreath interval (9), and tidal volume (5) and other ventilatory parameters. Spontaneous short-term variation of the resistance to flow into and out of the lung has not been reported in peer-reviewed articles, even though asthma is a disease characterized by spontaneous variation in airway obstruction (4, 14, 19). Variability of obstruction is usually assessed clinically by variation in diurnal measurements of peak flow, and several weeks of measurement are usually necessary to document it or the effect of therapy (4, 19, 30). We hypothesized that variation in airway caliber would be measurable in normal and asthmatic lungs over a much shorter time period and that this variation would be excessive in asthma. We therefore measured variation in total respiratory input impedance (Zrs) by the forced oscillation technique (13, 31) in normal subjects under different conditions and in asthmatic patients. These results have previously been reported as log-log frequency distributions of variation of individual measurements of Zrs from the mean (24, 26). In the present communication, we present these results as frequency distributions of Zrs. Both methods of analysis support our hypotheses. We discuss the fluctuations of Zrs that we measured in light of the behavior of complex systems.

The word complexity, when used in this sense, describes self-organizing systems that function far from thermodynamic equilibrium. They require a continuous source of external energy, which they dissipate to create and maintain order (16). The development of order diminishes the system's entropy, which is a measure of the amount of disorder or randomness within the system. The energy sources, which in biological systems are derived from the atmosphere and from food supplies, have greater entropy than the systems they serve (1, 2, 16). Thus the energy is used to de-

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crease entropy, and order is created. As Schulz (27) has said, one unscrambles an egg by eating it. Biological systems spontaneously evolve to a state of greater organization, and therefore of less entropy, by utilizing external energy sources; the total entropy of the universe increases as required by the second law of thermodynamics.

The continuous utilization and dissipation of energy create emergent phenomena and then maintain them by what we call homeostasis. However, it is clear that maintenance of homeostatically controlled parameters is within particular boundaries, and the parameters continuously fluctuate within them. Fluctuations in biological systems have generally been studied by power laws, power spectra, autocorrelation analysis, and other means (5, 16). Yet frequency distributions have the attractive property that they can be used to calculate probabilities of particular events occurring in a given time period and, thus, in medicine may be prognostically useful. Inasmuch as entropy is tightly linked to probability, these distributions contain information about the thermodynamic state of the system and its distance from equilibrium, which may provide pathophysiological insights with therapeutic implications.

METHODS

Subjects

Six healthy subjects (5 men and 1 woman), between 30 and 40 yr of age with no history of pulmonary disease or respiratory infection in the 2 wk before the experiment, were recruited from our research group. All the subjects proved to be normoresponsive, with a fall of <20% in forced expiratory volume in 1 s at a methacholine (MCh) dose of 32 mg/ml administered by aerosol. One subject is a mild smoker. Ten adult, ambulatory asthmatic patients fulfilling the American College of Chest Physicians-American Thoracic Society criteria for the diagnosis of asthma were recruited from the chest clinic of the Montreal Chest Institute, volunteered for the experiment, and gave informed consent. Their anthropometric and functional characteristics are shown in Table 1. Their condition as assessed clinically by the respirologist in charge of the clinic was stable or worsening.

Table 1. *Clinical characteristics of asthmatic patients*

Subj	Age, yr	Gender	Smoking	Pred FEV_1, %	FEV_1/FVC	Asthma Severity	Stability
GL	60	M	No	91	0.73	Mild	W
LC	17	F	Yes	79	0.71	Mild	W
MT	53	F	No	85	0.68	Mild	W
VB	25	F	No	85	0.74	Mild	SW
DD	41	F	No	70	0.60	Moderate	W
HA	70	F	No	92	0.70	Moderate	S
AR	29	M	Yes	83	0.70	Severe	S
BZ	54	F	No	72	0.58	Severe	W
IB	33	M	Yes	64	0.53	Severe	W
WC	28	F	No			Mild	S

Asthma severity and stability were determined by patients' physician. Stability was evaluated as worsening (W), stable (S), and slightly worsening (SW). M, male; F, female; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Measurements

Zrs was measured by forced oscillations at the mouth produced by a loudspeaker powered by a sine-wave generator at 6 Hz (13, 31). The front end of the loudspeaker was encased in a chamber connected to the mouthpiece by a round 2-in. port. Subjects breathed to and from the room through a large, wide-bore tube placed in parallel with the loudspeaker. This provided only a small flow resistance to breathing at normal respiratory frequencies but a high inertance to the rapid accelerations of gas produced by the loudspeaker. Thus very little of the flow oscillation generated by the loudspeaker was lost through the wide-bore tube, and almost all entered the subjects' respiratory tract. Flow was measured by a Fleisch no. 2 pneumotachograph placed between the mouthpiece and the wide-bore tube and coupled to a Validyne DP 45-16 transducer. A continuous, steady, biased flow of fresh air at 0.2 l/s through the wide-bore tube was produced by connecting a side tap at the mouthpiece to a negative pressure source, thereby minimizing dead space. Pressure at the mouth (Pm) was measured by connecting the mouthpiece to a Validyne MP45-1 transducer by a short length of tubing.

Protocol

All measurements were performed between 1100 and 1500 to minimize circadian variation. Asthmatic patients continued their usual medication. During the experiment, the forced oscillations were applied as the subjects breathed quietly on the mouthpiece with cheeks supported by their hands for 15 min. Pm and flow were measured continuously, giving ~5,400 separate measurements of Zrs as the ratio of amplitude of Pm to amplitude of flow calculated on a per cycle basis. Measurements were made in all subjects while they were seated. Normal subjects were also tested seated and supine before and 5 min after MCh (32 mg/ml) administered by aerosol. Asthmatic patients were not studied supine or given MCh. We assessed between-day variation in normal subjects by comparing three sets of control data taken on different days.

Data Analysis

Data were digitized at 256 Hz by LABDAT (RHT InfoDat, Montreal, PQ, Canada), and Zrs was measured six times per second as ratio of amplitude of Pm to amplitude of flow. The measured impedance represents the combined effects of elastic, flow-resistive, and inertial resistances to flow into and out of the respiratory system. Increasing severity of airway obstruction in asthma is characterized by an increase in dynamic elastance and pulmonary resistance and, thus, an increase in impedance. However, in a sinusoidally oscillating system, the pressures acting on elastic and inertial resistances tend to cancel, and at the resonant frequency they do so completely, so that only pulmonary resistance is measured. Inasmuch as 6 Hz is close to the resonant frequency of the respiratory system (13, 31), our measurement of Zrs was dominated by respiratory resistance. Thus variation in Zrs reflected variation in pulmonary resistance and, to a lesser extent, variation in dynamic elastance and inertia.

Artifacts of Zrs were eliminated by an envelope technique, consisting of a plot of each measurement of Zrs on the ordinate vs. flow on the abscissa. We could then identify and delete outlying data consisting of large values of Zrs at zero flow, which we assumed were due to swallowing or transient airway occlusion by the tongue. This was an infrequent

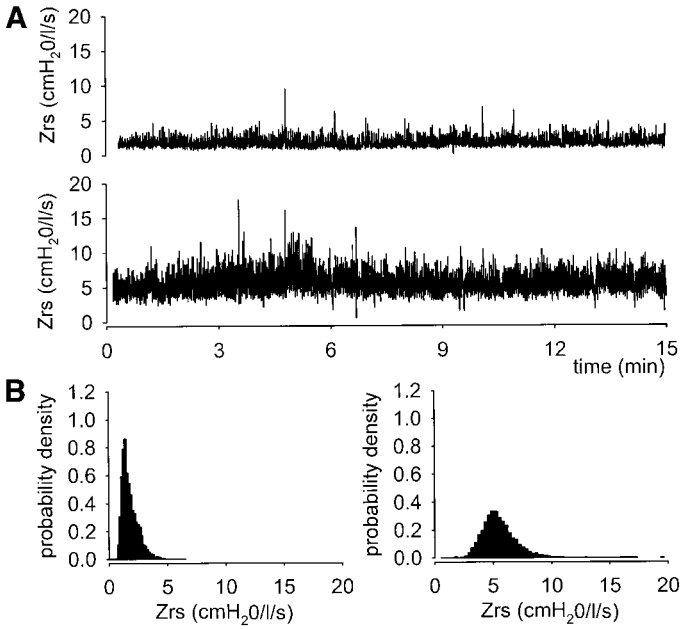

Fig. 1. *A*: raw data of total respiratory impedance (Zrs) measured at 6 Hz over a 15-min period in a normal subject (*RC*, *top trace*) and an asthmatic patient (*LC*, *bottom trace*). *B*: probability density distributions of Zrs for data in *A* in a normal subject (*left*) and an asthmatic patient (*right*).

occurrence and was not different between normal subjects and asthmatic patients.

We constructed frequency distribution curves of Zrs and lnZrs with frequency normalized by expressing it as a fraction of the total number of measurements and for choice of bin width (60 bins), thus obtaining the probability density distributions. We measured the mean and SD (μ and σ, respectively, for lnZrs), kurtosis, skewness, and significance of differences between Gaussian and log-normal frequency distributions. We report modified kurtosis, obtained by subtracting 3 from the mathematical standard kurtosis, so that a Gaussian distribution has a kurtosis of zero.

For statistical analyses we used paired *t*-tests and Wilcoxon signed-rank tests to make comparisons among normal subjects under various conditions and unpaired *t*-tests to compare normal subjects and asthmatic patients. Values are means ± SE. The χ^2 and Kolmogorov-Smirnov tests were used to determine whether the data were significantly different from normal or log-normal distributions. $P < 0.05$ was taken as statistically significant.

RESULTS

Distributions of Zrs

Figure 1*A* shows two examples of Zrs over the 15-min time period. Mean Zrs was 2.8 and 5.5 $cmH_2O \cdot l^{-1} \cdot s$ in the normal subject and the asthmatic patient, respectively. The asthmatic patients as a group had significantly higher values of Zrs than the normal subjects: 5.01 ± 0.90 vs. 1.88 ± 0.10 (SE) $cmH_2O \cdot l^{-1} \cdot s$ ($P < 0.001$). As shown in Fig. 1, the variation of Zrs was also larger in the asthmatic patients. To analyze the nature of this variation, we first determined whether the distributions of Zrs were well approximated by normal or log-normal distributions. Figure 1*B* shows the probability density distributions of Zrs in the normal subject and the asthmatic patient shown in Fig. 1*A*. The skewness and kurtosis were 1.15 and 2.73, respectively, in the normal subject (*CK*) and 1.0 and 3.1, respectively, in the asthmatic patient. The data are poorly described by a Gaussian function (where skewness and kurtosis are zero) but clearly show that variability is greater in the asthmatic patient than in the normal subject.

The probability density distributions of Zrs in all seated normal subjects before MCh and in the asthmatic patients are shown in Fig. 2*A*. Average values of kurtosis and skewness for the distributions of Zrs are given in Table 2 for normal subjects in each condition and for asthmatic patients. Skewness was 1.23 ± 1.15 and 1.49 ± 1.29 (SD) for normal subjects, averaged over all four conditions, and asthmatic patients, respectively. In neither group were these mean values within 1 SD of zero. For kurtosis, these values were

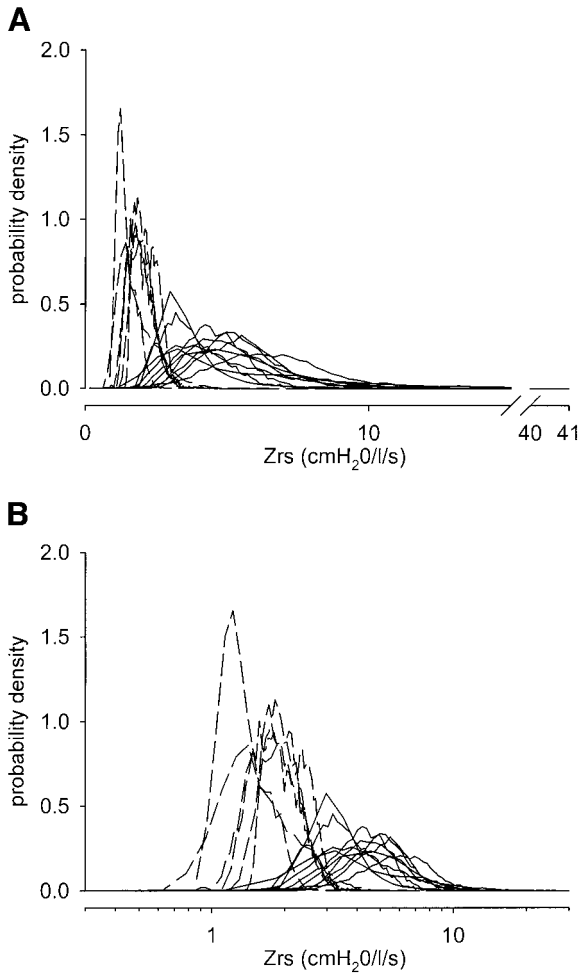

Fig. 2. *A*: probability density distributions of Zrs for all normal subjects in the seated position before methacholine (MCh; dashed lines) and all asthmatic patients (solid lines). *B*: probability density distributions of Zrs plotted on a logarithmic scale for normal subjects (solid lines) and asthmatic patients (dashed lines).

Table 2. *Test of normal and log-normal distributions*

	Zrs		ln Zrs	
	Skewness	Kurtosis	Skewness	Kurtosis
Normal subjects				
Upright	1.12	4.00	0.24	0.24
Supine	0.89	2.56	−1.13	17.29
MCh upright	1.40	14.73	−0.31	3.33
MCh supine	1.55	9.74	−0.46	5.23
Means ± SD	1.23 ± 1.15	7.67 ± 15.23	−0.41 ± 0.86	6.58 ± 12.1
Asthmatic patients	1.49 ± 1.29	9.53 ± 18.45	−0.25 ± 0.88	4.11 ± 5.92

Values for asthmatic patients are means ± SD. Zrs, respiratory impedance; MCh, methacholine.

7.67 ± 15.23 and 9.53 ± 18.45, respectively. Kolmogorov-Smirnov and χ^2 tests showed highly significant differences from a normal distribution. Thus the data are not Gaussian. The probability density distributions of Zrs plotted on a logarithmic scale are shown in Fig. 2*B*.

Figure 3 is an example in a normal subject (*RC*) of the raw data of Zrs in seated and supine positions before and after MCh. Individual distributions of Zrs in normal subjects before and after MCh in seated and supine positions are shown in Fig. 4*A*. The data for one subject (*BK*) where the *x*-axis is a logarithmic scale are shown in Fig. 4*B*. The r^2 values from normal subjects in all conditions and asthmatic patients for the actual vs. the theoretical distributions were >0.92, with one exception, with a mean value of 0.97 ± 0.03 (SD). Nevertheless, the χ^2 test showed that every distribution was significantly different from log-normal ($P = 0.05$). On the other hand, the Kolmogorov-Smirnov tests showed no significant differences from log-normal distributions for all conditions in normal *subject JS* and before MCh in the supine position and after MCh in the upright position in *subject CK*. Probability density distributions in two asthmatic patients (*WC* and *HA*) were also not significantly different from log-normal by this test. Table 3 shows r^2 values for the least-squares fit of the probability density distributions to log-normal distribution functions.

The calculated skewness and kurtosis of the lnZrs distributions are shown in Table 2. In pooled normal subjects, the skewness of lnZrs magnitude was one-third that of Zrs, and the magnitude of the kurtosis of lnZrs was less than that of Zrs. In asthmatic patients, the skewness of lnZrs was one-fifth that of Zrs, and the magnitude of the kurtosis of lnZrs was one-half that of Zrs. In pooled normal subjects, we found a skewness of lnZrs of −0.41 ± 0.86 and kurtosis of lnZrs of 6.58 ± 12.0. Both values are approximately one-half of their SDs and thus are only ~0.5 SD away from zero. In the asthmatic patients, skewness of lnZrs was −0.25 ± 0.88 and kurtosis of lnZrs was 4.11 ± 5.92. Because skewness and kurtosis were less for lnZrs than for Zrs and are not very different from zero, as we would find for a log-normal distribution, we conclude that Zrs is better described by a log-normal than a normal distribution. Although Zrs is not quite a log-normally distributed variable, it is nearly log-normal in most subjects.

Influence of Posture and MCh on Zrs

The mean values of the log-normal probability density distributions (μ) in the normal subjects before MCh in upright and supine positions, as shown in Table 3, were significantly less than in the asthmatic patients ($P < 0.0001$ and $P < 0.005$, respectively), whereas after MCh in upright and supine postures they were not. In contrast, the mean values of the SD of the log-normal probability density distributions (σ) were significantly less than in asthmatic patients before and after MCh in the upright position ($P < 0.05$ and $P < 0.02$, respectively), whereas in the supine

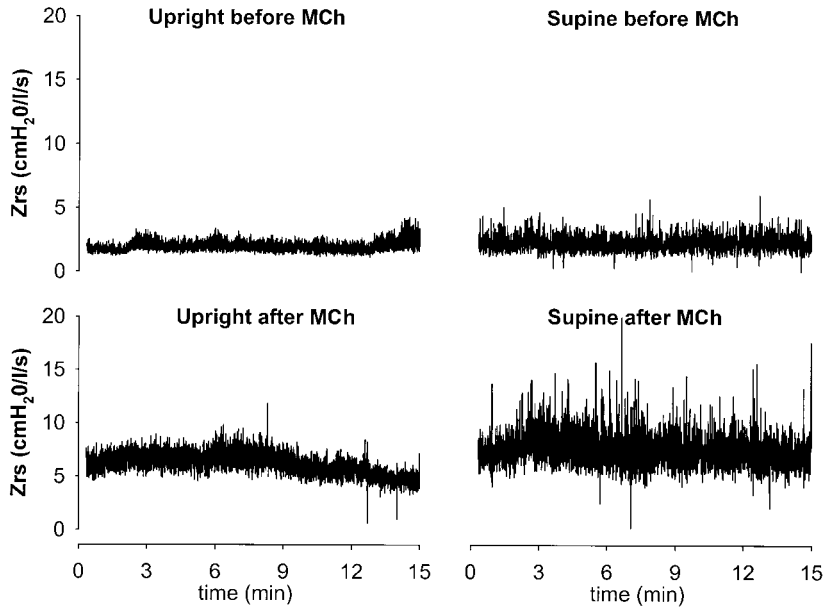

Fig. 3. Raw Zrs data in a normal subject (*CH*) before and after MCh in seated and supine positions.

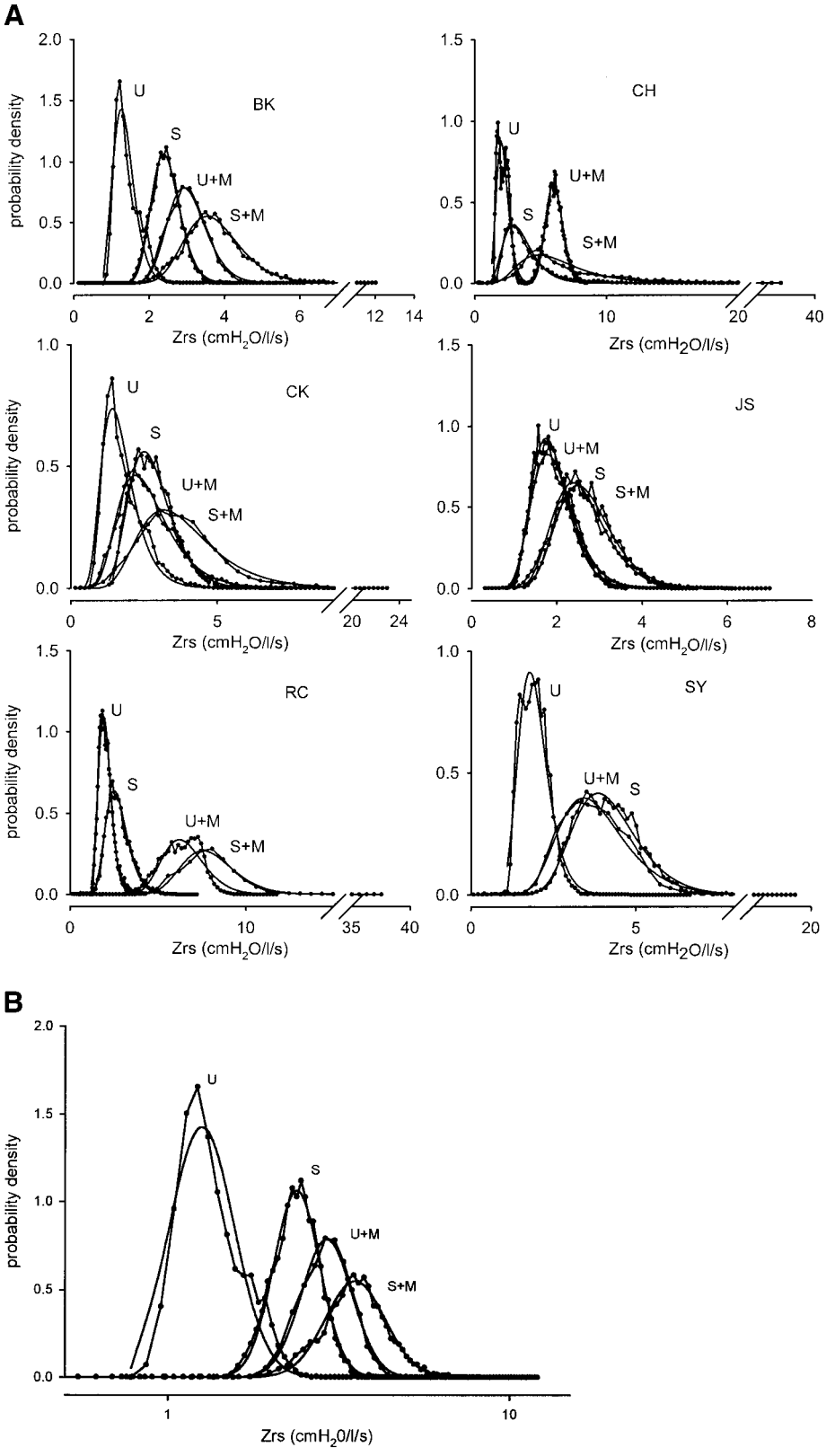

Fig. 4. *A*: individual probability density distributions of Zrs in normal subjects in upright (U) and supine (S) positions and after MCh (M). ●, Data points; solid lines, best least-squares fit of a log-normal distribution (Levenberg-Marquardt method using Matlab). *B*: Zrs in a normal subject replotted on a logarithmic scale. ●, Data points; solid lines, best-fit curves.

position the differences were not significant. It appears that activation of airway smooth muscle leads primarily to airway obstruction, as reflected in μ, whereas the supine posture leads primarily to spontaneous variability, as reflected in σ.

Neither intervention alone caused normal subjects to behave as asthmatic patients, but when the interventions were combined, the degree of obstruction and its variability were statistically indistinguishable from those in the asthmatic patients.

Table 3. *Mean and standard deviation of ln Zrs*

	μ	*P**	σ	*P*	r^2†
Normal subjects					
Upright	0.59 ± 0.06	<0.001	0.24 ± 0.03	<0.05	0.933 ± 0.021
Supine	1.07 ± 0.09	<0.005	0.29 ± 0.09	NS	0.981 ± 0.004
MCh upright	1.27 ± 0.19	NS	0.22 ± 0.03	<0.02	0.970 ± 0.015
MCh supine	1.47 ± 0.20	NS	0.32 ± 0.06	NS	0.966 ± 0.014
Asthmatic patients	1.59 ± 0.06		0.34 ± 0.03		0.981 ± 0.005

Values are means ± SE. μ, mean; σ, standard deviation; NS, not significant. *Significance of difference vs. asthmatic patients. †Least-squares fit of probability density distributions to log-normal distribution function.

Relationship Between μ and σ

A plot of σ vs. μ in all subjects under all conditions is shown in Fig. 5. There was no correlation between the degree of obstruction as assessed by μ and the spontaneous variation in airway caliber as assessed by σ. This is consistent with the results shown in Table 3 indicating that activation primarily increases the degree of obstruction whereas the supine posture primarily increases variability. Figure 4, however, shows between-individual variability in the different effects of activation and posture. In *subject JS*, MCh had no effect, so that all the increase in Zrs and its variability were due to changing from the seated to the supine posture. In *subject SY* the effects of MCh and posture were almost indistinguishable (data for *subject SY* after MCh in the supine position were bimodally distributed with a significant fraction of Zrs measurements <1.0 $cmH_2O \cdot l^{-1} \cdot s$; these data were discarded as unreliable). The contrast between the increase in variability produced by the supine position and the increase in mean Zrs produced by MCh is most clearly seen in *subjects CH* and *RC*.

Between-Day Variation in Normal Subjects

When three sets of data were compared from normal subjects in the upright posture but acquired on different days by repeated measures, there was no significant difference in mean impedance ($P = 0.888$) and standard deviation of impedance ($P = 0.241$). Thus the day-to-day variation in Zrs and its variability within normal subjects were small.

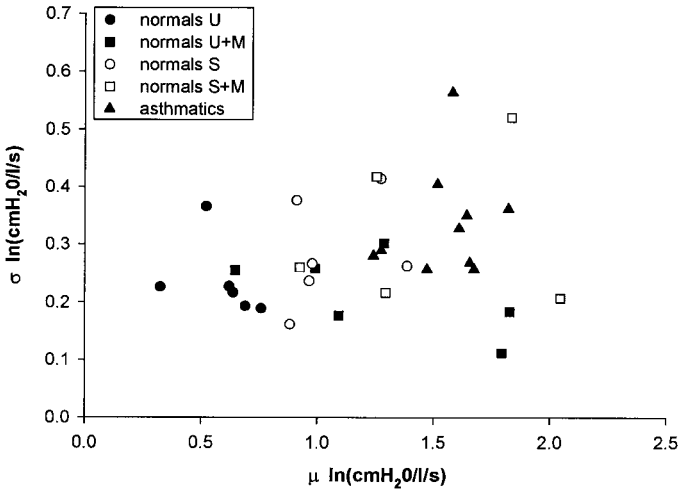

Fig. 5. Standard deviation (σ) of lnZrs vs. mean value (μ).

DISCUSSION

Main Findings

In this study we have shown that spontaneous variation in airway caliber in normal subjects and asthmatic patients can be assessed over a period of minutes, rather than the weeks required when variability is assessed by diurnal variation in peak expiratory flow rate (19). The variation in Zrs we measured was nearly, but not quite, log-normal (Tables 2 and 3). The mean value of lnZrs was not correlated with its standard deviation (Fig. 5). Thus the degree of airway obstruction does not predict its variability. Mean Zrs and its variability were less in the normal subjects in the seated position than in the asthmatic patients. Both μ and σ increased with MCh and in the supine position but not into the range of the asthmatic patients with either intervention alone (Table 3). However, when MCh was combined with the supine position, normal subjects behaved like asthmatic patients. MCh activates airway smooth muscle, while the supine position, by decreasing lung volume and lung elastic recoil pressure, unloads it. Thus the combination of activation and unloading of normal airway smooth muscle reproduced in normal lungs the same degree of obstruction and the same spontaneous variability in airway caliber that occur in asthma.

Critique of Methods

The raw measurements of impedance show that variation occurred rapidly and slowly over all time scales within and between breaths. Within-breath variation could be due to lung volume and flow effects. About 250 breaths made a complete data set for each individual. Thus a systematic increase in Zrs due to a decrease in lung volume should be observed ≥750 times during the data collection (with Zrs measured at 6 Hz and an expiratory time of 2 s there would be ~3 measures of Zrs near end-expiratory lung volume for each breath), whereas variability due to flow should occur >500 times during the data collection period, inasmuch as there are two flow peaks for each respiratory cycle. If it is assumed that there is only one measurement at each peak flow, the combined effects should affect at least

(1,250/5,400) × 100 = 23% of the measurements. Similarly, if expiratory flow limitation caused most of the variability in airway caliber in asthmatic patients, ~50% of all measurements of Zrs (with the assumption of a duty cycle of 0.4) would be systematically higher than the other 50%. This would result in a bimodal distribution with a substantial number of measurements at the highest levels of Zrs. Figures 2 and 4 show that such discontinuities were not observed in normal subjects or asthmatic patients. Thus we do not believe that expiratory flow limitation, volume, and flow effects explain the differences in probability density distributions between normal subjects and asthmatic patients or the effects of posture and MCh on variation in normal subjects.

Conceivably, some of the variation in Zrs could be due to noise. However, it would have to be some type of noise that systematically increased with activation and unloading. Such a source of noise is difficult to imagine. The dissociation between μ (the signal) and σ (the supposed noise), as shown in Fig. 5, not only makes this unlikely, it also indicates that spontaneous variation in airway caliber is not simply a function of the degree of obstruction. During transient periods of high impedance, the measurement of Zrs will be sensitive to low values of the magnitude of flow oscillations. Random errors in measurement of a small denominator could possibly lead to large errors in the estimate of Zrs. However, this source of noise is dependent on the variation itself; the amplitude of flow is low only because the impedance is high. The error may be large, but only because the signal is large. For these reasons, we believe that the variations in Zrs that we measured reflect continuous variations in the configuration of the tracheobronchial tree.

Because variations occurred rapidly, we believe the only parameter that could change sufficiently quickly to account for the data is the fraction of the total number of cross bridges in airway smooth muscle that are attached. If this is so, the dynamic configurational changes of the tracheobronchial tree are due to variations in smooth muscle tone in addition to the well-known changes in transmural pressure that occur with volume and flow. We believe that the hyperdynamic nature of the configurational changes in asthma reflects altered smooth muscle behavior that is mimicked in the normal lung by a combination of activation and unloading.

The changes are not so rapid that they occur in one cycle. Close examination of the signal (data not shown) reveals that Zrs changes from maximum to minimum in ~0.5 s. Because the change in Zrs in a given airway scales as the airway's radius to the fourth power, the rate of change of the airway's impedance is faster than the rate of change of its radius because of the induced harmonics. If each airway is independent of its neighbors and the configurational changes are all out of phase with one another with different cross-bridge cycling rates, then the most probable state is half of the airways dilating and the other half constricting. However, for brief periods of time, a substantial majority could be constricting or dilating simultaneously, when sudden large decreases or increases in Zrs would be interspersed with more average ones. Furthermore, the multiplicative nature of the addition of hydraulic resistances in parallel might give rise to additional harmonics, also increasing the rate of change of Zrs.

Thus we suggest that the rapid changes in Zrs occur because it is a multiplicative power function possibly modified by harmonics, measuring the ensemble of configurational changes throughout the whole lung with some airways dilating and others constricting in series and in parallel. We believe it is unlikely that the rapid variations are due to airways closing and reopening, because multiple openings and closings in a single breath during inspiration and expiration are physiologically improbable.

In the ensuing paragraphs we will first discuss the implications of spontaneous variations in homeostatically controlled parameters for physiology in general using variations in airway configuration as an example. Then we will discuss our interpretation of the results in terms of the pathophysiology of asthma.

Homeokinesis

Homeokinesis and the homeokinetic code. In addition to airway caliber, many homeostatically controlled systems show nonrandom, nonperiodic, systematic variations in time (5, 9, 11, 12, 18, 25, 32, 33, 35). Systematic variations in airway caliber means that there are systematic variations in dead space. This, combined with variations in tidal volume, will result in breath-by-breath variations in CO_2 elimination and O_2 uptake. These will be propagated into systematic variations in O_2 pulse and acid-base balance and so on down the line. Fluctuations in one parameter lead to similar fluctuations in others.

Indeed, the state that we call homeostasis and that is essential for health appears to be characterized by continuous fluctuations. It would seem that homeokinesis is a more appropriate term (38). We tentatively define it as the ability of an organism functioning in a variable external environment to maintain a highly organized internal environment fluctuating within acceptable limits by dissipating energy in a far-from-equilibrium state. This definition has a number of implications. First, it states that variations in the internal environment are normal and result from energy consumption. It implies that lack of variation and excessive variation are abnormal. It indicates that failure to utilize and dissipate external energy sources will result in breakdown of homeokinesis, and it suggests that this might also occur with excessive energy utilization and dissipation.

Between-individual variation is required for natural selection in Darwinian evolution. A particular variation can confer survival benefit, so that the individual possessing it adapts to new challenges that lead to

extinction in other individuals lacking the variation. Similarly, it could be that within-individual variation may be required if an individual must adapt to changing conditions. We have speculated elsewhere (24) that healthy variation signifies adaptability, in much the same way a tennis player awaiting a serve continually shifts from side to side to respond appropriately to the placement of the serve.

Although continuous fluctuations are normal, our results indicate that in disease they can become excessive. On the other hand, lack of variation in pulse rate is characteristic of heart failure and is a risk factor for serious arrhythmias (17, 28). Similarly, in comatose patients, breathing is more regular than normal. Deepening coma is characterized by increasing regularity of respiratory rate, which accurately predicts outcome (20). If normal variation is healthy and disease is characterized by both excessive and too little variation, it is clear that variation contains an encoded message that needs to be deciphered, quantified, analyzed, and understood. Understanding the homeokinetic code should give insight into what constitutes health and the mechanisms of disease. This study represents a beginning attempt to do so for the maintenance of airway caliber in health and its breakdown in asthma.

Breaking the homeokinetic code: probability, entropy, and disease. The second law of thermodynamics states that the entropy of isolated systems can never decrease. On the other hand, living organisms function far from equilibrium and, when considered in a closed thermodynamic system, exist in a very statistically improbable configuration. These highly ordered systems maintain their order precisely because of their ongoing consumption of external energy (the system is not closed). The description of the variation of a particular system by frequency distribution curves characterizes the probability for a measure of the system (in our case, Zrs) to achieve a particular value. Some values of Zrs are common, while others are rare. What does this mean physiologically?

We model the dynamic nature of the tracheobronchial tree as follows. We define each value of Zrs as a macrostate of the lung. A given configuration of the whole tracheobronchial tree we define as a macroconfiguration. Each macrostate contains a set of different macroconfigurations that give rise to that value of Zrs. We define a microstate as the spatial distribution of the fraction of the total number of airway smooth muscle cross bridges that are attached in a given airway and a microconfiguration as the resulting configuration of that airway. Presumably, there can be a large set of microstates giving rise to a single microconfiguration. We envision that the fundamental phenomenon underlying the continuous change in Zrs is continuous variation in microstate in every airway so that each airway's microconfiguration is continuously changing. In this sense, the lung is heterogeneous, with spatial heterogeneity between airways in their microconfigurations and inhomogeneities in macroconfiguration between regions. There is also temporal heterogeneity of the microstate within an airway and of the macrostate of the lungs, both of which change continually. With such heterogeneity, to calculate the lung macroconfiguration at any instant would require information about the microconfiguration of every airway contributing to Zrs both serially and in parallel.

We believe that the magnitude of variation in microstates and microconfigurations depends, in part, on the degree of smooth muscle activation. When the smooth muscle is totally inactivated, no cross bridges are attached, and there should be no variation in micro- or macroconfiguration independent of those resulting from volume or flow effects. When activated, the variation in microstates and microconfigurations increases as the degree of smooth muscle activation increases, leading to increasing variation in macroconfigurations and in macrostates.[1] However, as smooth muscle becomes progressively activated, it consumes more energy and thus moves farther from thermodynamic equilibrium. As the system moves farther from equilibrium, its entropy decreases and the probability of statistically improbable macroconfigurations and macrostates increases. If this is so, the variation in Zrs is a measure of distance from thermodynamic equilibrium and an index of entropy.

The number of potentially accessible macroconfigurations is huge. Assume that the total number of airways that contribute to Zrs is 250,000; assume that each airway can access three microconfigurations, normal, dilated, and constricted, and that each acts independently of the others. The total number of accessible macroconfigurations is $3^{250,000}$ or $\sim 10^{100,000}$. If each microconfiguration could change every millisecond, it would take far longer than the age of the universe to cycle through all accessible macrostates. Evidently, in a lifetime, only a tiny fraction of the accessible macroconfigurations can be sampled. If all airways were independent, the chances that all the airways would narrow simultaneously in an individual's lifetime would be vanishingly small. Such an event would be highly ordered and would be a condition of low entropy. A much more probable event would be when about half the airways were narrowing and the remaining half dilating, with their distribution in the tracheobronchial tree being random. Thus small deviations from mean Zrs are more probable than large deviations, and our probability distribution curves show that this is the case (Figs. 1*B* and 2). Asthma, however, is a condition where highly improbable macrostates and macroconfigurations appear to be occurring almost all the time. Asthma might therefore be classified as a disease of abnormally low entropy, in which airway smooth mus-

[1]The similar values of σ shown in Table 3 in upright normal subjects before and after MCh (0.24 vs. 0.22) do not signify that the variations were the same in absolute terms but that the variations were proportional to mean lnZrs (the coefficient of variation of Zrs was unchanged; see APPENDIX), which increased >2-fold after MCh. Thus MCh increased the variation in absolute terms, although not into the asthmatic range (Table 3).

cle is farther from thermodynamic equilibrium than normal, because it dissipates abnormally large quantities of energy. In fact, this is a rather trivial conclusion: we know that asthma is a disease of abnormal smooth muscle activation (presumably by inflammatory agonists) that increases the muscle's metabolic rate and, thus, its energy consumption. On the other hand, the low variability in heart rate in congestive heart failure (17, 28) and of respiratory rate in coma (20) indicates that a statistically improbable state is unlikely to occur. Congestive heart failure and coma might thus be classified as high-entropy states in which there is too little energy dissipation, resulting in inability to adapt to new conditions (such as exercise in congestive failure), because the system is too close to thermodynamic equilibrium.

If all systems that comprise living things must function far from thermodynamic equilibrium to maintain low entropy, it would seem probable that health requires the system to be just the right distance from equilibrium with just the right amount of entropy. Illness will result when the organism or part of it becomes too far from or too close to equilibrium. Inasmuch as the measurement of variation within a system appears to be a measure of distance from thermodynamic equilibrium, it has the potential of being a measure of health and an indicator of disease. It might do this by quantifying the probability of a given macrostate occurring. When the probability of an unlikely macrostate is abnormally high and the system appears too far from equilibrium, the therapeutic objective would be to decrease the system's energy dissipation. When the probability of a likely macrostate is too low, the system's energy dissipation should be increased.

Asthma

Smooth muscle activation and unloading and the pathophysiology of asthma. In asthma the variation of airway caliber appears to be an exaggeration of normal behavior. The effect of unloading in the supine posture before and after activation by MCh in normal subjects sheds light on this "exaggeration." We found that unloading alone resulted in variability of Zrs equal to that in asthmatic patients. Thus the variable airway obstruction that characterizes asthma is mimicked in normal subjects merely by lying down. Combining this with activation brought the degree of obstruction in normal subjects into the asthmatic range (Fig. 4, Table 3). A similar combination of increased activation and unloading abolishes the plateau on the bronchial dose-response curve, removing the normal protection against unlimited airway narrowing (6); it induces gas trapping and inhibits the dilating effects of a deep inspiration (29). These are characteristic features of asthma (10, 22, 23). Evidently, normal airway smooth muscle can be made to behave like asthmatic smooth muscle in almost all respects. One does not need to invoke an abnormality in airway smooth muscle to explain the disease. Increased activation, unloading, and decreased tidal stretch are sufficient.

If we define a macrostate as the set of lung macroconfigurations that results in a particular value of Zrs, it is evident that asthmatic lungs spend only a small percentage of their time in macrostates that are within the normal range (Fig. 2). Furthermore, in asthma, many more macrostates occur in a given time period than in upright normal subjects before MCh. The variation of a macrostate away from its mean value occurs on average 3.5 and as much as 5 orders of magnitude more frequently than normal (24). This is not explained simply by activation by MCh, which mimicked asthma in terms of μ but not σ. Thus asthma is not entirely explained by excessive energy consumption displacing airways farther from thermodynamic equilibrium, inasmuch as this does not account for the configurational variability.

Smooth muscle unloading, which does account for the fluctuations, has a number of deleterious consequences. First, it increases the velocity of shortening according to the muscles' force-velocity relationship. Although the level of activation of a muscle determines its power output, it is the load it acts against that determines how much of the power is partitioned into velocity of shortening and how much into force development. If the load is large, more of the power will be expressed as force; if it is low, it will be expressed more as velocity of shortening (34). Bates et al. (3) showed that the rate of change of pulmonary resistance in rats given intravenous MCh was 18 times faster at a distending pressure of 2 cmH_2O that at 6 cmH_2O. The effect of load on shortening velocity of airway smooth muscle is substantial.

Although unloading of smooth muscle is unproven in asthma, Jackson et al. (15) provided convincing data that the velocity of smooth muscle shortening is increased. After a deep breath, the impedance to airflow fell as much in asthmatic patients as it did in normal subjects given MCh but rose 3.5 times faster after resumption of tidal breathing, clearly demonstrating an increase in shortening velocity.

A second deleterious effect of unloading is increased smooth muscle shortening. With unloading, the degree of shortening will be greater for any degree of activation. This is presumably the reason for the disappearance of the plateau on the dose-response curve (6) as well as for gas trapping (29). A third effect is to decrease the tidal stress applied to the smooth muscle by the elastic recoil pressure of the lung. Insufficient tidal stress may not produce the potent bronchodilitation resulting from tidal breathing that Fredberg et al. (8) emphasized as necessary to maintain normal airway patency. Finally, unloading may be responsible for the abnormal response to deep inspiration that characterizes asthma, not only because the velocity of shortening is increased, but also because the smooth muscle is insufficiently stretched.

Activation appears to interact with unloading, in the sense that it makes events such as a change in posture,

which normally carry no risk, events with significant pathophysiological effects. Moving farther from equilibrium may therefore create instability in ways not directly related to increased energy consumption by magnifying fluctuations so that they become dangerous. How does this happen?

If an airway has three microconfigurations, dilated, normal, and constricted, activation will increase the probability of a transition from the normal to the constricted microconfiguration and decrease the probability of transition from the normal to the dilated microconfiguration. Increasing the velocity of shortening increases the rate of configurational change and the number of macrostates that occur in a given time period. These changes are strongly biased toward an increase in those configurations resulting from constriction and away from those resulting from dilatation. Because decreasing load leads to greater bronchial narrowing at constant activation and resistance is inversely proportional to airway radius to the fourth or fifth power (36), the greater constriction will interact with the change in transition probability to markedly increase the values of Zrs for a given macroconfigurational change. This may explain the nearly log-normal frequency distribution of Zrs.

If airway smooth muscle unloading occurs in asthma, the most likely cause is unlinking of airways and parenchyma, presumably by peribronchial edema or inflammatory exudate. Certainly, peribronchial inflammation is a prominent pathological feature of the disease (7). Loss of elastic recoil, a not uncommon feature of asthma (37), will also unload smooth muscle.

We previously pointed out the predictive features of short-term variability of airway caliber (24). Measuring this variability is easy and requires little patient cooperation. It could be accomplished on rising in the morning at home, the volatility during the next 24 h predicted, and treatment adjusted accordingly. Although this would require a prospective clinical trial, the ability to predict life-threatening attacks of asthma and introduce appropriate preventive therapy could reduce asthma mortality.

APPENDIX

Because the distributions of Zrs are quite close to log-normal distributions, it is relevant to note the relationships between the descriptive parameters μ and σ of the log-normal distribution function and the statistical parameters of Zrs. Recall that for a variable that is log-normally distributed (e.g., Z), μ is the mean of ln(Z) and σ is the standard deviation of ln(Z). However, it can also be shown that the mean of Z is related to μ and σ as

$$\text{mean}_Z = e^{\mu + \sigma^2/2} \qquad (A1)$$

A more direct relation between the distribution of Z and μ and σ is provided by the median of Z (14a) as

$$\text{median}_Z = e^{\mu} \qquad (A2)$$

Thus if Zrs were exactly described by a log-normal distribution, then values of Zrs greater than e^{μ} would occur 50% of the time. The standard deviation (SD_Z) is also related to μ and σ as

$$SD_Z^2 = e^{2\mu + \sigma^2}(e^{\sigma^2} - 1) \qquad (A3)$$

Finally, it can be shown that the coefficient of variation of Z (COV_Z) is related to σ (but not to μ). By definition

$$COV_Z = SD_Z/\text{mean}_Z \qquad (A4)$$

then since *Eq. A3* can be rewritten as

$$SD_Z^2 = e^{2\mu + 2\sigma^2} - e^{2\mu + 2\sigma^2} \qquad (A5)$$

we can easily solve for the square of *Eq. A4* using *Eq. A5* divided by the square of *Eq. A1* giving

$$COV_Z^2 = e^{\sigma^2} - 1 \qquad (A6)$$

Solving *Eq. A6* for σ^2 gives

$$\sigma^2 = \ln\,(COV_Z^2 + 1) \qquad (A7)$$

Thus, insofar as Zrs can be described by a log-normal distribution, σ is functionally dependent on the coefficient of variation of Zrs and, thus, on the mean and SD of Zrs. Indeed, the coefficient of variation of Zrs using *Eq. A7* predicted σ within 0.4 ± 7% (±SD pooling all data), indicating that the distributions were generally not that different from log-normal (Fig. 6). Furthermore, for small COV_Z ($COV_Z \ll 1$), $\sigma \approx COV_Z$ (as can be seen in Fig. 6). This is because the series expansion for $\ln(x + 1)$ gives

$$\ln\,(x + 1) = x - \frac{x^2}{2} + \frac{x^3}{3} - \frac{x^4}{4} + \cdots$$

For $x \ll 1$, the higher-order terms vanish and $\ln(x + 1) \approx x$. Thus we have a simple means to interpret μ and σ from Zrs, via the median (*Eq. A2*) and the coefficient of variation (*Eq. A7*), respectively, of Zrs.

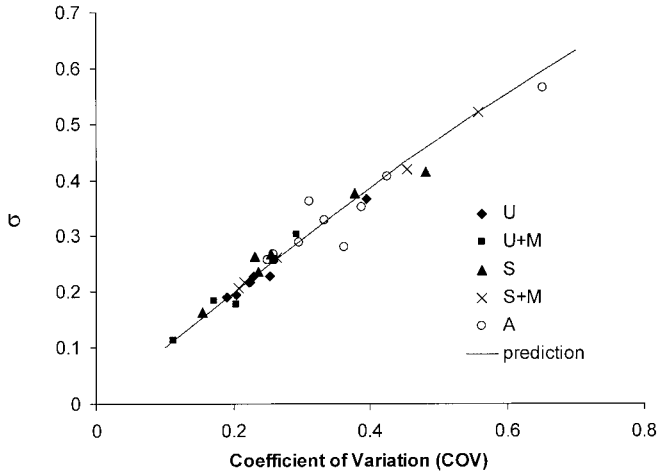

Fig. 6. σ predicted from the coefficient of variation of Zrs. Points are for the different groups as in Fig. 4, with A representing asthmatic patients; curve is the prediction based on *Eq. A7*.

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