Homeokinesis and short-term variability of human airway caliber

CHENG-LI QUE,1 C. M. KENYON,1 R. OLIVENSTEIN,1 PETER T. MACKLEM,1 AND GEOFFREY N. MAKSYM2
1Inspiraplex Respiratory Health Network of Centres of Excellence, Meakins Christie Laboratories, Montreal Chest Institute, Royal Victoria Hospital, McGill University, Montreal, Quebec H2X 2P4; and 2School of Biomedical Engineering, Dalhousie University, Halifax, Nova Scotia, Canada B3J 3H5
Received 29 March 1999; accepted in final form 20 March 2001

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 after Mch and 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

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: P. T. Macklem, Inspiraplex, Montreal Chest Institute, 3650 St. Urbain, Montreal, PQ, Canada H2X 2P4 (E-mail: macklem@meakins.lan.mcgill.ca).
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; FVC, forced vital capacity.

Table 1. Clinical characteristics of asthmatic patients

<table>
<thead>
<tr>
<th>Subj</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Smoking</th>
<th>Pred FEV1, %</th>
<th>FEV1/FVC</th>
<th>Asthma Severity</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>GL</td>
<td>60</td>
<td>M</td>
<td>No</td>
<td>91</td>
<td>0.73</td>
<td>Mild</td>
<td>W</td>
</tr>
<tr>
<td>LC</td>
<td>17</td>
<td>F</td>
<td>Yes</td>
<td>79</td>
<td>0.71</td>
<td>Mild</td>
<td>W</td>
</tr>
<tr>
<td>MT</td>
<td>53</td>
<td>F</td>
<td>No</td>
<td>85</td>
<td>0.68</td>
<td>Mild</td>
<td>W</td>
</tr>
<tr>
<td>VB</td>
<td>25</td>
<td>F</td>
<td>No</td>
<td>85</td>
<td>0.74</td>
<td>Mild</td>
<td>SW</td>
</tr>
<tr>
<td>DD</td>
<td>41</td>
<td>F</td>
<td>No</td>
<td>70</td>
<td>0.60</td>
<td>Moderate</td>
<td>W</td>
</tr>
<tr>
<td>HA</td>
<td>70</td>
<td>F</td>
<td>No</td>
<td>92</td>
<td>0.70</td>
<td>Moderate</td>
<td>S</td>
</tr>
<tr>
<td>AR</td>
<td>29</td>
<td>M</td>
<td>Yes</td>
<td>83</td>
<td>0.70</td>
<td>Severe</td>
<td>S</td>
</tr>
<tr>
<td>BZ</td>
<td>54</td>
<td>F</td>
<td>No</td>
<td>72</td>
<td>0.58</td>
<td>Severe</td>
<td>W</td>
</tr>
<tr>
<td>IB</td>
<td>33</td>
<td>M</td>
<td>Yes</td>
<td>64</td>
<td>0.53</td>
<td>Severe</td>
<td>W</td>
</tr>
<tr>
<td>WC</td>
<td>28</td>
<td>F</td>
<td>No</td>
<td>56</td>
<td>0.73</td>
<td>Mild</td>
<td>S</td>
</tr>
</tbody>
</table>

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; FEV1, 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 iner- tance 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. Artefacts 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
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 χ² 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 1A shows two examples of Zrs over the 15-min time period. Mean Zrs was 2.8 and 5.5 cmH₂O·l⁻¹·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) cmH₂O·l⁻¹·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 1B shows the probability density distributions of Zrs in the normal subject and the asthmatic patient shown in Fig. 1A. 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. 2A. Average values of skewness and kurtosis 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. 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).](image)

![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).](image)
7.67 ± 15.23 and 9.53 ± 18.45, respectively. Kolmogorov-Smirnov and χ² 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. 2B. 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. 4A. The data for one subject (BK) where the x-axis is a logarithmic scale are shown in Fig. 4B. The r² 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 χ² 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 r² 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 positions...
position the differences were not significant. It appears that activation of airway smooth muscle leads primarily to airway obstruction, as reflected in \( \mu \), whereas the supine posture leads primarily to spontaneous variability, as reflected in \( \sigma \).

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.

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.
Table 3. Mean and standard deviation of ln Zrs

<table>
<thead>
<tr>
<th></th>
<th>μ</th>
<th>P&lt;0.001</th>
<th>σ</th>
<th>P&lt;0.05</th>
<th>r²†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upright</td>
<td>0.59 ± 0.06</td>
<td>&lt;0.001</td>
<td>0.24 ± 0.03</td>
<td>&lt;0.05</td>
<td>0.933 ± 0.021</td>
</tr>
<tr>
<td>Supine</td>
<td>1.07 ± 0.09</td>
<td>&lt;0.005</td>
<td>0.29 ± 0.09</td>
<td>NS</td>
<td>0.981 ± 0.004</td>
</tr>
<tr>
<td>MCh upright</td>
<td>1.27 ± 0.19</td>
<td>NS</td>
<td>0.22 ± 0.03</td>
<td>&lt;0.02</td>
<td>0.970 ± 0.015</td>
</tr>
<tr>
<td>MCh supine</td>
<td>1.47 ± 0.20</td>
<td>NS</td>
<td>0.32 ± 0.06</td>
<td>NS</td>
<td>0.966 ± 0.014</td>
</tr>
<tr>
<td>Asthmatic patients</td>
<td>1.59 ± 0.06</td>
<td></td>
<td>0.34 ± 0.03</td>
<td></td>
<td>0.981 ± 0.005</td>
</tr>
</tbody>
</table>

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 cmH2O·L⁻¹·s⁻¹; 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.

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 CO₂ elimination and O₂ uptake. These will be propagated into systematic variations in O₂ 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, $Z_{rs}$) to achieve a particular value. Some values of $Z_{rs}$ 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 $Z_{rs}$ 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 $Z_{rs}$. 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 $Z_{rs}$ 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 $Z_{rs}$ both serially and in parallel.

We believe that the magnitude of variation in microstates and macroconfigurations 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 macroconfigurations increases as the degree of smooth muscle activation increases, leading to increasing variation in macroconfigurations and in macrostates. 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 $Z_{rs}$ 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 $Z_{rs}$ 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 $10^{100,000}$. 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 $Z_{rs}$ are more probable than large deviations, and our probability distribution curves show that this is the case (Figs. 1B 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 $\sigma$ 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 $\ln Z_{rs}$ (the coefficient of variation of $Z_{rs}$ 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).
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 cmH2O that at 6 cmH2O. 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 bronchodilatation 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

$$\text{mean}_Z = e^\mu + \sigma^2$$  \hspace{1cm} (A1)

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

$$\text{median}_Z = e^\mu$$  \hspace{1cm} (A2)

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

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

$$\text{COV}_Z = SD_Z / \text{mean}_Z$$  \hspace{1cm} (A4)

then since Eq. A3 can be rewritten as

$$SD_Z^2 = e^{2\mu + \sigma^2} - e^{2\mu + 2\sigma^2}$$  \hspace{1cm} (A5)

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

$$\text{COV}_Z^2 = e^{\sigma^2} - 1$$  \hspace{1cm} (A6)

Solving Eq. A6 for $\sigma^2$ gives

$$\sigma^2 = \ln (\text{COV}_Z^2 + 1)$$  \hspace{1cm} (A7)

Thus, insofar as Zrs can be described by a log-normal distribution, $\sigma$ 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 $\sigma$ 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 ≪ 1), $\sigma \approx$ COV Z (as can be seen in Fig. 6). This is because the series expansion for ln(x + 1) gives

$$\ln (x + 1) = x - x^2/2 + x^3/3 - x^4/4 + \cdots$$

For $x \ll 1$, the higher-order terms vanish and ln(x + 1) ≈ 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.

We are grateful to Bela Suki and Andrew Jackson for helpful discussions and particularly to Sol Permutt for extremely helpful and constructive criticisms of this work.

This study was supported by the Medical Research Council of Canada.

Fig. 6. $\sigma$ 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.