Temporal complexity in clinical manifestations of lung disease

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The respiratory system includes many nonlinear feedback mechanisms and a network of subsystems that are interacting with each other (1, 17, 46). The respiratory system is also an active part of an even more complex structure of the entire human body and the environment. As all physiological systems, the well-regulated respiratory system is highly adaptive but is also attracted to a set point, or attractor (1, 7, 17, 46). The corresponding state of the system is dynamic rather than static with inherent delays in the regulatory feedback loops that result in complex temporal fluctuations of the output variables associated with breathing such as tidal volume (36), biomarkers, or symptoms (37). Indeed, there is a large body of evidence describing variability in tidal breathing, changes in lung function over minutes and over days, changes in bronchial reactivity in health and disease, and changes in inflammatory markers over time (61, 71). All these will result in fluctuations of respiratory symptoms, which give rise to a given “temporal” clinical phenotype (37).

Variability likely arises from internal regulatory mechanisms, but these are also influenced by a variety of environmental triggers, some of which are also correlated in time (93). Like many other physiological systems, the respiratory system has memory, and environmental triggers can have cumulative effects, such as repeated exposures to allergen leading to increased symptoms and variation in respiratory function associated with asthma. Furthermore, the respiratory system may be particularly susceptible to some of these triggers during growth and development (88). While growth and development are slow processes, they have a clear impact on how breathing frequency and variability in lung function change with age (75). The respiratory system can also be exposed to abrupt changes in environmental inputs, which can dramatically alter the nature of the steady-state condition or the phenotype. The most impressive example of this may be birth; however, a change in habitat or a change in treatment of a disease can also lead to a state transition during which fluctuations can drive the system away from its current dynamic behavior characterized by the corresponding attractor.

The purpose of this review article is to shed light on the nature and to some extent the origin of temporal fluctuations in respiratory system related variables. Additionally, we also address the clinical significance of fluctuations and the issue of how to deal with transition processes associated with certain medical conditions.

Why does the respiratory system display fluctuating behavior?

The respiratory system provides gas exchange for the entire body. This is a complex task because the system and its components, which build a network of interacting modules [modularity (1, 47)], are constantly exposed to different and time-varying stimuli. The respiratory system can adapt to such conditions, but at the same time it needs to maintain stable
function [robustness (1, 7, 47)]. It has been shown that adaptability results in continuous fluctuations of many homeostatically controlled physiological parameters (e.g., 16, 64, 76, 89). Based on thermodynamic considerations, it has recently been proposed that homeostasis is not an appropriate description of fluctuating living systems. Instead, homeokinesis has been suggested (53, 64, 92), which is tentatively defined as the ability of an organism to utilize external energy sources to maintain a highly organized internal environment fluctuating within acceptable limits under nonequilibrium conditions (53). In such a nonequilibrium state, factors facilitating adaptation to environmental triggers are likely to be balanced by factors that maintain stability (7) (Fig. 1).

In fact, although Fig. 1 depicts a balance between control and lack of control, life represents an ongoing process under nonequilibrium conditions, with energy inputs from the environment from which a portion goes into mechanical work as nonequilibrium conditions, with energy inputs from the environment from which a portion goes into mechanical work as we move and interact with our environment, and as we breathe and pump fluids, but the major portion is dissipated as heat through metabolic processes. If this heat could not be transported to the environment, this would result in an increase in the thermodynamic entropy of the body, but because the heat is dissipated not all the entropy is retained. As a consequence of energy flowing in and heat generated and transported out, the entropy of the system must also fluctuate. It can be considered that the living processes function to maintain order at the cell, organ, and whole body level, with entropy and energy always in flux, sustaining the system under nonequilibrium steady-state conditions. The absolute thermodynamic entropy of the body is not accessible, but the system has several time-varying signals, for which it is possible to calculate a related form of entropy from information theory, known as the Shannon entropy (70). The Shannon entropy quantifies the degree of information present in the fluctuations in that particular signal, and there are several signal analysis approaches that attempt to assess this (69). The more detail required to describe the fluctuations in the signal, the larger the entropy and the more complex the signal. Note that a completely random signal has the largest entropy with the smallest predictability.

In Fig. 1, the region in the center of the balance can be thought to represent a normal amount of energy consumption and entropy exportation characterizing healthy complexity of a fluctuating physiological process such as respiration. This notion is reminiscent of Macklem’s idea that life exists in a transitional region where fluctuations and normal variation are present, and which is between ordered systems with low entropy and metabolic activity and chaotic systems with high entropy and energy flux (53, 54). Like other measures of complexity, entropy calculations that identify patterns in the time series show that ventilatory flow (33) and respiratory irregularity decrease in critically ill or ventilated patients (30), which is represented to the left in Fig. 1. The system in this region is too rigid with low entropy and limited adaptability, and the respiratory pattern becomes simple depicted schematically as a limit cycle on a phase plot exploring with limited variation around a single state. Alternatively, due to internal changes or external stimuli, a system may leave the attractor region in the middle toward a state that displays more complex highly variable limit cycles such as shown in the pattern on the right. That disease may be expressed by changes in the variation of physiological variables either to reduced variation and simpler periodicity or to increased variation and more complex variation is not new (13, 38, 39). Indeed, it has been established that a shift toward increased stability in the heart with reduced heart rate variability is predictive of myocardial infarction (59). Another example in the respiratory system may be gradual airway wall remodeling in severe asthma or chronic obstructive pulmonary disease (COPD), which reduces adaptability, and ventilation is more limited. On the other hand, when respiration becomes increasingly irregular such as during panic disorder (19), this can be interpreted as a disturbed balance with too much energy flux, and measures of the respiratory pattern may indicate too high entropy that leads to a loss of control as frequent exacerbations in poorly controlled asthma, as we will discuss further below. Such a shift can be triggered by an increase in environmental stimuli or changes within the system. Again, maturation and aging can also alter the maintenance of this balance between stability and adaptability. For example, diseases related to neonatal immaturity can be understood as delayed and disturbed adaptive processes resulting in instability and loss of control (36), and many phenomena tending to increased rigidity may be found in senescence (61). Before characterizing the nature of fluctuations, we need to emphasize that the middle position does not correspond to equilibrium. Instead, inputs and outputs are well balanced, and the system has just the right range of complexity, which can vary depending on metabolic demands and sleep (18) and is represented by a system that is adaptable to external or internal stimuli with fluctuations that are varied and complex, but not out of control.

**Fig. 1.** A model of the homeokinetic nonequilibrium steady state in health and how diseases shift the balance. Normally a system is stable and it easily adapts to external stimuli, and fluctuations are normal. This is the healthy state or attractor in the middle (7). Changes in the system or environment can tip it toward either the left or the right. On the left, the system is too stable and ignores external stimuli. The system is too rigid with little fluctuations as shown by the lack of variation in the limit cycles on the scale. On the right, the system is unstable and environmental stimuli easily excite the system to have exceedingly large fluctuations and loss of control. Maturation of the developing respiratory system improves robustness moving it to the normal range, while senescence may increase rigidity.
CHARACTERIZATION OF TEMPORAL VARIABILITY

As we have seen, fluctuations of a physiological variable are a consequence of the system being held under a nonequilibrium steady-state condition. Characterizing the fluctuations should thus carry information on this steady state, and changes in the fluctuations may signify abnormalities. These fluctuations can be characterized in several ways. First, the extent of fluctuations can be characterized from the temporal variations far better than the simple variance and coefficient of variation by computing the histogram or probability distribution of the variable. Often, the distribution of physiological signals displays a long tail that is best visualized on a double logarithmic scale. If the tail decays linearly on log-log graph, the distribution is said to have a power law tail (76). Since the linear decay on the log-log graph has no characteristic peaks or features at any particular scale, the power law is said to show a scale-free or self-similar behavior. The significance of such a long tail is that the probability of a “rare” event can be orders of magnitude larger than if the distribution was a Gaussian. Examples include interbreath intervals (IBI) (36, 80). Examining how the variable follows itself in time, it becomes obvious that physiological signals often show temporal correlations. In this case, one can use the power spectrum, which displays the frequency content and any periodicity or the autocorrelation function to characterize the correlations. If the correlations span several orders of magnitude, the signal is said to have long-range correlations. A widely used method to quantify such correlations is called the detrended fluctuation analysis [DFA (58, 60)]. By detrending the fluctuating signal prior to analysis, this technique is relatively robust to nonstationarities or trends in the time series. In this analysis of temporal complexity, if the fluctuation function in DFA increases linearly on the double logarithmic graph, then a single number, the slope or exponent of the fluctuation function, fully characterizes the nature of the correlations. If the exponent $\alpha$ is 0.5 the signal is uncorrelated and if $\alpha$ is larger than 0.5, the signal is long-range correlated or fractal, with $\alpha = 1$ representing 1/f noise (60). To quantify fractal properties of a time series, additional analysis methods, including determination of the fractal dimension (3), power spectrum analysis (80), Hurst rescaled range analysis (42), or the Fano factor and the Allan factor (32), have been used. The details of many relevant techniques quantifying variability can be found in the review by Seely and Macklem (69).

Other methods that have been proposed to quantify the complex behavior of breath-to-breath tidal breathing time series are measures of entropy, correlation dimensions, surrogate data analysis, and reduced linear, autoregressive modeling (e.g. 2, 4, 72). However, many of these methods are sensitive to noise when applied to short time series (62). In clinical practice, the length and frequency of monitoring are often limited due to short time access to the patient or poor cooperation. These limitations may be minimized (91) by using the noise titration technique described by Poon et al. (62).

RESPIRATORY VARIABILITY FROM MINUTES TO MONTHS

In this section we briefly review several aspects of respiratory variability at different time scales. This topic was recently described in the Comprehensive Physiology (78), and here we provide summary material needed to give background to the final section on clinical consequences. It is well established that the respiratory rhythm is controlled by complex interactions within a network of neuronal circuits, receiving afferent input from chemo- and stretch receptors as well as higher brain centers (16). The respiratory rhythm generator in the brain stem gates and integrates these inputs and creates an oscillatory output. However, the respiratory pattern is not perfectly periodic, and neither is it perfectly random. The variation in the respiratory output results from the interaction of noisy internal and external inputs to the respiratory oscillator and a respiratory “gate” that opens during inspiration and closes during expiration. This results in significant variability in IBI which is just one way variation in respiration has been characterized as introduced above, and neuronal models have been able to generate similar statistical properties for IBI as seen in humans and animals (2, 15, 29, 36). Power law distributions calculated from IBI time series have been reported in fetal breathing in sheep (80), in human infants (36, 49), and human adults (27).

As summarized in Ref. 78, breath-to-breath tidal breathing patterns have also been examined with respect to their long-range correlation pattern (12, 20, 61, 68, 90) as well as their entropy characteristics (31, 81). Interestingly, many of these techniques have been used to quantify maturational breathing dynamics of preterm infants. It is thus conceivable that disorders related to immaturity of breathing may be considered as failed or delayed adaption of control resulting in a shift of the steady-state condition in Fig. 1 toward less stability and loss of control. Future studies should examine whether new mathematical algorithms can be used in the clinical setting to identify infants at risk for apnea and sudden death (SIDS).

Short-term variability in airway impedance. Power laws and temporal correlations are also present in the variation in respiratory impedance, Zrs, obtained by continuous tracking using the forced oscillation technique (56, 65). By delivering small-amplitude pressure oscillations with the forced oscillation technique usually at or near the resonance frequency, intra- and interbreath variation in Zrs can be obtained. Although fluctuations in Zrs are also influenced by the variability of upper airway function, the positioning of the subject (64), and breath-to-breath tidal volumes (26, 44), the origin of these fluctuations in Zrs is thought to reflect in part time-dependent changes in airway smooth muscle tone (48).

To date the greatest attention to the variation in Zrs has been to the shapes of the distributions of Zrs or the amplitude characteristics. When the variation is expressed as a squared difference from the mean Zrs, defined as Zvar, the distribution of Zvar follows a power law over several decades (31). The magnitude of variation in impedance can be assessed directly by the standard deviation of Zrs or the standard deviation of the log of Zrs. Sometimes the resistance is extracted from the impedance as the real part to better reflect airway diameter, especially when the oscillation frequency may be farther from resonance (48). Variation in Zrs is thought to reflect fluctuations in airway caliber that may be elevated in asthma, due to increased activity and tone of the airway smooth muscle (56, 64). Indeed variation in Zrs is elevated in asthma obtained at 6 Hz in adults (64) and over a range of frequencies in children (48, 86). Additionally, when variation in Zrs is assessed by its standard
deviation, it is also strongly dependent on the average airway caliber (25), increasing with methacholine activation and with unloading in the supine position (25), while decreasing with albuterol (48). That variation in Zrs depends on airway diameter is tellingly illustrated by the strong correlation of the standard deviation of Zrs to Zrs itself as reported by Diba et al. (25) with correlation coefficients greater than 0.6, and less correlated in children reported by Lall et al. (48) with correlations less than 0.35. A possible mechanism for the coupling of the standard deviation of Zrs to Zrs through changes in diameter was provided by Lall et al. (48) in a single airway model. When assessed by the standard deviation of the logarithm of SD (lnZrsSD) this correlation largely disappears and Que et al. (64) demonstrated variation in lnZrs can be dissociated from airway narrowing during high dose methacholine 32 mg/ml in healthy adults. Thus, while Diba et al. (25) concluded that the correlation of the standard deviation of Zrs with Zrs may diminish its clinical utility, the lack of a perfect correlation suggest that there is information in variability that is not contained in the magnitude of Zrs. Therefore, the presence of variation may provide a view into airway function indicative of fluctuations in airway diameters throughout the airway tree (56, 64).

Currently, there are differences among the findings in amplitude variation in Zrs in asthma that may depend on the magnitude of the differences in mean airway impedance between asthma and healthy subjects. Asthmatics had Zrs 3.0 cmH2O·l−1·s higher in Que et al. (64) and they found both the standard deviations of Zrs and logZrs to be elevated in asthma, while asthmatics had Zrs only 1.0 cmH2O·l−1·s higher in Diba et al. (25) and they found only the standard deviation of Zrs was elevated in asthma. In a recent study with no differences in Zrs in asthma, Muskulus et al. (56) also found no differences in either measure of variation of Zrs. Finding significant differences in fluctuations of Zrs in asthma thus appears to require a significant difference in airway caliber between populations. In children where Zrs is larger due to smaller lungs, fluctuations in Zrs are significantly larger in asthma than in healthy children (48, 86) and it is also possible that subjects may have to be symptomatic to exhibit large fluctuations. Using robust maximum likelihood methods, Muskulus et al. (56) confirmed Zvar exhibited power law behavior in half of a group of asthmatic and healthy subjects, supporting complex dynamics underlying Zrs. Further, Muskulus et al. also examined the temporal characteristics of Zrs in asthma, COPD, and healthy subjects using measures of self-similarity including detrended fluctuation analysis and Wasserstein distance-based phase-space analysis. While there were no differences among groups in the DFA exponents, there were specific and sensitive differences between COPD and the other groups using the Wasserstein distance technique, indicating that the fluctuations in impedance have temporal features indicative of a nonlinear dynamic system and that a cluster of features may be distinguishing for disease. These are intriguing findings although it remains to be examined what functional changes in impedance may be used in the future as risk predictors.

While the patterns in the variation of Zrs are to be investigated, its origins, the variation in activation of airway smooth muscle could be due to many factors including coupling of agonist deposition to flow pattern (6), changes in relaxation following constriction, and even changes in loading (34), and all of these can vary throughout the airway tree. Indeed spatial heterogeneity of airway constriction is established to be an intrinsic feature in asthma, measured both by forced oscillation and imaging techniques (87). Imaging also reveals that while spatial ventilation heterogeneity in asthma is largely persistent within repeated measures within a day or within even months, a substantial fraction of ventilation defects change in location or size (23, 24) that theoretically could vary within a single inspiration (6). Thus some of the variation in airway resistance is likely the result of time-varying spatial heterogeneity of airway tone in normal and asthmatic subjects. Increased variation in airway smooth muscle function and the development of spatial heterogeneity would represent a right shift in the balance in Fig. 1 with increasing fluctuations and loss of stability and control.

Long-term variability in airway function measured over days and weeks. Diba et al. (25) reported no association between fluctuations in airway function over minutes measured by Zrs and fluctuation of day-to-day lung function measured by peak expiratory flow (PEF). The reason may be due to the fact that different mechanisms dominate fluctuations over short and long time scales. For example, long time scale effects include circadian rhythms, as well as day-to-day variations in environmental inputs, which can have lagged or cumulative effects (37) and changes in bronchial reactivity. The underlying mechanism have recently been summarized (78).

The majority of studies have used only descriptive statistics such as standard deviations or coefficient of variation to characterize long-term variability. Recently, however, Frey et al. (35) examined twice daily PEF fluctuations in chronic asthmatics from a long-term clinical trial using DFA and, as shown in Fig. 2, found evidence that these data exhibited fractal-type long-range correlations (60). In a temporal process that displays long-range correlations, the magnitude of fluctuations that occurred in the past is correlated to current as well as potentially future values. The strength of these long-range correlations, characterized by the DFA exponent, are influenced by the integrated contribution of many factors including
external stimuli and inflammation, immunological, remodeling, and mechanical processes. This finding suggests that asthma as a chronic disease displays complex behavior coming from a nonlinear dynamic system. The internal memory of the system is related to disease severity and represents the overall dynamics of the disease in a comprehensive, integrative manner (37).

CONSEQUENCES OF TEMPORAL BEHAVIOR OF LUNG DISEASE FOR THE CLINICIAN

Considering the respiratory system in health or in disease as a dynamic, nonlinear network of subsystems with memory has some intriguing consequences for the clinician. Probably the most fundamental implication for the clinician is the limited predictability of the temporal behavior of such a complex system. Intuitive to the experienced clinician, the temporal behavior of such complex systems cannot be fully understood most of the time even if the individual components and pathways of a particular disease are determined. Although a single biomarker derived from one such pathway may not carry information about all the subsystems involved in the disease process, there is new evidence that the temporal behavior of a disease state might be clinically useful for patient management. Next, we consider several clinically useful issues related to temporal complexity.

Monitoring. Monitoring of chronic complex diseases is one of the major challenges in systems biology and medicine (10, 11). Due to the complexity of the interactions including their temporal behavior, a multidimensional approach is needed (37). Apart from clinical symptoms, quality of life, lung function, bronchial hyperresponsiveness and FeNO, also exhaled breath condensates using metabolomic or proteomic approaches have been used to characterize lung disease. Some of these biomarkers can only be assessed once or twice, but some biomarkers have the potential to be determined on a daily basis. In these cases, additional information can be gained by analyzing their temporal pattern in relation to the fluctuations of the environmental stimuli and the temporal behavior of the clinical symptoms (37). As discussed above, long-range correlations are indicative of memory and hence the temporal behavior of symptoms and biomarkers reflect the history of the patient’s condition and can be quantified using the methods mentioned above. This is particularly interesting since such methods offer the possibility of patient-initiated, unbiased and automated assessment of biomarkers (e.g., electronic lung function monitoring). Since healthcare costs tend to inflate, such tools become increasingly important in the field of telemedicine. Regular monitoring allows a more rigorous assessment of severity, disease control, and external influences such as triggers and medication. Understanding the lung as a complex system may be useful in making treatment decisions and predicting the patient’s behavior during transition processes caused by a change of environment or changes in treatment. In many chronic diseases, particularly in asthma and COPD, there is a trend toward personalized medicine, meaning that each subphenotype may need a different treatment approach. This may be possible only with the help of proper and long-term monitoring that allows the use of complex systems approach toward personalized assessment of therapy and risk prediction.

Severity vs. control. Measures of variability amplitude have been shown to be associated with bronchial reactivity and asthma severity in both adults and children (37, 66, 78); however, the long-range temporal correlation properties may add an additional dimension that could be useful to disentangle the issues of asthma severity vs. asthma control, a clinically very important issue (56a, 67). Asthma severity can be considered as the intrinsic intensity of the disease and is measured most easily and directly when a patient is not under long-term treatment. Asthma control is the extent to which the manifestations of the disease (i.e., symptoms, functional impairments, and risk of exacerbations) can be minimized by treatment. While long-range correlations can provide information about the stability of a complex system, the mean value of the fluctuating parameter should also be taken into account. Recently, Thamrin et al. (82) showed that in severe asthmatics, the DFA α computed from PEF data is high and independent of severity suggesting a shift toward the left in Fig. 1, while the mean PEF seems to be lower and is the dominant characteristic in the more uncontrolled patients. This is consistent with the hypothesis that in uncontrolled severe asthmatics, the airways behave as rigid pipes with severe obstruction. In mild to moderate asthmatics, however, α and the mean PEF are lower in uncontrolled patients, indicating a less deterministic and more unstable temporal airway behavior, consistent with a shift toward the right side of the balance in Fig. 1. This novel finding is consistent with the hypothesis that the term “uncontrolled asthma,” according to GINA guidelines (56a), is more related to fixed therapy-resistant airway obstruction in the group of severe asthmatics, whereas in mild to moderate asthmatics the term “uncontrolled” is more related to unstable, very reactive airways. These findings may add to the body of evidence that severe asthmatics, which, by definition, cannot be easily controlled using standard high-dose asthma medication, are a different entity or phenotype than mild to moderate asthmatics. Fluctuation analysis may help to distinguish these two phenotypes.

Phenotyping. In obstructive airway disease, phenotyping is becoming increasingly more important since it is now realized that in the future, therapy will be more and more phenotype specific. Analysis of lung function variability has been shown to be able to distinguish between cough-variant asthma and classical asthma for example (45). Using the forced oscillation technique, Lall and colleagues (48) have shown in children, that variability of resistance is significantly different in “mild persistent” asthmatics in comparison to the “intermittent” and “moderate persistent” asthma phenotype. This was particularly true after administration of albuterol. Fluctuation analysis in phase space using Wasserstein distance technique as mentioned above can distinguish between the “asthma” and “COPD phenotype” of obstructive airway disease (56). A particular asthma phenotype is the classical allergic asthma phenotype, which usually responds well to inhaled corticosteroids. In a post hoc analysis of the CHARISM trial (22), where asthma symptoms were recorded electronically in parallel with daily exhaled nitric oxide (FeNO) measurements over several months, Stern et al. (74) found that fractal-type long-range correlations also exist in daily FeNO time series. Interestingly, cross-correlation analysis showed a good association between the daily FeNO time series and the time series of the daily symptom scores, and this was particularly strong in patients...
with frequent exacerbations. This work demonstrated that temporal phenotyping may benefit from the comparison of one fluctuation biomarker in time to the fluctuations in symptoms. Future studies will have to investigate whether such temporal analysis is useful to identify the best biomarker that could be used to monitor a specific phenotype of obstructive airway disease.

**Impact of external influences, drugs, and medication.** Environmental factors have been shown to influence fractal properties of breathing in the lung. For example, Akay and Mulder (3) have demonstrated that maternal alcohol intake modifies the fractal characteristics of fetal breathing in utero. Not only toxic substances but therapeutic interventions too can modify fractal properties of temporal behavior of the respiratory system. Frey et al. (35) showed that in a group of mild to moderate asthmatics, with medication that was given four times daily regular short-acting β2-mimetics (with long night interval) compared with placebo, the short-acting agonists significantly changed the nature of correlations in the PEF time series such that the PEF series approached a random and hence less predictable process with higher risk of exacerbations. The presence and extent of long-range correlations were not affected by twice daily long-acting β2-agonists, where the drug action is more homogeneously distributed over the day period. The consequences of such results are relevant for future drug trials as well as for studies of the effect of toxic substances or pollutants on the respiratory system. It is clear that not only the drug action itself but also the timing of medication needs to be considered. Future trials with the recording of serial observations are needed to provide additional information in comparison to a two-point (exposure-outcome) observation study.

**Transitions and treatment decisions.** Clinical decisions are often related to transition processes either because the patient abruptly changes his environment or the clinician alters the treatment. A classical clinical question that occurs in stable asthmatic patients is whether or not inhaled corticosteroids (ICS) can be stopped without subsequent loss of control. Many biomarkers (e.g., bronchial reactivity, FeNO) measured just prior to the steroid withdrawal have been suggested to be predictive for the loss of asthma control; however, many of these require a doctor’s visit. Recently, Thamrin et al. (84) have shown that comparing the variability of PEF 2 wk prior to and 2 wk after the cessation of the ICS has a similar predictive power regarding loss of control as FeNO (84). Thus, using home-monitoring PEF devices, fluctuation analysis is a cheap tool that can be automated for clinical guidance of therapy decisions. Other clinical decisions include the start of a new drug such as long-acting β-agonists in addition to corticosteroid. Due to the ongoing controversy related to the potential deleterious side effects of long-acting β-agonist treatment in asthmatics, a biomarker is needed that could indicate whether or not patients will favorably respond to the treatment. In another study, Thamrin et al. (83) showed that long-range correlations of twice daily PEF series assessed during a placebo phase predicted the subsequent response to long-acting β-agonists after initiation of the treatment. Interestingly, however, correlation analysis failed to predict the response to short-acting β-agonists. Future studies are needed to evaluate multiple variability measures of symptoms and biomarkers to achieve the best medical decisions.

**Exacerbation risk in individual patients.** Estimating risks of rare and potentially dangerous events are one of the crucial, but notoriously difficult, challenges in clinical medicine. A straightforward and simple approach is the identification of clinical risk factors derived from population based epidemiological data, but also the identification of the frequency distribution characteristics of these events in the individual patient. As an example for the latter approach, in immature infants the distribution of interbreath intervals shows a power law (e.g. 36). Based on the exponent of this power law distribution, the risk for a very long IBI (or apnea) can be estimated on an individual basis. Power laws have also been found in the distribution of clinical respiratory symptoms in infants (79) or respiratory impedance (56, 65). While power laws have been used to predict earthquakes for decades (40), they have so far not been widely used in clinical medicine. In 1996, Macklem (52) pioneered the hypothesis that time series analysis could be used to predict the risk of future changes in lung function. The variation of impedance is well described by power law probability distributions, like the frequency distribution for earthquake magnitude. Thus like predicting earthquake risk for a particular location, he proposed it could be possible to predict an individual’s risk for experiencing high impedance values, or equivalently the period of time for which a threshold impedance value was exceeded (65). Such predictions need not be limited to power laws; as long as the data allow a reliable construction of the distribution of sizes or intervals, appropriate probabilistic statements can be made. These considerations fit well with the current increasing demand in personalized medicine to calculate future risk of patients encountering deteriorations in lung function or asthma attacks. More recently, Frey et al. (35) introduced the conditional probability (π) that given the PEF today, a patient will encounter a future obstructive episode (e.g. with PEF < 80% predicted) as an improved risk predictor. The risk π calculated from a time series of the patient’s individual functional behavior over time is therefore not only a traditional risk factor based on population statistics (e.g., smoking), but represents the patient’s individual or personal risk. It is important to note that in contrast to the simple probability of an event calculated as the relative frequency, π also depends on the correlation properties of the PEF series of the last few weeks, and thus on the functional history of the patient’s condition (37). If a patient visits the doctor with a current PEF of 95% predicted, the risk of an exacerbation in the next month depends strongly on the value of α derived from the PEF series from the last 2 months. The risk of encountering an exacerbation with a PEF < 80% in the upcoming month is 18% if α is high (α = 0.8), but the risk is as high as 83% if α is low (α = 0.55). In practice, for the individual patient is not easy to calculate since the reference period usually does not contain very many observations with low PEF, and new techniques need to be developed that can be applied to short data sequences. Using a refined prediction method for short series, Thamrin et al. (85) have recently demonstrated that the observed number of exacerbations in severe asthmatics is indeed correlated with π derived from PEF series measured in the past 2 months in individual patients.

**Externally applied fluctuations.** We have seen that various physiological signals and biomarkers show significant variability and the statistical and correlation properties of these signals often change in characteristic ways in disease reflecting a shift
in the balance in Fig. 1. There is a growing body of evidence that the normal function of biological and physiological systems can benefit from externally applied stimuli or forced oscillation technique devices (21, 41, 43, 51, 57, 63, 77). For example, it has been shown experimentally that cardiac arrhythmia can be suppressed by appropriately controlling chaotic behavior (41). The fact that stochastic stimuli delivered to a physiological system can improve the performance of the system may be due to the excitation of subtle dynamic nonlinearities in a complex system with threshold behavior. If the stimulus is low, smaller than the threshold, then the phenomenon is called stochastic resonance in which a small amount of noise is added to a subthreshold signal and depending on the level of noise, the system displays an optimum response at a certain noise level (55). Furthermore, large but irregularly occurring signals such as action potentials in neurons can be regularized with the addition of noise. This mechanism has been exploited recently by Bloch-Salisbury et al. (14) who applied low-level exogenous mechanical stimulation to preterm babies using a mattress with embedded actuators that delivered white noise sensory stimulation between 30 and 60 Hz. While the stimulation was subthreshold not causing arousal or any other detectable behavioral changes, it resulted in a 50% reduction in the variance of IBIs and a 50% reduction in the incidence of large IBIs. Remarkably, this improved stability of respiratory control was also associated with a 65% reduction in the time period required to reach oxygen desaturation. As another example, consider mechanical ventilation that saves patients with respiratory failure by cyclic delivery of oxygen to the lungs. However, mechanical ventilation can also generate injury called ventilator-induced lung injury (VILI) (28). One potential reason is that mechanical ventilators eliminate the natural variability of tidal volume and frequency in normal subjects (50). Indeed, a relatively new ventilation mode called variable ventilation, in which tidal volume and rate are varied on a cycle-by-cycle basis, reduces VILI (9, 73) as well as chronic diseases (28). One potential reason is that mechanical ventilators eliminate the natural variability of tidal volume and frequency in normal subjects (50). Indeed, a relatively new ventilation mode called variable ventilation, in which tidal volume and rate are varied on a cycle-by-cycle basis, reduces VILI (9, 73) as well as chronic diseases (28).

CONCLUSIONS

In this review, we have examined approaches to analyze and interpret the temporal pattern exhibited by several respiratory-related variables. We have argued that adaptability on the one hand, and fluctuating inputs on the other hand, necessarily lead to complex temporal behavior often characterized by long-range correlations and/or power-law distributions. Today, we have appropriate tools to analyze these patterns and even use them for risk prediction. In the future, these techniques should be developed and used to better monitor the patients’ behavior over time for rational patient management. These techniques may also help to increase the awareness of clinicians that the temporal behavior of complex systems can only be predicted within statistical limits, even if all the individual components of the involved processes can be identified and measured. Clinical experience and intuition clearly have their role in dealing with the complexity of chronic disease processes. Quantitatively analyzing the past behavior and history of the patient with the tools that the science of complexity offers will achieve two things: it will help us obtain new insight into the underlying mechanism of temporal behavior of the disease, and it will help us make personalized predictions in guiding therapy.

DISCLOSURES

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

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