Invited Editorial on "Irregularities and power law distributions in the breathing pattern in preterm and term infants"

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THERE HAS BEEN A LONGSTANDING DESIRE to develop an index that concisely describes the breath-to-breath irregularity of breathing. Such an index might be useful for distinguishing potentially pathological respiratory arrhythmias from "normal" variability in the breathing pattern or for describing the maturational development of respiratory control mechanisms in neonates. Early approaches (see Refs. 4, 5) were based on simple statistics of breath-by-breath values of respiratory pattern variables, e.g., SD of tidal volume. More recent studies have used power spectral analysis, comb filtering, and autoregressive modeling to characterize breathing pattern variability (6, 8, 9, 10, 12). However, although one can detect components of respiratory variations that meet the criteria of these analyses, often the detected components either appear to change unexpectedly with time or account for only a small percentage of total respiratory variability.

Contemporary methods of variability analysis derived from the fields of stochastic systems and nonlinear dynamics (2, 11, 15) often utilize a global index that is capable (theoretically) of characterizing the variability in a signal over broad frequency and/or time ranges. The paper by Frey et al. (7) applies the concept of power law distributions to the analysis of breathing patterns of preterm and term infants and concludes that a simple index α, the slope of a log-log plot of a type of histogram of respiratory intervals, can characterize variability in breathing pattern in a global sense. Furthermore, this index increases with postconceptional age (PCA) in both preterm and term infants and, therefore, may be an indicator of maturation of the respiratory rhythm generator. As the authors note, because of large interindividual variability α is not useful as an indicator of maturation in individual infants, but its ability to represent the relative likelihood of occurrence of long hypopneas in an infant may be clinically noteworthy.

The analysis method developed by Frey et al. (7) identifies the intervals between breaths, the tidal volumes for which exceed a threshold specified as the mean tidal volume + 1 SD. [The descriptor "interbreath intervals (IBIs)" is somewhat misleading, since most intervals encompass more than one breath.] These IBIs are expressed as a normalized histogram, and a linear fit is made to the "tail" of a log-log plot of the histogram. The slope of this line is α. The paper is convincing in that the authors' data are well fit by a straight line (average squared correlation coefficient of the fitted data points was 0.973 ± 0.025), and the paper notes that normally distributed IBIs would yield a large negative value for α. One might ask, however, how the observed values for α compare with these expected for a null hypothesis based on a breathing pattern that is regular, except for some default uncorrelated noise. For example, one null hypothesis might be a breathing pattern in which respiratory rate is constant and tidal volume exhibits uncorrelated random variations. It is easy to demonstrate from simulations that this latter pattern yields logarithmic histograms having tails that are approximately linear with slopes near the same range as seen in the data of the paper discussed. There are important differences, however; e.g., the IBI range of the apparently linear relation seems to be significantly smaller in the simulated data, and α may be independent of the SD of the simulated data (implying that it might be difficult to explain changes in α). These results derived from a simplistic model do not dispute the findings of the paper but do substantiate the need to define the statistical limits of the method of Frey et al. A related question is whether the computation of α exhibits a bias that depends on the number of data points available. This point may be important if the length of data records differs between studies.

To substantiate their experimental findings, the authors (7) also analyzed the output of a mathematical model of respiratory rhythm generation (3) subjected to noise disturbances. Arguably, other, more recent models of this type (1, 14) better represent the present thinking of the field, although the model used may provide helpful insights. It should be noted, however, that Botros and Bruce (3) did not test and validate their model for the low values of tonic neural input to first neuronal group (TNI_1) that are invoked by Frey et al. (7) to explain the generation of power law IBI data by the model. One also must consider whether the disturbance effect of noisy physiological afferent inputs that are distributed asynchronously across a population of physiological ramp-inspiratory neurons (I neurons) would be comparable to adding a large noise stimulus in a model having only one TNI_1 input and one I neuron.

In the original paper of Botros and Bruce (3), vagal stretch-receptor afferent input directly influenced two neuronal pools, the early-inspiratory and the postinspiratory neurons. The hypothesis of Frey et al. (7) that vagal afferents might be the source of the noisy disturbances to the I neurons contradicts the original structure of the model and needs to be evaluated further on the basis of physiological results. Generally, pulmonary stretch afferents have not been thought to directly affect I neurons.

There is an interesting parallel between the hypothesis that small values of tonic input to I neurons may combine with noisy disturbances to produce irregular breathing (7) and another recent hypothesis regarding the genesis of apneas in neonates; Paydafar and Buerkel (13) have suggested that at low levels of respiratory drive the expiratory trajectory of the respiratory oscillator passes near a singularity in its behavior. Thus a small noisy disturbance potentially can drive the oscillator close to the singularity and produce a prolonged arrhythmic period or, during this arrhythmic period, drive the oscillator back toward its natural rhythm. Consequently, both hypotheses suggest that at low respiratory drives the influence of noisy disturbances on respiratory rhythm is magnified by the dynamic properties of the respiratory oscillator. In the model of Paydafar and Buerkel, contraction of the phase plot toward the singularity is assumed to be due to decrease of chemoreceptor drive, and the possible role of chemoreceptor afferents as a source of disturbances to TNI_1 should be examined.

To address the specific mechanisms underlying these new findings (7), it is probably necessary to develop an animal model that exhibits similar behavior. Then a simple experiment would be to assess the distribution of IBIs before and after vagotomy at various PCA. Similarly, one could determine the influence of changing chemoreceptor drive on IBIs. In addition, it may be possible to determine the role of specific afferent inputs, or of the specific configuration of the respiratory rhythm generator, by modifying neurotransmission at various loci in the brain stem.

The authors have been appropriately cautious about inferring mechanisms on the basis of observing a power law distribution of IBIs. Although one would like to draw inferences about the temporal structure of the breathing pattern, such speculations are premature. For example, the occurrence of long IBIs could result from occasional grouping of breaths having tidal volumes that are too low relative to metabolic demand or from the presence of occasional very large breaths that cause the tidal volume threshold to be artificially high relative to metabolic demand. The types of mechanisms that might generate these two types of data may be very different. In fact, it may be difficult to attribute the power law behavior to a single mechanism. Because of the existence of multiple feedback loops that control breathing, variability generated at one site may reverberate throughout the respiratory control system, creating multiple interactions encompassing multiple time scales (4). Furthermore, the temporal relationships of breath-to-breath variations of respiratory pattern variables seem to be at least as important as the magnitude of their fluctuations. Clearly, this interesting paper will motivate a variety of future studies.

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