Complexity and respiratory growth: a developing story

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IN A RECENT VIEWPOINT ARTICLE in the *Journal of Applied Physi-ology*, Macklem (10) pointed out that use of the term ho-meostasis to describe biological systems is perhaps outdated and that study of physiology should, instead, be directed toward the idea of homeokinesis. Living systems are complex, and the fact that continuous fluctuations in physiological pa-rameters exhibit nonlinearities allows adaptability of living systems to external environments. Methods of quantifying complexity in physiological signals have largely been estab-lished while studying cardiac dynamics and, subsequently, used to characterize respiratory rhythms. These methods com-prise fractal approaches, such as power law behavior, de-trended fluctuation analysis, and correlation dimension, or chaotic approaches, such as the largest Lyapunov exponent. They have shown that respiratory patterns in early life behave in accordance with power laws (9), fractal dynamics (2, 5), and even chaos (13).

Information theory is yet another approach used to investi-gate this complexity. Shannon (12) devised his original version of entropy as a means of quantifying the amount of information contained in a message transmitted through a communication channel. Increased entropy is characterized by more information, higher irregularity, and lower predictability and, thus, could be construed as increased complexity. Similar to other measures of complexity, entropy calculations have also been applied to respiratory patterns only relatively recently. By use of different respiratory parameters, irregularity has been shown to be increased in hypercapnia (8), in ventilated patients who failed to be weaned from the ventilator (6), and during a panic disorder (4). In this respect, most of the work has come from the intensive care specialists, who have been particularly concerned with quantifying respiratory rhythms for some time.

Studying complexity may lend an integrative perspective on respiratory growth and development in the first few weeks of life, a period of radical changes that involve a multitude of neurophysiological processes taking place simultaneously (1). Even for full-term infants, the first few weeks of life represent a stage of continuing lung development and not just growth: the lungs not only increase in size; they also become more complex in structure as alveolarization continues postnatally. Chest wall and pulmonary mechanics are also altered: re-sistance decreases with the increased diameters of the airways, chest wall compliance decreases, and lung compliance in-creases, while lung volume is dynamically maintained. Since studies in this age group are generally performed during sleep, it also becomes important to consider that the relative propor-tion of the different sleep phases changes with age, accompa-nied by altered stretch receptor, as well as chemoreceptor, sensiti-vities to hypercapnic and hypoxic conditions. These alterations coincide with apparent morphological changes to the respiratory centers in the brain.

In this issue of the *Journal of Applied Physiology*, Engoren et al. (7) used entropy-based analysis to determine respiratory rhythm as a function of age and weight in preterm infants. They found that increasing age and size was related to increasing complexity in tidal volume and respiratory rate variability. This is the first systematic study to apply entropy methods to the more fundamental question of physiological development and maturation of the lungs. Engoren et al. explored a variety of entropy measures in their well-performed study: approximate and sample entropies, which quantify the conditional probability of occurrence of similar time epochs, and base scale and forbidden word entropies, which quantify the probability of occurrence of similar patterns. They also examined cross entropies between tidal volume and respiratory rate. In doing so, the authors showed that base scale and forbidden word entropies, which have been proposed to be more suited to nonstationary physiological signals, are more sensitive in showing the relationship with age and size.

It is worth noting that these novel tools are yet to be optimized for investigations in the lung, and sometimes phys-iological intuition, although essential, is not sufficient to elim-inate the uncertainty involved in determining appropriate pa-rameters for the analyses. The sensitivity analysis approach used by Engoren et al. (7), as well as by Cernelc and co-workers (5), where the effect of the parameters on results is first determined systematically and also compared with shuffled data, is one way to alleviate this problem.

Some immediate open questions arise from the study. Is the increase in entropy only a feature of prematurity? Will healthy, full-term infants also show the same increase with age, if at all, or perhaps at a different rate? Does the increase in complexity reflect maturation of neurorespiratory control processes or, alternatively, a changing flow pattern owing to an increasingly complicated lung structure with a different distribution of time-dependent mechanical structures? In preterm infants, the postnatal process of alveolarization is even more incomplete and more susceptible to changing environmental conditions. Engoren et al. examined only infants with mild disease due to their prematurity. It is therefore unclear how the gain in entropy would change in infants with more severe chronic lung disease of infancy. The very likely effect of sleep stage on breathing patterns may also be critical and needs to be addressed more thoroughly.

Furthermore, the relationship between entropy and other measures of complexity already used in the literature is also of interest. Do the different measures of complexity present a united front in suggesting that maturation brings about an increase in complex respiratory behavior, or do they represent different aspects of this behavior? Frey et al. (9) found that the slope of the long tail of the power law distribution of inter-breath intervals in infants became steeper (i.e., closer to a normal distribution) with maturation and tended to be less steep in preterm than in full-term infants of similar postnatal...
age. Cernelc et al. (5) found no trends with fractal dynamics of tidal volume; however, the infants studied were of similar age and size. Clearly, the data from the few studies available have yet to build a consistent picture, although the field of respiratory complexity is in its early days. Furthermore, with regard to the interpretation of complexity, is it “better” to have more or less complexity? Is there likely to be an “optimum” degree of complexity, providing a balance between too much predictability (loss of adaptability) and too much irregularity (loss of determinism)?

To add to the picture, it is interesting to note that the fractal-like scaling exponent quoted for infants (2, 5) tended to be higher than those for adults (11), albeit for different parameters, i.e., tidal volume and interbreath intervals, respectively. More systematic comparative studies are required to firmly establish any trends. Moreover, on the other end of the spectrum, senescence appears related to a breakdown of fractal dynamics (11).

From a clinical point of view, it is increasingly apparent that lung function follows a certain course throughout life and that this course is predetermined early in life (3). The study by Engoren et al. (7) and future studies may provide clues as to whether complexity in respiratory control or structure has a role in this preprogramming, especially if the relevant changes are primarily in the temporal pattern, rather than merely in the magnitude, of the signal. In introducing new tools to examine such patterns in a more comprehensive manner, taking into account changes over time, the study of complex behavior marks an exciting new chapter in the growth and development story. It also offers a step forward from the current, more subjective nature of clinical observation.

The potential for risk prediction of diseases using these measures is also attractive, especially in the context of monitoring premature infants and those who are at risk for diseases such as sudden infant death syndrome. Macklem’s viewpoint article (10) was followed by an engaging series of discussions suggesting that a better understanding of diseases as complex, dynamic systems may drive the push toward preventing them before they occur. This is perhaps of particular relevance in these early stages of life.

REFERENCES