VENTILATORY CONTROL INSTABILITY forms the theoretical basis for respiratory control disorders ranging from apnea to weaning failure from mechanical ventilation. While ventilatory arrhythmia has multiple mechanisms, an underlying issue is quantifying the arrhythmia. The article by Nemati et al. (14) in the July 2011 issue of the Journal of Applied Physiology takes a significant step in this direction. In this manuscript, the authors adopt a novel approach to assess ventilatory stability using the spontaneous breathing pattern. They based their method on trivariate autoregressive modeling using ventilation, end-tidal \( PCO_2 \), and \( PO_2 \) to estimate “loop gain” of the respiratory control system in sheep. They analyzed spontaneous breathing to characterize the dynamics of the respiratory control system and to determine the propensity for ventilatory instability. Their methodology is straightforward and resolves a number of the technical difficulties of experimental determination of loop gain.

Classical physiology is grounded on the principle of homeostasis in which regulatory mechanisms act to reduce variability and to maintain a steady state, e.g., “set point” (9). With this model of behavioral control, fluctuations are often dismissed as “noise” of little or no significance. However, as argued by Ary Goldberger in his editorial (9), many systems in nature operate away from an equilibrium point, and their control systems aim to maintain homeodynamic, as opposed to homeostatic, physiology. Homeodynamics underlie the variability and complex temporal patterns manifested in physiologic signals.

Cherniack and coworkers (5) applied a systems engineering approach to respiration, describing a controller (brain stem respiratory pattern generator), sensors (chemo- and mechanoreceptors), and a plant (airway, chest wall, muscles, and pulmonary tissue). This system maintains numerous controlled variables within their homeodynamic ranges, but is also responsible for rapidly changing ventilation in response to often-unpredictable stimuli. Brain stem pattern generation and processing of sensory information are reflected in the integrated motor response (breathing pattern), including variability in phase duration and pattern. Thus the respiratory system can be effectively modeled as a circuit with feedback in which the loop gain is the response to a disturbance divided by the disturbance itself.

The strong theoretical underpinnings for loop gain as a model of ventilatory control have been bolstered and refined by empirical testing and measurement. Historically, measures for the stability of a rhythmic oscillation relied on the variability of the pattern and on the response to a perturbation, in particular the relaxation time or how quickly (the number of cycles needed) the oscillation returned to its intrinsic cycle period after a brief perturbation (16). Of course, the more variable the pattern the harder it is to determine when the oscillation returns to baseline. Nevertheless, this approach was applied to understanding the neural control of respiration in both reduced preparations and humans. In reduced preparations the brief perturbation was a resetting stimulus like superior laryngeal stimulation (7, 15). In these studies stability of the respiratory pattern was enhanced by hypercapnia and depended on an intact dorsolateral pons (7, 15). In humans, the stability of the respiratory cycle can be assessed by testing with pseudorandom binary stimulation, which challenges the respiratory system with either hypoxia or hypercapnia, delivered in repeatable but random like sequences such that the autocorrelation function of the sequence approximates that of white noise. Thus the loop gain of the impulse response can be determined mathematically by cross-correlating the test input with measured output (10). In these studies, the patients with obstructive sleep apnea (OSA) compared with a control group had a higher peak response and shorter settling and response duration times (10). These differences were observed in wakefulness, indicating that OSA patients had abnormal dynamics in their respiratory control that could contribute to ventilatory instability during sleep (10).

Nemati et al. developed an approach to characterize and quantify overall loop gain that may prove clinically relevant, as subjects would not need to participate in complex protocols. In addition to congestive heart failure and obstructive sleep apnea highlighted by the authors, the ability to assess respiratory instabilities could have other applications. For instance, respiratory pattern variability decreases in restrictive lung disease (3, 13) and in septic and acutely ill patients (1). In contrast, pattern variability increases in patients with obstructive lung disease (13), panic disorder (17), and sleep-disordered breathing during the wake-sleep transition (11). This computational tool could assess how closed loop gain plays a role in these changes in ventilation.

In addition to evaluating mechanisms of instability, this tool could be applied to track patients to determine recovery or disease progression (12). A bedside assessment of respiratory instability would assist in the evaluation of weaning from mechanical ventilation in critically ill patients, which is a challenging task. The benefits of early successful extubation must be weighed against the risks of unnecessary delay and premature weaning attempts. A few clinical studies have examined novel indexes based on respiratory pattern variability (RPV) to predict extubation failure. For example, Engoren (8) studied patients who required either prolonged (>7 days) or brief (>12 h) ventilatory support. Breathing patterns were recorded during spontaneous ventilation with 5 cmH2O posi-
tive end-expiratory pressure [increased lung volume may affect these measures (6)]. Patients with prolonged ventilation and who failed a weaning trial had increased complexity of the tidal volume (VT) time series as measured by Approximate Entropy compared with patients who were successfully weaned after prolonged and brief ventilation. In distinct contrast Bien et al. (2) noted that decreased RPV was associated with a high incidence of weaning failure. In this study, RPV was measured by coefficient of variation (CV) and Poincaré plot analysis of respiratory intervals and VT. Other studies support both increases and decrease in RPV but a critical factor in these studies is that these are single rather than multiple measures over time. A simple assessment of closed loop gain could provide information at multiple time points and whether the propensity for respiratory instability is decreasing or increasing.

Finally closed loop gain would affect both RPV and complexity but these variables can change in opposite directions, and it is our perspective that a comprehensive analysis will include multiple analytical techniques to capture different aspects of pattern variability (12). Taken together, the available studies suggest that measurements of RPV hold potential not only as weaning but also as health indexes. Nemati et al. provide a computational tool that can provide insight for further study.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES