What to do about apnea of prematurity?

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APNEA of prematurity and resultant intermittent hypoxic episodes are universal in preterm infants. These events range from presumably benign “periodic” breathing to clinically significant events that may require mechanical ventilation. Persistence of these events is a major factor in prolonging the hospitalization of preterm infants. Even though it is unclear whether this early instability of respiratory control is associated with longer-term morbidity in this high-risk population, there is great pressure to provide treatment for prevention of these episodes (Fig. 1). An interdisciplinary team from the University of Massachusetts, Worcester, may now be providing us with the beginnings of a novel new therapeutic approach for this problem.

Instability of neonatal respiratory control is often the first manifestation of a cardiorespiratory or metabolic disturbance that accompanies altered homeostasis in preterm infants (1). The mechanisms whereby respiratory patterns are so vulnerable to diverse stimuli are not known. However, this has been the impetus to develop a variety of therapeutic approaches based on mechanosensory and proprioceptive stimulation. In fact, over the last 30 years such approaches have included cyclic tactile stimulation, oscillatory and nonoscillatory water beds, and even olfactory stimulation. While often effective, these approaches have tended to be impractical and have not transitioned to clinical practice. As a result caffeine therapy has emerged as the mainstay of therapy, resulting in both respiratory and neurodevelopmental benefit despite lingering concerns about manipulating adenosinergic and related neurotransmitter function in early life (7, 10).

In their study in the Journal of Applied Physiology, Bloch-Salisbury et al. (3) have demonstrated that their novel technique of stochastic mechanosensory stimulation is able to stabilize respiratory patterns in preterm infants as manifest by a decrease in respiratory pauses and an almost threefold decrease in percentage of time with oxygen saturations <85%. Interestingly, the level of stimulation employed was below the minimum threshold for behavioral arousal to wakefulness, thus inducing no apparent state change in the infants, and the effect could probably not be attributed to the minimal increase in sound level associated with stimulation. The role that noisy inputs play in promoting rhythmic, stable neural network activity is, as of yet, unknown. Computational models suggest that noisy inputs can play an important role in transforming neurons from dysrhythmic activity to regular, oscillatory bursting (8, 9). Growing evidence from cortical and spinal neural networks suggests that stochastic excitatory and inhibitory inputs are crucial for “balancing” neurons at a point of optimal sensitivity for sudden state changes—with appropriate inputs, these neural networks generate synchronous network output crucial for behavior (2, 6).

Fig. 1. A summary of possible benefits accruing from greater stability of respiratory patterns in preterm infants.

The respiratory rhythm-generating circuitry within the central nervous system (CNS) depend on intrinsic rhythmic activity and sensory afferent inputs to generate breathing movement. The respiratory central pattern generator within the medulla exhibits complex nonlinear behavior when isolated from synaptic inputs but can generate stable rhythms with appropriate excitability in vitro (4, 8). Furthermore, phasic sensory afferent input from lung stretch receptors promotes more regular breathing pattern (11), yet, even with vagal afferents intact, breathing exhibits nonlinear complexity (5). The interplay between phasic and stochastic inputs to respiratory regions of the brain stem is, essentially, completely unknown at the circuit level, but Fig. 1 illustrates potential parallel pathways for these inputs within the respiratory control network and potential patient benefits.

The role that mechanical stimulation plays in promoting regular breathing has been documented anecdotally but remained unquantified until now. Bloch-Salisbury et al. (3) have taken an important step in demonstrating the role that controlled stochastic inputs can play in benefiting neonates, and we believe this holds great significance in promoting nonpharmacological intervention to improve neonatal outcome.

REFERENCES


