Published in final edited form as:

Respir Physiol Neurobiol. 2013 November 1; 189(2): 211–212. doi:10.1016/j.resp.2013.09.006.

Clinical challenges to ventilatory control☆

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Breathing is essential for survival. Clinical disorders that challenge breathing often have severe consequences, potentially leading to catastrophic ventilatory failure and death. In some cases, we believe that we know the “primary cause(s)” of a particular breathing disturbance, but that limited understanding is not always sufficient to explain the clinical phenotype. For example, as indicated by its name, airway obstruction seems to be the primary cause for breathing cessation (or apneas) in Obstructive Sleep Apnea. However, genetic predisposition, reflex mechanisms, neuromodulatory mechanisms associated with sleep states, hypoxic and oxidative stress, mechanisms of central respiratory rhythm generation and alterations at the level of motor nuclei play equally important roles in this disorder (Kheirandish-Gozal and Gozal, 2013; Plataki et al., 2013; Ramirez et al., 2013a). With Chronic Obstructive Pulmonary Disease (COPD), impaired breathing seems to result primarily from impaired pulmonary mechanics caused by lung/airway obstructions (Jacono, 2013). But, hypoxia and hypercapnic conditions alter intrinsic properties of muscles, chemoreceptor signaling and central respiratory control. Some breathing disorders result from specific gene mutations, such as Rett Syndrome, a neurological disorder caused by mutations in the *Mecp2* gene (Ramirez et al., 2013b), but the mutation causes multiple alterations in synaptic transmission and neuromodulation and disturbed breathing, which in turn has secondary consequences to aspects of respiratory control. Many suspect that Sudden Infant Death Syndrome (SIDS) results from impaired function of the serotonergic nervous system, but the genetic predisposition and/or prior experiences (Paterson, 2013), make this a highly complex syndrome (Garcia et al., 2013). Thus, although in many instances we seem to know the primary cause of clinical disorders that impair breathing, we are beginning to realize that the clinical phenotype is the result of a complex interplay of multiple mechanisms that are still poorly understood— even in the best known examples.

This Special Issue of Respiratory Physiology and Neurobiology on “Clinical Challenges to Ventilatory Control” was conceived and edited by Drs. Ramirez, Mitchell, Baker-Herman

☆This paper is part of a special issue entitled “Clinical Challenges to Ventilatory Control”, guest-edited by Dr. Gordon Mitchell, Dr. Jan-Marino Ramirez, Dr. Tracy Baker-Herman and Dr. Dr. David Paydarfar.

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and Paydarfar. Our motivation was to review relevant clinical disorders and provide mechanistic insights into a broad range of breathing disorders with distinct etiology. Individual contributions to this special issue draw attention to common features in ventilatory control disorders, and the fact that the “primary causes” initiate complex, interactive processes in the peripheral and central nervous systems. This interplay ultimately impairs (or preserves) breathing and, in some instances, leads to forms of dysautonomia resulting from disturbed coupling between breathing and other physiological systems, such as the cardiovascular system.

Many breathing disorders are associated with chronic intermittent hypoxia (CIH). For example, Di Fiore et al. (2013) discuss the “perfect storm” leading to apnea of prematurity. While premature birth may be the “primary cause” the article describes how immature development of the respiratory control system leads to respiratory instability that, together with underdeveloped lungs (and resultant lung injury), leads to recurrent apneas and CIH. In turn, CIH causes immediate and long-lasting morbidities (Di Fiore et al., 2013, Williamson et al., 2013). CIH and oxidative stress is also characteristic for central and obstructive sleep apneas, as well as Rett Syndrome. The immediate and long-term morbidities associated with these disorders are discussed in several articles of this special issue (Ramirez et al., 2013a,b; Kheirandish-Gozal and Gozal, 2013, Plataki et al., 2013).

In each case, the clinical phenotype is not caused by factors considered to be their “primary cause” alone, but by a complex multimodal interplay. Understanding this complex interplay will ultimately be of great importance as we develop treatments for distinct breathing disorders. Williamson et al. (2013) for example proposes that multimodal physiological measurements are critical for developing specific treatment of apnea of prematurity. These measurements include heart-rate variability, breathing variability, entropy measurements and sleep state. Considering ventilatory control as a non-linear dynamical system is one approach to address the complex nature of this interplay (Williamson et al. (2013), and it will help to unravel the vicious cycle associated with recurrent hypoxemia resulting from (central or obstructive) apneic events (Williamson et al., 2013).

Although CIH can be an important cause of long-term detrimental changes that transcend immediate effects on the respiratory system, brief intermittent hypoxia elicits potentially beneficial effects such as up-regulation of growth factors that are neuro-protective, and respiratory motor plasticity. Respiratory plasticity may compensate for the “primary cause” of clinical disorders that impair breathing. Brief intermittent hypoxia (versus CIH) can also be harnessed to trigger long-lasting respiratory motor plasticity as a treatment for devastating clinical disorders that compromise breathing, such as cervical spinal injury (Johnson and Mitchell, 2013) or motor neuron disease (Nichols et al., 2013). Respiratory plasticity has considerable potential to compensate for, or induce functional recovery in a range of breathing disorders (Strey et al., 2013; Mantilla and Sieck, 2013; Johnson and Mitchell, 2013; Dimarco and Kowalski, 2013; Nichols et al., 2013).

We hope that this Special Issue will inspire a serious dialog between basic scientists that study cellular and systems-level mechanisms controlling breathing, and clinicians that treat the clinical disorders that compromise breathing. Even though clinicians and physiologists

share a deep interest in breathing, unfortunately there is often a disconnect between these disciplines. Whereas basic scientists may have a deep understanding of the impact of intermittent hypoxia, genetic contributions to neurological disorders, or mechanisms of respiratory rhythm generation and neuromodulation, they are often unaware of the significance of these mechanisms in the complex interplay underlying particular breathing disorders or their associated dysautonomia. Conversely, clinicians are most often fully aware of the complexity of a breathing disorder, but often fail to consider sometimes well-known mechanisms that drive this complexity. We are confident that a better integration between the basic sciences and clinicians is essential to truly understand, and ultimately treat and cure clinical disorders leading to severe breathing disturbances.

References

- Di Fiore JM, Martin RJ, Gauda EB. Apnea of prematurity – Perfect storm. *Respiratory Physiology and Neurobiology*. May 28.2013 (Epub ahead of print).
- Dimarco AF, Kowalski KE. Activation of inspiratory muscles via spinal cord stimulation. *Respiratory Physiology and Neurobiology*. Jun 7.2013 (Epub ahead of print).
- Garcia AJ 3rd, Koschnitzky JE, Ramirez JM. The physiological determinants of sudden infant death syndrome. *Respiratory Physiology and Neurobiology*. Jun 2.2013 (Epub ahead of print).
- Jacono FJ. Control of ventilation in COPD and lung injury. *Respiratory Physiology and Neurobiology*. Jul 12.2013 (Epub ahead of print).
- Johnson RA, Mitchell GS. Common mechanisms of compensatory respiratory plasticity in spinal neurological disorders. *Respiratory Physiology and Neurobiology*. May 28.2013 (Epub ahead of print).
- Kheirandish-Gozal L, Gozal D. Genotype-phenotype interactions in pediatric obstructive sleep apnea. *Respiratory Physiology and Neurobiology*. Apr 3.2013 (Epub ahead of print).
- Mantilla CB, Sieck GC. Impact of diaphragm muscle fiber atrophy on neuromotor control. *Respiratory Physiology and Neurobiology*. Jul 2.2013 (Epub ahead of print).
- Nichols NL, Van Dyke J, Nashold L, Satriotomo I, Suzuki M, Mitchell GS. Ventilatory control in ALS. *Respiratory Physiology and Neurobiology*. May 18.2013 (Epub ahead of print).
- Paterson DS. Serotonin gene variants are unlikely to play a significant role in the pathogenesis of the sudden infant death syndrome. *Respiratory Physiology and Neurobiology*. Jul 10.2013 (Epub ahead of print).
- Plataki M, Sands SA, Malhotra A. Clinical consequences of altered chemoreflex control. *Respiratory Physiology and Neurobiology*. May 13.2013 (Epub ahead of print).
- Ramirez JM, Ward CS, Neul JL. Breathing challenges in Rett Syndrome: Lessons learned from humans and animal models. *Respiratory Physiology and Neurobiology*. Jun 28.2013a (Epub ahead of print).
- Ramirez JM, Garcia AJ 3rd, Anderson TM, Koschnitzky JE, Peng YJ, Kumar G, Prabhakar N. Central and peripheral factors contributing to obstructive sleep apneas. *Respiratory Physiology and Neurobiology*. Jun 11.2013b (Epub ahead of print).
- Strey KA, Baertsch NA, Baker-Herman TL. Inactivity-induced respiratory plasticity: protecting the drive to breathe in disorders that reduce respiratory neural activity. *Respiratory Physiology and Neurobiology*. Jun 28.2013 (Epub ahead of print).
- Williamson JR, Bliss DW, Paydarfar D. Forecasting respiratory collapse: theory and practice for averting life-threatening infant apneas. *Respiratory Physiology and Neurobiology*. Jun 2.2013 (Epub ahead of print).