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Mini-Symposium: Infant upper airway and ventilatory control

Development of ventilatory control in infants

John L. Carroll *, Amit Agarwal [1]

University of Arkansas for Medical Sciences, Department of Pediatrics, Division of Pulmonary Medicine, Arkansas Children's Hospital, mail slot 512-17, 1 Children's Way, Little Rock, Arkansas 72212

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SUMMARY

Most abnormalities of ventilatory control in infants are due to immaturity or abnormal development of ventilatory control. This includes a broad range, from rare disorders like congenital central hypoventilation syndrome to common problems such as apnoea of prematurity. Development of the ventilatory control system, including central respiratory rhythmogenesis and central and peripheral chemoreception, begins early in gestation and continues for weeks or months after birth. Development of the neural components of central rhythmogenesis and their highly complex interconnectivity results from complex, timing-sensitive interactions between patterning and other genes, transcription factors and neurotrophic factors. At birth, nearly all aspects of ventilatory control remain immature, especially in preterm infants; and postnatal maturation can be altered by hypoxia, toxins and other stressors. Clinical care may be greatly enhanced by increased awareness of ventilatory control maturation and related disorders.

INTRODUCTION

Mammals have developed a complex system of specialized neuronal groups in the brainstem that tightly regulate oxygen intake and carbon dioxide removal by controlling two major groups of muscles: the 'respiratory pump' muscles regulating inhalation/exhalation and the 'valve muscles' that regulate air flow. These neuronal groups form a central pattern generator (CPG) in the medulla and pons that, in addition to driving resting breathing, must rapidly adapt to changing metabolic demands during exercise, respond to environmental stressors (e.g., hypoxia) and must integrate breathing with swallowing, coughing, vomiting and other activities.[1,2] In spite of its obvious importance for survival, ventilatory control is immature at birth in human infants and requires time to fully mature.

Ventilatory control development begins early in gestation. Foetal breathing movements are one of the earliest motor behaviours and generation of rhythmic foetal breathing is essential for normal antenatal lung growth and development.[3,4] Prenatally, the respiratory control system must develop to a point of "readiness" such that, at the moment of birth, the infant can generate an adequate breathing rhythm and tidal volume. However, although 'ready' to function at birth, ventilatory control in the term newborn is immature, unstable and will not achieve mature, adult-like levels for weeks or months. Infants born prematurely are forced into independent air breathing with an even less mature ventilatory control system; "physiological immaturity" may be associated with apnoea, respiratory dysrhythmias, impaired responses to hypoxia and hypercapnia, and other problems.[5,6]

The relatively long human gestation and period of postnatal maturation allows ample opportunity for ventilatory control development to be altered by hypoxia, hyperoxia, drugs, stress and other influences that may profoundly change the trajectory of

* Corresponding author. Tel.: +1 501 364-1006; Fax: +1 501 364 3930.
E-mail addresses: carrolljohnl@uams.edu (J.L. Carroll), agarwalamit@uams.edu (A. Agarwal).
[1] Tel.: +1 501 364 1006; Fax: +1 501 364 3930.

Abbreviations: ALTE, apparent life-threatening event; ANS, autonomic nervous system; ATP, adenosine triphosphate; BötC, Bötzinger complex; CB, carotid body; CCHS, congenital central hypoventilation syndrome; CNS, central nervous system; CO_2, carbon dioxide; CPG, central pattern generator; CSN, carotid sinus nerve; cVRG, caudal ventral respiratory group; DRG, dorsal respiratory group; E1, early expiratory phase; E2, late expiratory phase; E-aug, expiratory augmenting neurons; EGR2 (aka KROX20), early growth response 2 (gene); e-I, early-inspiratory; FRC, functional residual capacity; H^+, hydrogen ion; HASH-1 (aka ASCL1), achaete-scute complex homolog 1 (gene); HIF, hypoxia inducible factor; Hox, homeobox; HOXA1, homeobox A1 (gene); HOXA3, homeobox A3 (gene); HOXB2, homeobox B2 (gene); I, inspiratory phase; I-aug, augmenting (ramp) inspiratory; K^+, potassium ion; late-I, late inspiratory; LMX1B, LIM homeobox transcription factor 1 beta (gene); MAFB, v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (gene); MASH-1, mammalian achaete-scute homologue (gene); NDN, necdin homolog (gene); NTS, nucleus tractus solitarius; O_2, oxygen; PET-1 (aka FEV), FEV (ETS oncogene family); pFRG, parafacial respiratory group; PHOX2A, paired-like homeobox 2a (gene); PHOX2B, paired-like homeobox 2b (gene); post-I, post-inspiratory neurons; pre-BötC, pre-Bötzinger complex; pre-I, pre-inspiratory; PWS, Prader-Willi syndrome; RNX (aka TLX3), T-cell leukemia homeobox 3 (gene); RTN, retrotrapezoid nucleus; rVRG, rostral ventral respiratory group; SIDS, sudden infant death syndrome; TASK-2 (aka KCNK5, K2P5.1), Twik-related acid sensitive K+ channel 2; V_E, minute ventilation.

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development and even the ultimate outcome.[5,7] Postnatal immaturity of ventilatory control in human infants is associated with a long period of vulnerability to environmental stressors and is believed to be a major factor in the pathogenesis of the sudden infant death syndrome (SIDS).[8]

DISORDERED RESPIRATORY CONTROL IN INFANTS AND CHILDREN

Clinical disorders involving ventilatory control during infancy and childhood range from rare genetic syndromes such as congenital central hypoventilation syndrome (CCHS) and Prader-Willi Syndrome to common problems such as apnoea of prematurity, bronchopulmonary dysplasia, apparent life-threatening events (ALTE) and SIDS. Perhaps surprisingly, given its relevance to a wide variety of disorders in infancy and childhood, ventilatory control tends to be a somewhat neglected topic in paediatric medicine.

Ventilatory control may be depressed or over-stimulated by a variety of external factors such as drugs, toxins, respiratory viral infections, sepsis and others that can induce hyperpnoea, tachypnoea, hyperventilation, hypoventilation, bradypnoea, respiratory dysrhythmias, apnoea and even death due to respiratory failure. Chronic lung disease, neurological disorders and neuromuscular disease may cause chronic hypercapnia, hypoxia and acidosis, leading to secondary alterations in ventilatory control. Central nervous system (CNS) tumours, infarction, haemorrhage, hydrocephalus and seizures may affect multiple aspects of ventilatory control, causing the full range of clinical abnormalities noted above.

Abnormal ventilatory control, from hyperpnea to respiratory failure, may also be caused by disorders involving congenital or acquired abnormalities of neurons and neural pathways directly involved in respiratory rhythm generation (Table 1). The common thread in this group of disorders is involvement of the brainstem due to immaturity, structural malformations or abnormal development of critical components required for breathing rhythmogenesis and its modulation. In these disorders, although the basic defects cannot be corrected, clinical care may be greatly enhanced by increased awareness of the ventilatory control abnormalities in each disorder, their clinical manifestations, time course and appropriate evaluation and management approaches.[9]

In preterm infants, breathing pattern is characterized by instability and nearly any form of stress, including simple alterations in body temperature, may cause apnoea.[10] Although preterm infants may suffer intraventricular haemorrhage and other neurological insults that could affect breathing control, their marked ventilatory instability and high frequency of apnoea and bradycardia are due typically to physiological immaturity.[6,11,12] All aspects of the ventilatory control system are immature in preterm infants including brainstem respiratory rhythmogenesis, central chemosensory responses to CO_2, peripheral chemoreceptor responses to hypoxia and the CNS modulation of the late decline in ventilatory response to hypoxia (see below). Both the frequency and severity of apnoea and bradycardia events correlate directly with the degree of immaturity.[13,14] During postnatal maturation, as the preterm infant approaches ~ 40 weeks postconceptional age, breathing stability normalizes and apnoea of prematurity typically resolves. Even preterm infants with extremely severe apnoea and bradycardia usually cease having such events by ~ 43 weeks postconceptional age.[13] Several excellent reviews have addressed apnoea of prematurity and its treatment during the neonatal period.[6,15]

Table 1
Disorders due to immature or abnormal ventilatory control

Physiological immaturity
○ Apnoea of prematurity
○ Periodic breathing, breathing pattern instability during infancy
Pathophysiology involving ventilatory control system
○ Congenital Central Hypoventilation Syndrome (CCHS)
○ Rapid Onset Obesity with Hypothalamic Dysfunction, Hypoventilation and Autonomic Dysregulation (ROHHAD)
○ Chiari malformations
○ Achondroplasia (with hypoventilation)
○ Prader-Willi Syndrome
○ Joubert's syndrome
○ Möebius syndrome
○ Rett syndrome
Probable vulnerabilities due to abnormal ventilatory control
○ Sudden Infant Death Syndrome (SIDS)

VENTILATORY CONTROL DEVELOPMENT – DYNAMIC AND VULNERABLE

Essential elements of ventilatory control include the brainstem sites of breathing rhythmogenesis, inputs from peripheral chemoreceptors and central chemoreceptor sites, lung, airway and other mechanoreceptors, and behavioural, cortical modulation (Figure 1). Contrary to earlier views, development of these neural components and their highly complex web of connections does not follow a rigidly predetermined genetic blueprint. Rather, the structural development of the ventilatory control system and differentiation of neurons into specific functional phenotypes results from extremely complex interactions between genes, transcriptional, neurotrophic and other factors operating under varying structural and temporal constraints as development proceeds. Neural crest cells, which migrate to form critically important components of the respiratory control system, arise from multipotent precursor cells that differentiate into various neuronal phenotypes in a process dependent upon specific transcription factors such as *PHOX2B*.[16,17] All of these dynamic processes are subject to alteration by external influences during development.

The term 'developmental plasticity' refers to long-term or persistent changes in respiratory control induced by 'experience' during 'critical periods' of development.[5] By definition, the same 'experience' occurring outside of the critical period would have no lasting effect. Developmental plasticity of ventilatory control

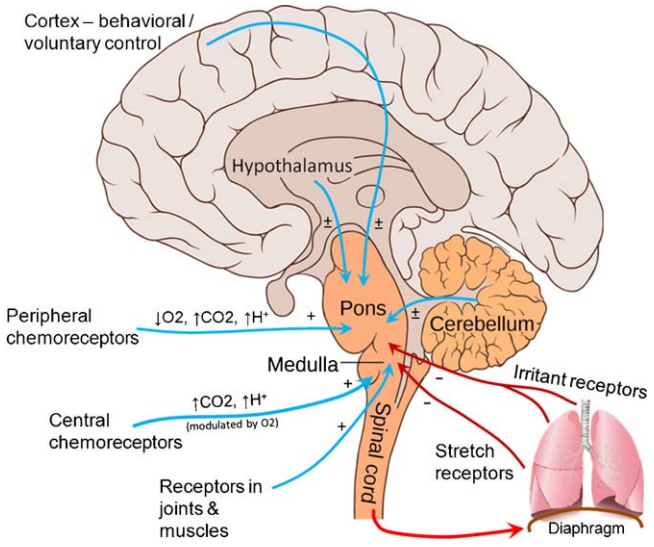

Figure 1. Overview of ventilatory control system. Central breathing rhythm is generated in the pons and medulla and modulated by multiple inputs. Symbols: (+) stimulatory, (-) inhibitory, (±) excitatory or inhibitory. Motor output drives diaphragm, upper airway and other respiratory muscle activity (not shown). Modified, from original drawing by P.J. Lynch and C.C. Jaffe.