7° Congreso Argentino de Neumonología Pediátrica
Jornada de Enfermería en Enfermedades Respiratorias Pediátricas Jornada de Kinesiología Respiratoria

El Control de la Ventilación en diferentes situaciones **Hipoventilación Central**

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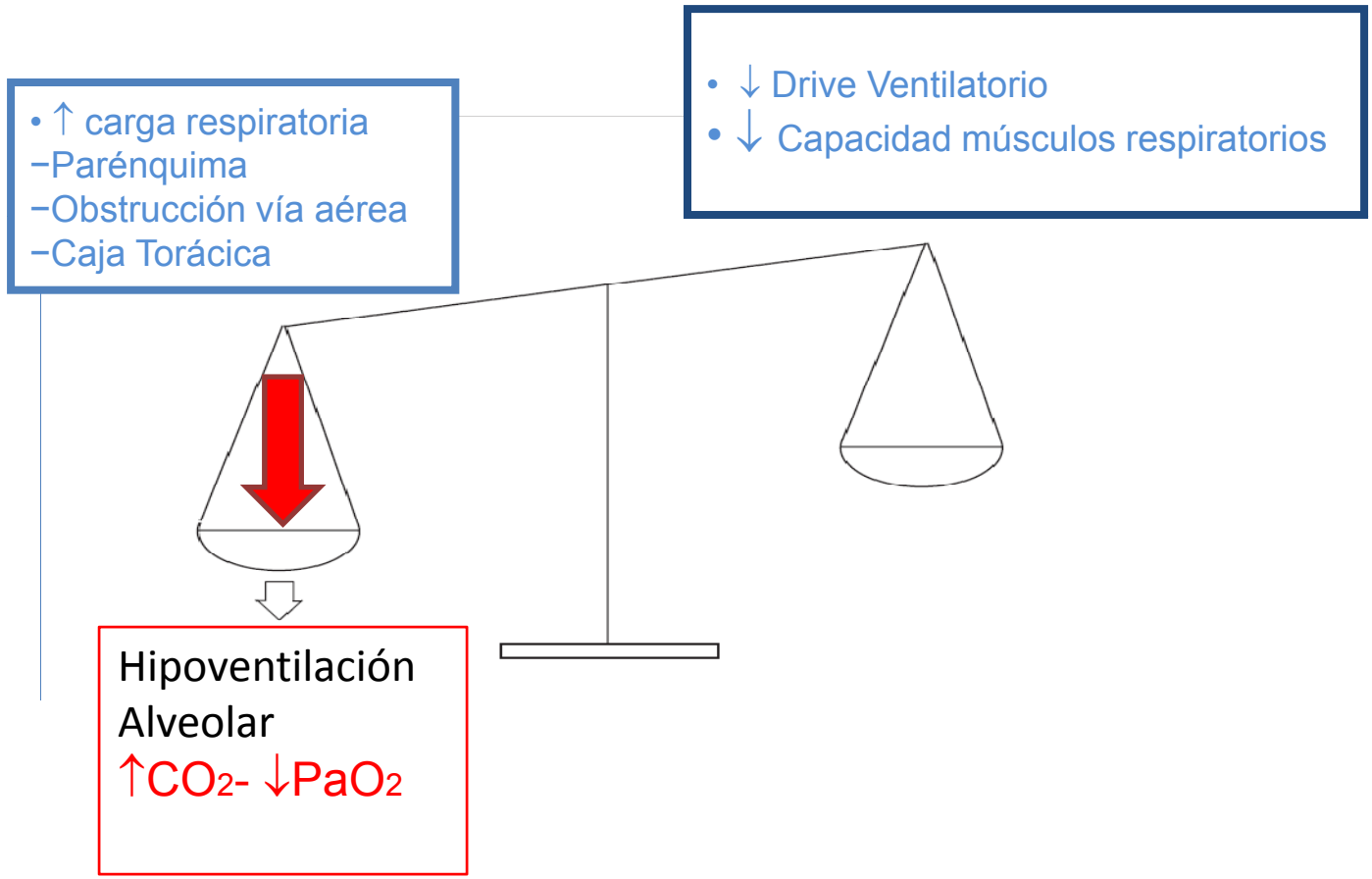
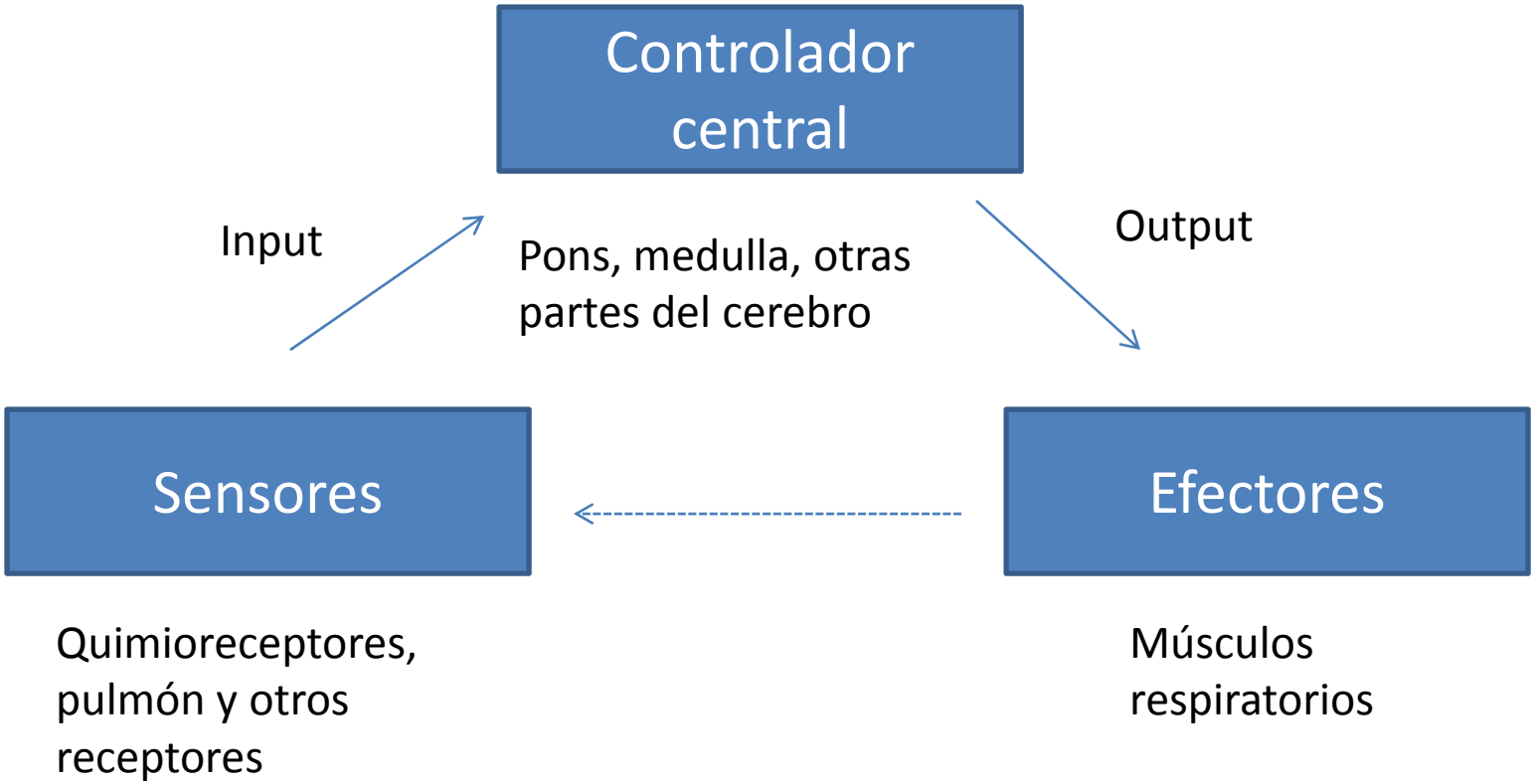
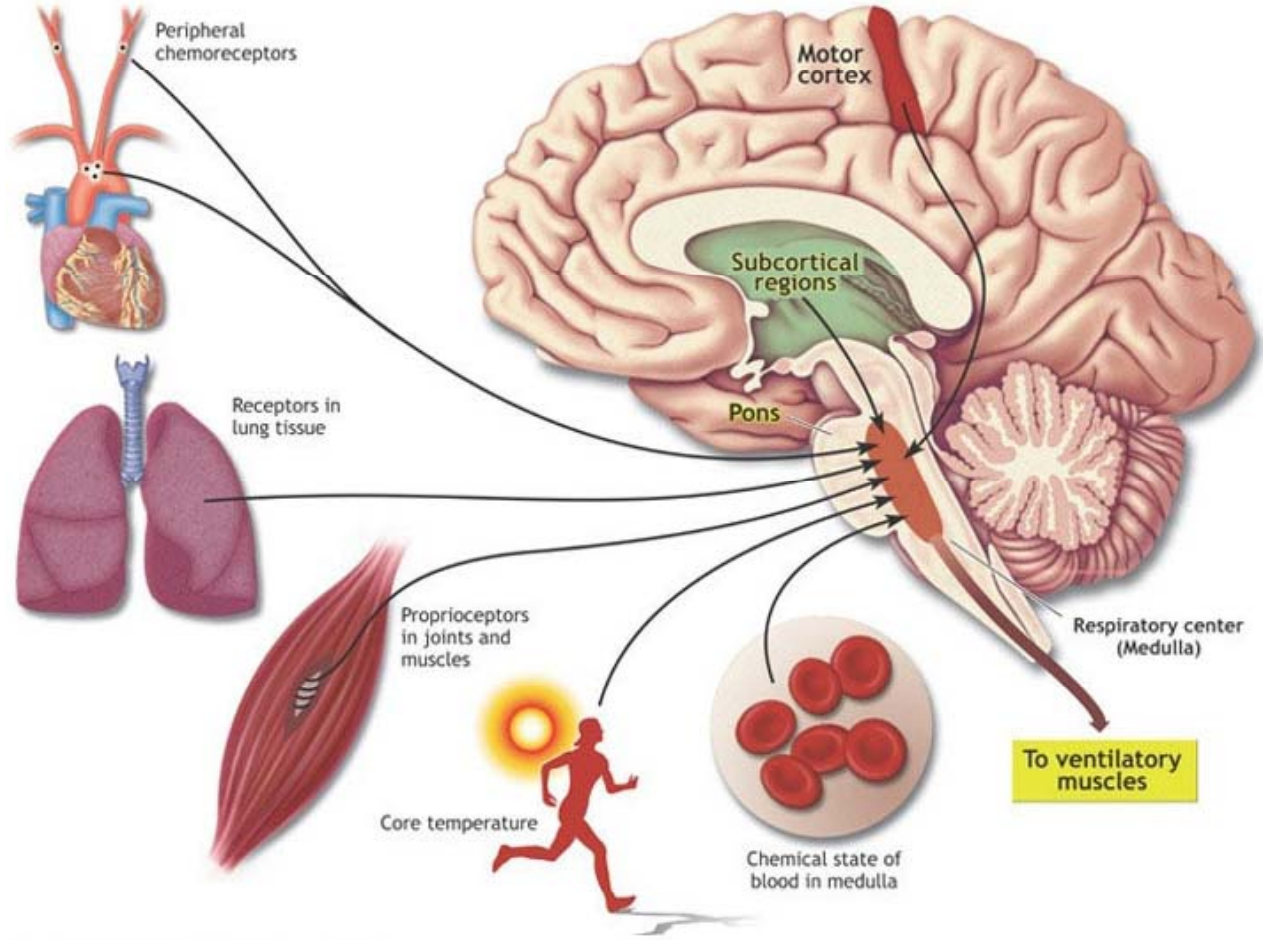
¿Porque puede estar alterada la ventilación?



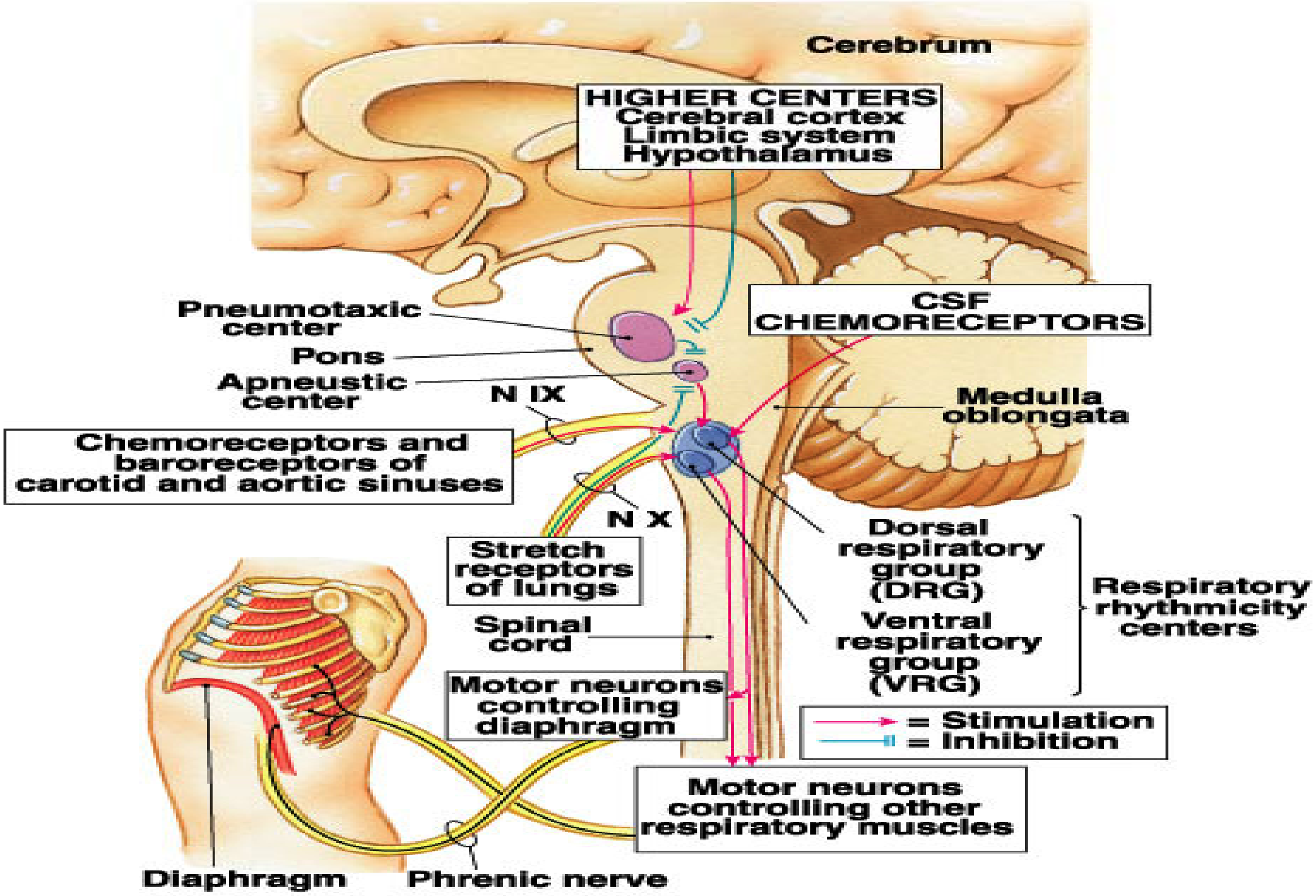
Control de la Ventilación



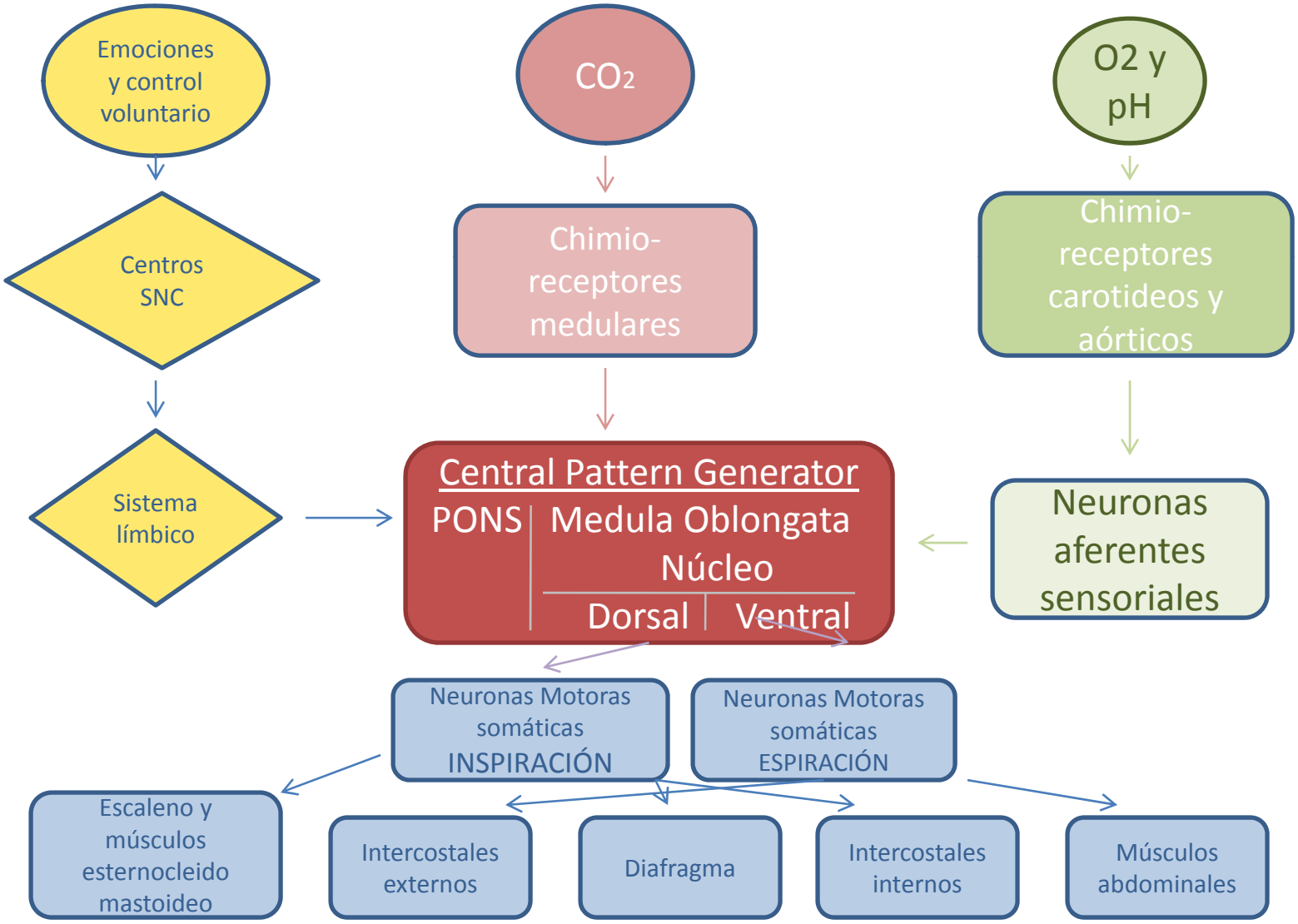
Control de la Ventilación



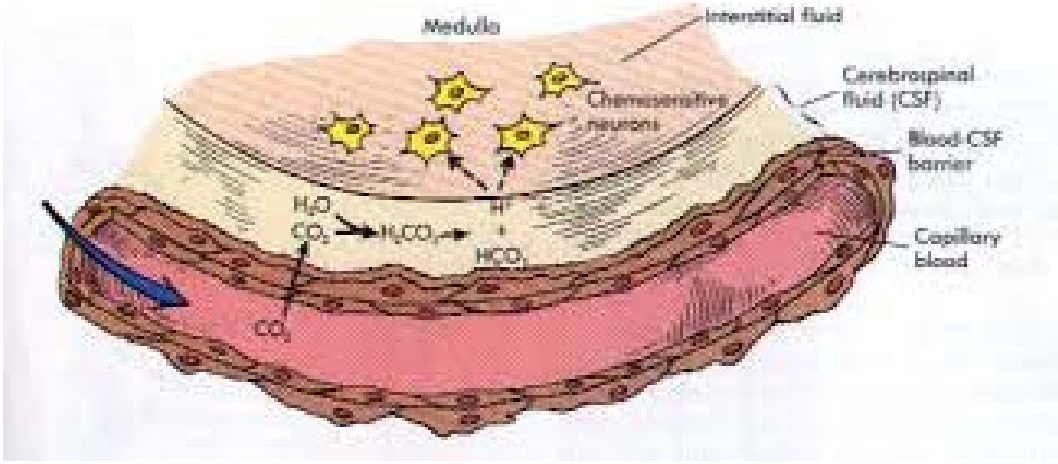
Estructuras en el tronco encefálico



Control de la Ventilación



Quimio-receptores medulares



- Nuúcleo ventral de la medulla
- Responde al pH del LCR
- CO2 difunde a través de la BHE
- pH normal es 7.32
- LCR tiene escaso poder buffer
- el $HCO3^-$ es controlado x el plexus coroideo

Quimio-receptores periféricos carotídeos y aórticos

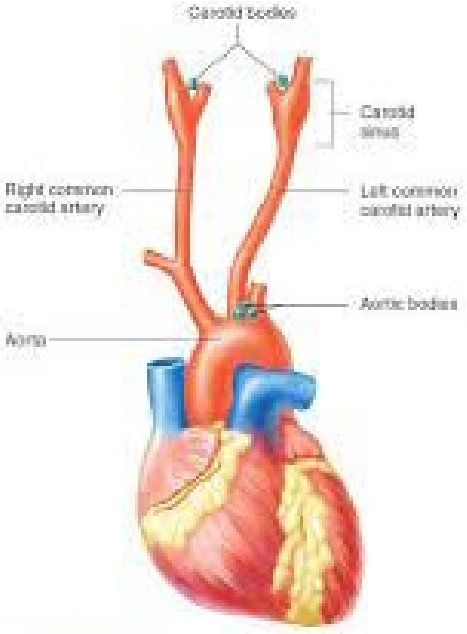
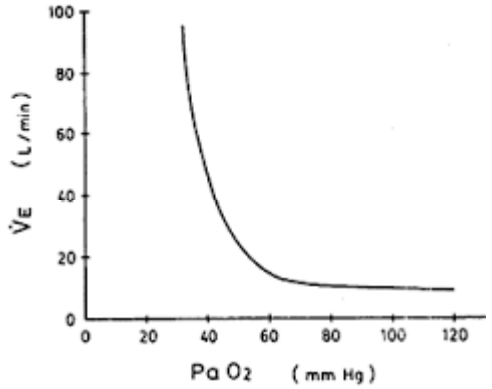


FIGURE 13–30
Location of the carotid and aortic bodies. Note that each carotid body is quite close to a carotid sinus, the major arterial baroreceptor. Both right and left common carotid bifurcations contain a carotid sinus and a carotid body.



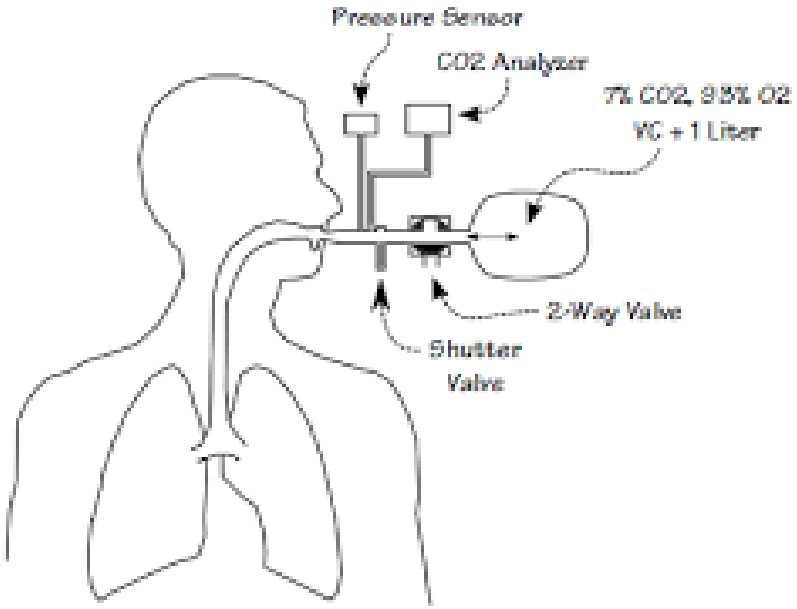
- Responden a PO2, PCO2 and pH
- Escasa respuesta en normoxia
- Muy alto flujo sanguíneo
- Responde a PaO2 (no a la venosa)
- Respuesta rápida

Otros receptores

- Receptores de estiramiento
- Receptores de irritación
- Receptores J o juxtacapilares
- Otros
  - Nariz y VAS
  - Musculos y articulaciones
  - Dolor y temperatura

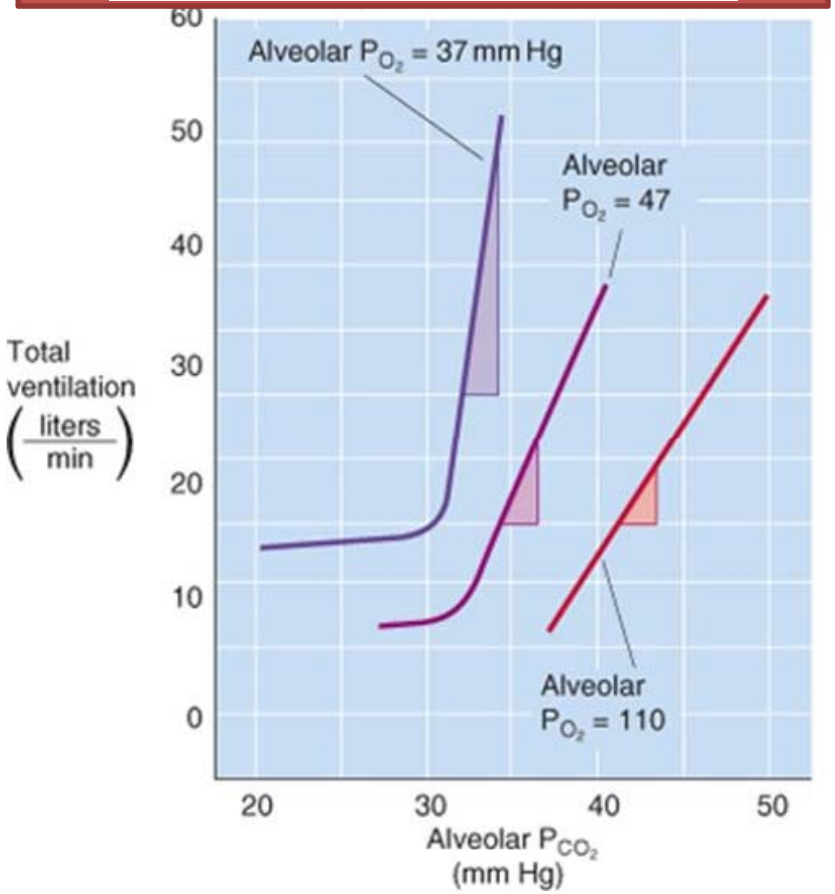
¿Como evaluar el control de la ventilación?

- Quimio-sensibilidad. ¿ Que respuestas medimos?
  - Respuestas a la Hipercapnia en condiciones de Normoxia/Hiperoxia
    - Dos métodos:
      - Técnica del circuito abierto: se inhalan diferentes concentraciones de CO2 (1-7%) hasta alcanzar el “steady state”.
      - Técnica de “re-breathing”: el paciente inhala de un circuito unidireccional que contiene un reservorio de CO2.

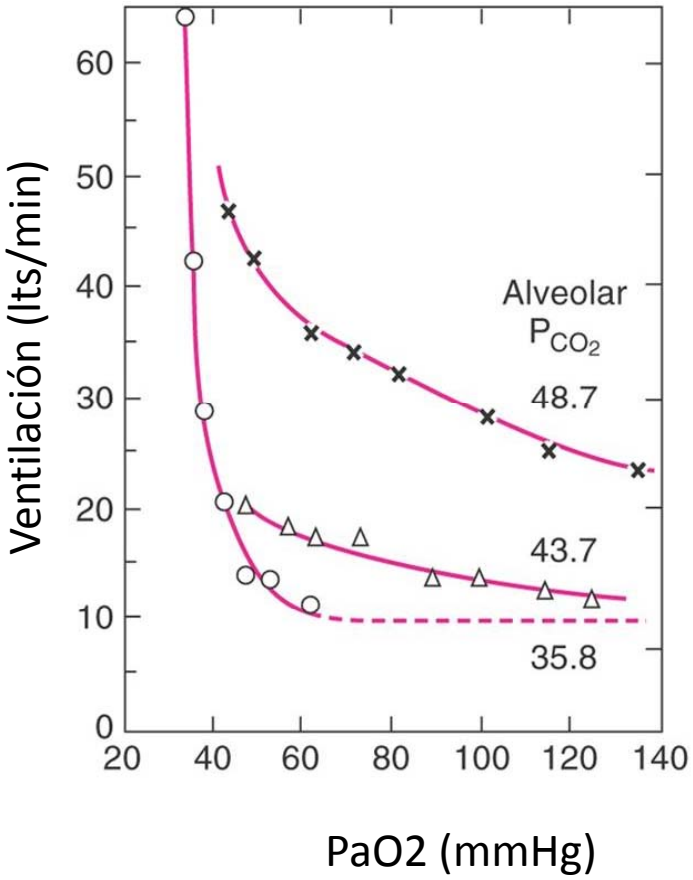


Respuestas Integradas

Respuesta ventilatoria a la PCO2



Respuesta ventilatoria a la PaO2



International Classification of Sleep Disorders

Capitulo de TRS: 6 subtipos de hipoventilación

1. Síndrome de hipoventilación obesidad
2. Síndrome de Hipoventilación Central Congénita
3. Hipoventilacion central de inicio tardío con disfunción hipotalámica
4. Hipo ventilación alveolar central idiopática
5. Hipoventilación en sueño relacionada con drogas
6. Hipoventilación en sueño relacionada a desordenes médicos (SPW, Chiari)

Síndrome de Hipoventilación Alveolar Central Congénita (SHACC)

Medicine (Baltimore). 1970 Nov;49(6):487-504.

Failure of automatic control of ventilation (Ondine's curse). Report of an infant born with this syndrome and review of the literature.

Mellins RB, Balfour HH Jr, Turino GM, Winters RW.

Síndrome de Hipoventilación Alveolar Central Congénita (SHACC) Presentación

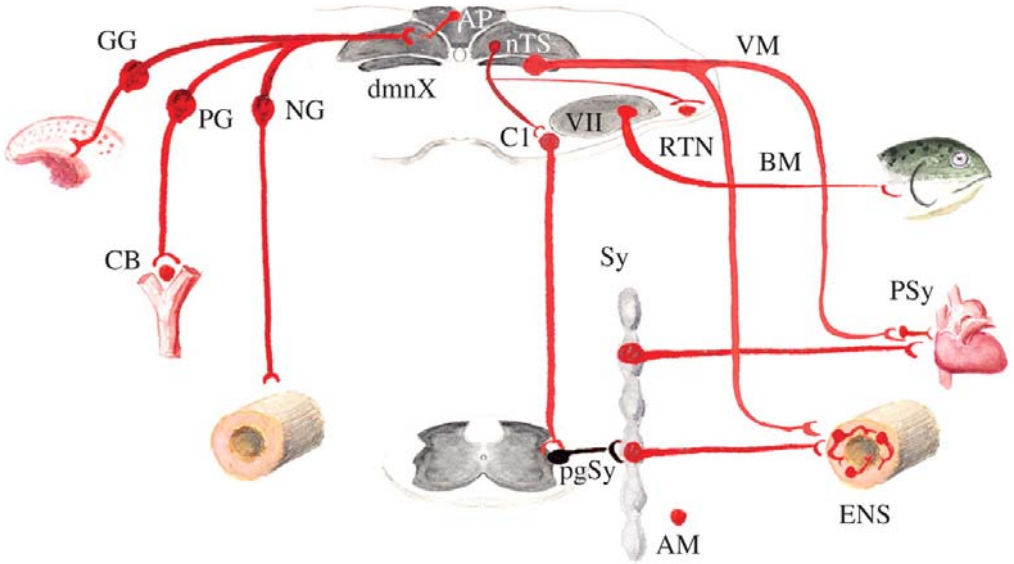
- Neonatal
  - **hypoventilación** con FR monótona y respiración superficial en sueño aislado o sueño y vigilia
  - disregulación del SNA
  - en algunos desarrollo anormal de las estructuras derivados de la cresta neural (i.e., enfermedad de Hirschsprung) y/o tumores originados en la cresta neural (neuroblastoma, ganglioneuroma, y ganglioneuroblastoma).

- Presentación tardía (LO-CCHS)
  - Luego del mes de vida
  - Apneas, cianosis, síncopes IRA, anestésicos, tto SAOS

SHACC
Diagnóstico

- **Hypoventilacion** (respuestas Ve a la hipercapnia e hipoxemia ↓
- Falta de percepción de asfixia y falta de despertar del sueño con desarrollo de compromiso fisiólogico secundario a hipercapnia e hipoxemia
- Ausencia de evidencia de enfermedad neuromuscular, cardíaca, pulmonar o lesión identificable en tronco que justifique los síntomas del SNA
- Mutación PHOX2B
- Síntomas de compromiso del SNA como espasmo del sollozo severo, falta de respuesta fisiológica a diferentes estímulos, respuesta pupilar a la luz disminuída, dismotilidad esofágica, constipación severa, sudoración profusa, temperatura basal disminuída, y percepción de ansiedad alterada

PHOX2B un regulador maestro de circuitos reflejos viscerales.



ıctures expressing *Phox2* genes

tures expressing *Phox2* genes. Structures depending only on *Phox2b* are in plain text. epending only on *Phox2a* are in italics; Structures depending on both genes are in bold. ır which no data is available yet are in small font. The spinal interneurons expressing ıot *Phox2b* have been omitted for clarity. VLM: ventro-lateral medulla.

PNS	CNS
Geniculate ganglion	*Oculomotor nucleus* (nIII)
Petrosal ganglion	*Trochlear nucleus* (nIV)
Nodose ganglion	Trigeminal nucleus (nV)
Carotid body	Facial nucleus (nVII)
Sympathetic ganglia	Nucleus ambiguus (nA)
Parasympathetic ganglia	Dorsal motor n. of the vagus (dmnX)
Ciliary	Salivatory nuclei
Sphenopalatine	Cochlear and vestibular efferent nuclei
Otic	Nucleus of the solitary tract (nTS)
Submandibular and sublingual	Area postrema (AP)
Paracardiac	(Nor)adrenergic centers: A1-5,
All others	**A6 (locus cœruleus)**, A7, C1-3
Enteric neurons	Retrotrapezoid nucleus
	Unidentified interneurons of the VLM

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Dubreuil Vet al. Phil. Trans. R. Soc. B 2009

Neuronas fuera del patrón de expresión PHOX2B

- Neuronas simpáticas preganglionares en la medula espinal
- Neuronas motoras respiratorias
  - Motoneuronas espinales somáticas que inervan
    - Diafragma
    - Músculos intercostales
    - Músculos abdominales

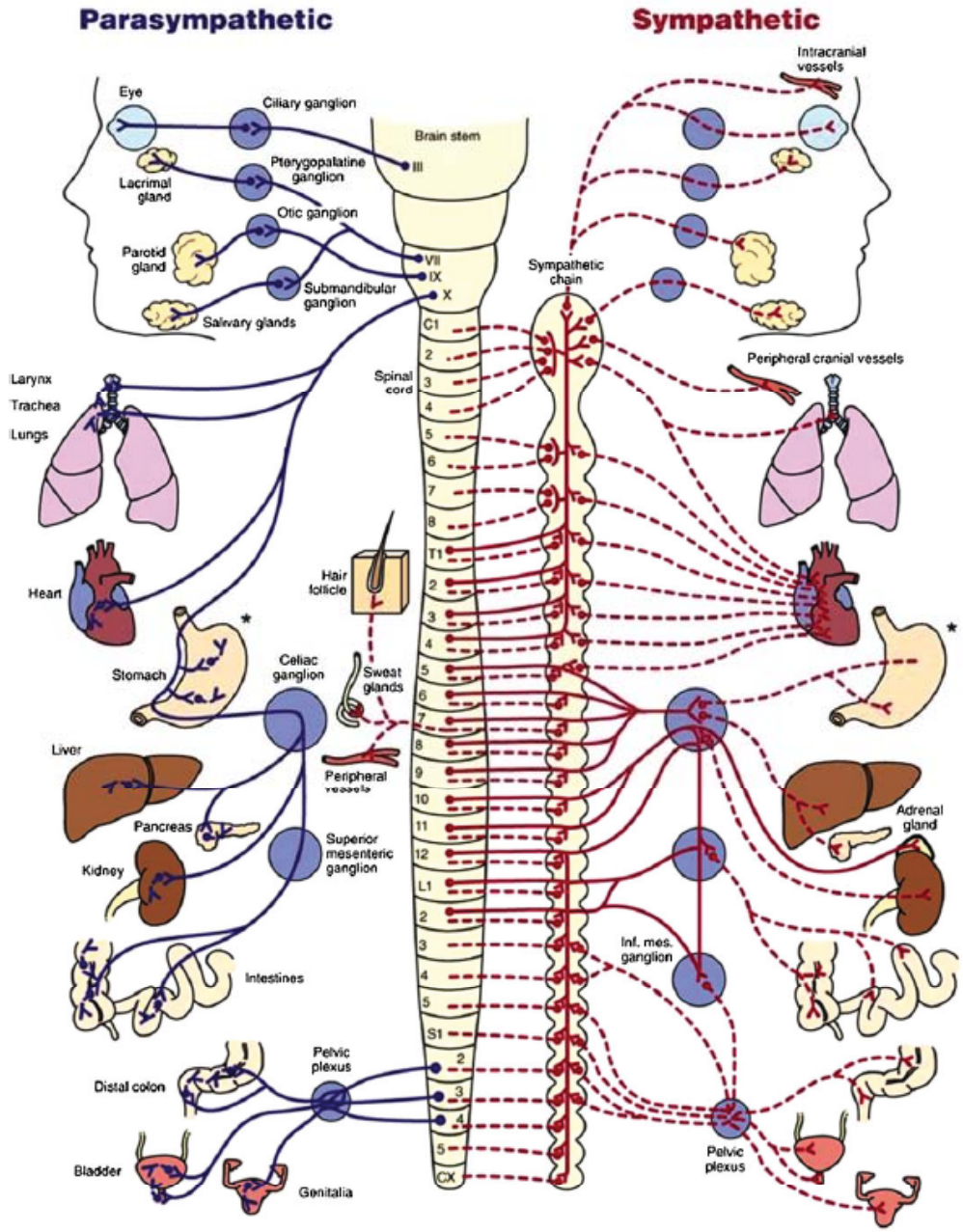


Fig. 1. Schematic of the ANS. This schematic figure demonstrates the organ systems affected by the sympathetic and parasympathetic nervous systems. The enteric system is not shown, but is grouped with the ANS.

Mutaciones en ratones
PHOX2B y el drive para respirar

eLIFE
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BREATHING

CO_2 in the spotlight

Optogenetic techniques have revealed that retrotrapezoid neurons are essential for sensitivity to carbon dioxide.

LUIS R HERNANDEZ-MIRANDA AND CARMEN BIRCHMEIER

1. **A human mutation in Phox2b causes lack of CO_2 chemosensitivity, fatal central apnea, and specific loss of parafacial neurons**
   V Dubreuil, N Ramanantsoa, D Trochet, V Vaubourg, J Amiel, J Gallego, JF Brunet, C Goridis
   Proceedings of the 2008

2. **Defective respiratory rhythmogenesis and loss central chemosensitivity in Phox2b mutants targeting retrotrapezoid nucleus neurons**
   V Dubreuil, M Thoby-Brisson, M Rallu, K Persson, A Patt Birchmeier, JF Brunet, G Fortin, C Goridis

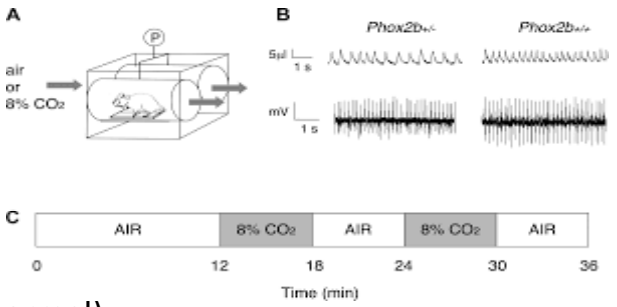
4. **Phox2b, congenital central hypoventilation syndrome and the control of respiration**
   C Goridis, V Dubreuil, M Thoby-Brisson, G Fortin, JF Brunet
   Seminars in Cell & Developmental Biology, 21, 814-822, 2010

9. **Breathing without CO_2 chemosensitivity in conditional Phox2b mutants**
   N Ramanantsoa, MR Hirsch, M Thoby-Brisson, V Dubreuil, J Bouvier, PL Ruffault, B Matrot, G Fortin, JF Brunet, J Gallego, C Goridis
   Journal of Neuroscience, 31, 12880-12888, 2011

Fenotipo ventilatorio en ratones con mutaciones PHOX2B

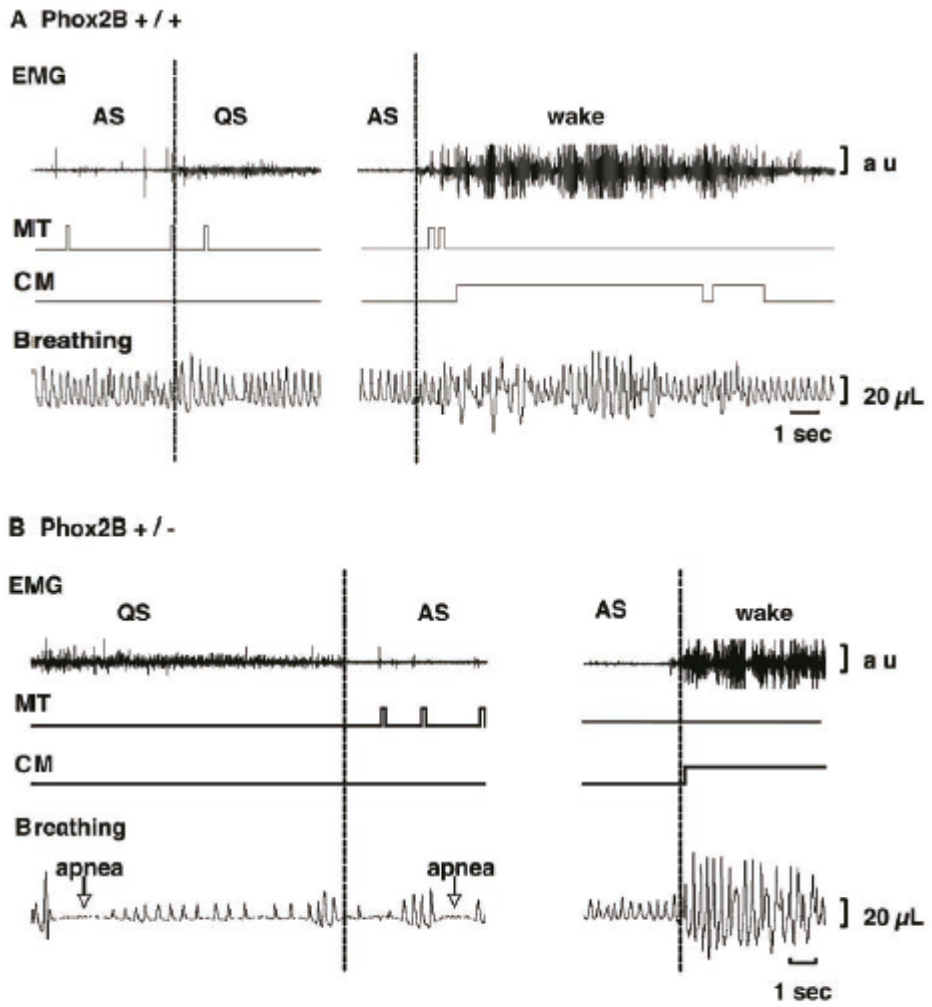
- Ratón knock out-homocigota (Phox2b -/-): fallecen intra-utero
- Ratón heterocigota Phox2b (+/-) : sobreviven y son fértiles

Estudio de control ventilatorio en ratones recién nacidos Phox2b +/-



- Respuestas ventilatorias (8% CO) :
  - ↓ 40% comparado con ratones phox2b +/+
  - mayor número y duración de apneas
  - diferencias son transitorias (hasta los 10 d)
- Respuestas ventilatorias a la hipoxia (5%O2)
  - Depresión Ventilatoria pos hipoxia acentuada (apneas y T_{TOT} anormal)
- Respuestas ventilatorias a la hiperoxia
  - Depresión ventilatoria acentuada y > duración de apneas.
  - Sugiere actividad tónica de los quimireceptores periféricos acentuada

Apneas en Ratones RN Heterocigotas PHOX2B +/-



Am J Respir Crit Care Med. 2005

Respuesta ventilatoria a la hipercapnia en ratones phox2b +/-

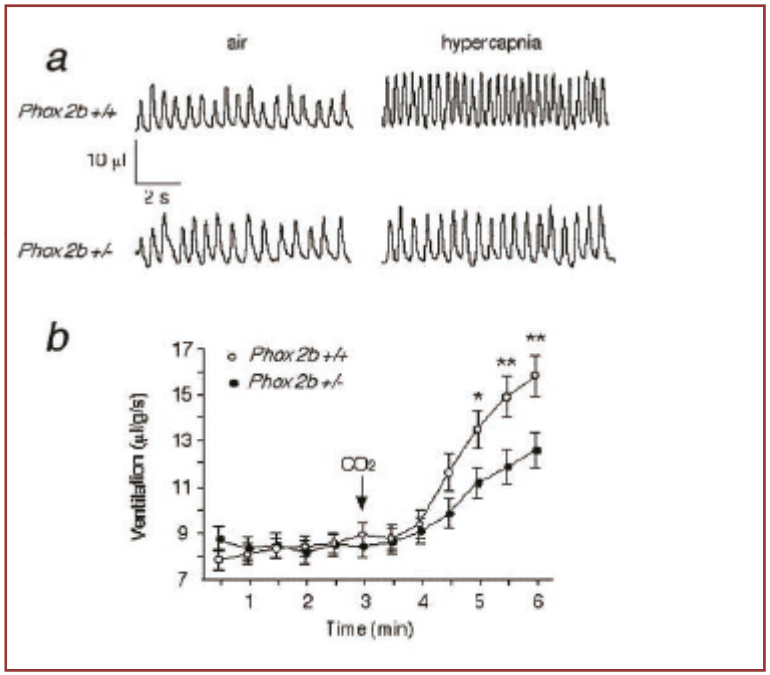


Fig. 2. Abnormal ventilatory response to hypercapnia in 2-day-old Phox2b$^{+/-}$ mutant mice. a: Ventilatory tracings in one Phox2b$^{+/+}$ pup (top) and one Phox2b$^{+/-}$ pup (bottom). Both pups had similar baseline ventilation but the Phox2b$^{+/-}$ pup showed a weaker ventilatory response to hypercapnia. b: Values are means ± SEM ([18], reproduced with permission of the Company of Biologists).

Dauger S, et al. Development 2003.

Phox2b controls the development of peripheral chemoreceptors and afferent visceral pathways

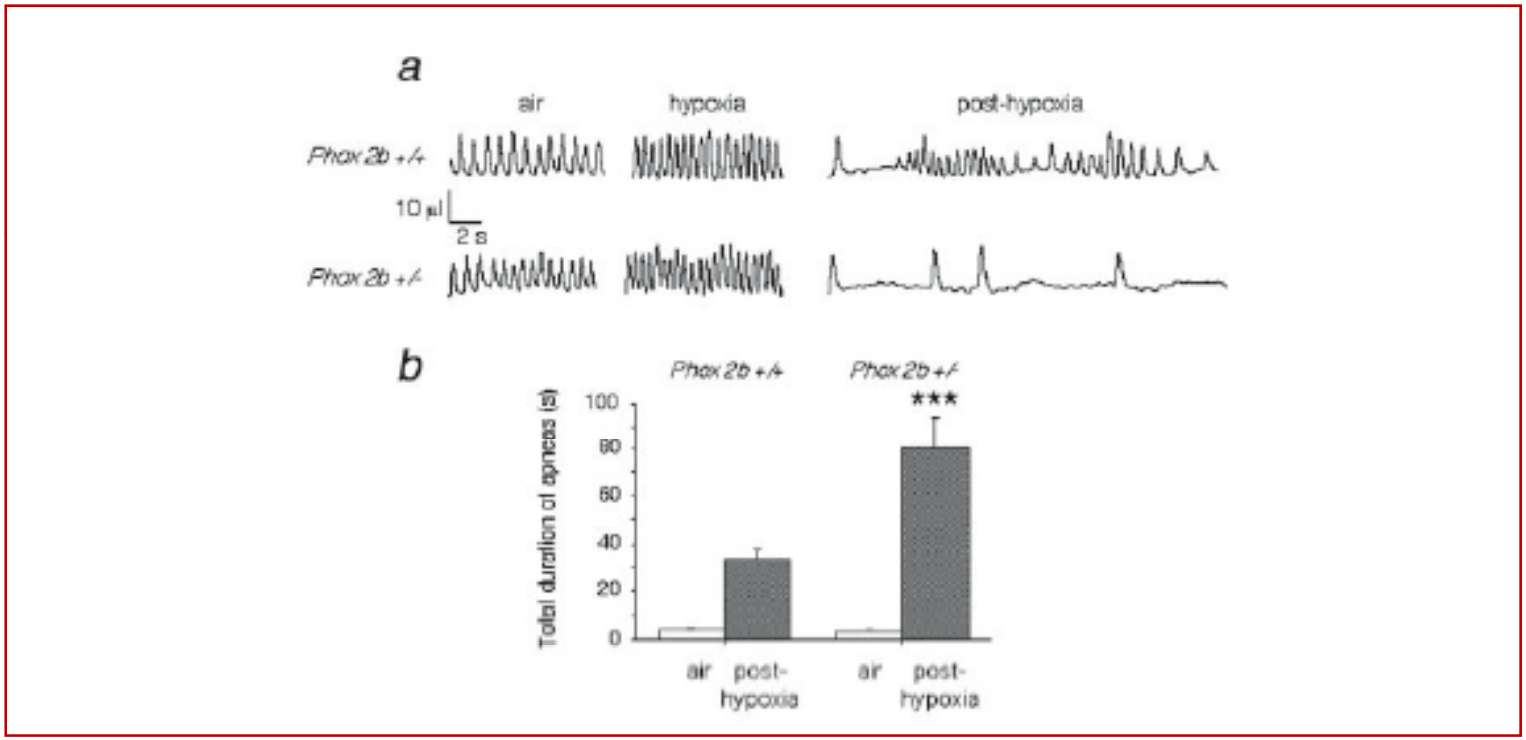
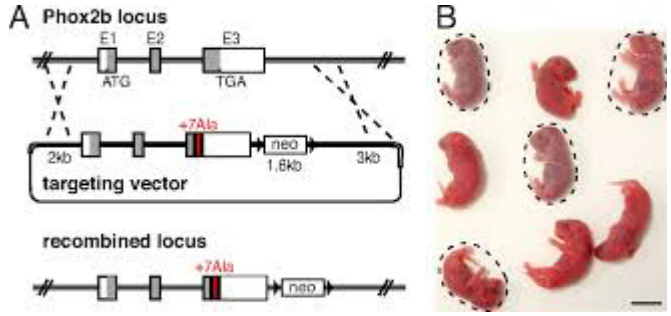


Fig. 3. Abnormal post-hypoxic depression in 2-day-old *Phox2b*$^{+/-}$ mutant mice. a: Ventilatory tracings in one *Phox2b*$^{+/+}$ pup (top) and one *Phox2b*$^{+/-}$ pup (bottom). Both pups had similar baseline ventilation and initial increases in ventilation, but the *Phox2b*$^{+/-}$ pup showed long post-hypoxic apneas. b: Total duration of apneas (defined as respiratory pauses longer than twice the duration of the preceding breathing cycle) while breathing air (3 min) and after hypoxia (6 minutes). Although the number of apneas was not different between the two groups (0.7 and 2.8 apneas/minute with air and hypoxia in *Phox2b*$^{+/-}$ pups and 0.8 and 2.8 apneas/minute in *Phox2b*$^{+/+}$ pups, respectively), apneas were considerably longer in *Phox2b*$^{+/-}$ mice (***$p<0.001$). Values are group means ± SEM ([18] reproduced with permission of the Company of Biologists).

Dauger S et al. Development 2003

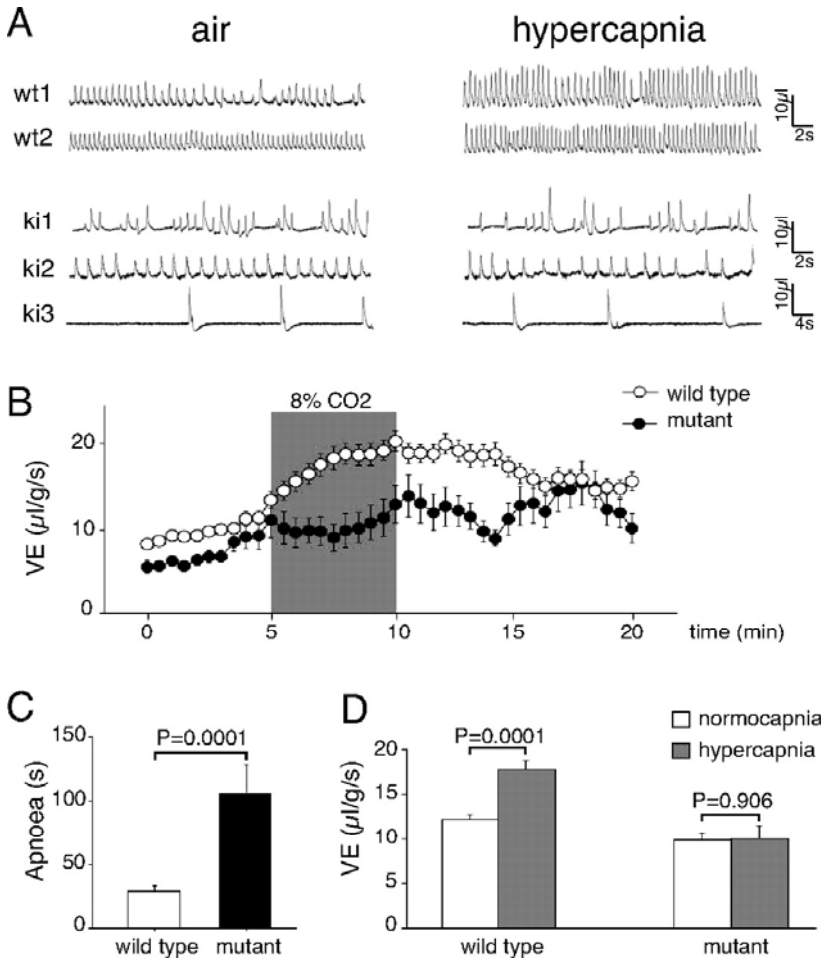
Fenotipo ventilatorio en ratones Phox2b (27Ala/+)

- Fallecieron en las primeras hs de vida
- Patrón respiratorio de las primeras hs mostró variabilidad inter-individual
  - Gasping
  - Respiración inestable + apneas
  - Respiración superficial con FR baja
  - V_E media baja
  - Mayor cantidad y duración de apneas
  - Ausencia total de respuesta ventilatoria a la hipercapnia
    - ➢ Defecto en la quimio-recepción central



Dubreuil V et al. PNA 2008

A human mutation in Phox2b causes lack of CO_2chemosensitivity, fatal central apnea, and specific loss of parafacial neurons



Dubreuil V et al. PNA 2008

Carbon dioxide chemoreception and hypoventilation syndromes with autonomic dysregulation

Michael S. Carroll,* Pallavi P. Patwari,* and Debra E. Weese-Mayer

Center for Autonomic Medicine in Pediatrics, Children's Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Marcus, 1991	56	8	CU	NA	<1 yr	0.4–12 yr	D/RB	S	10% CO_2/A	7/8 cases aroused to challenge with no ventilatory response, but required more time (reached higher P_{ETCO_2})
Weese-Mayer, 1992	109	32	CU	NA	early	median: 3 mo	SP: >70, CB	W/S	U	No ventilatory response to challenge
Shea, 1993	85	5	CU	NA	birth	8–17 yr	RB-2, CB	W	14% CO_2/A	Blunted ventilatory response. No subjective "breathlessness"
Gozal, 1993	32	5	CM	NA	<1 yr	9–14 yr	RB-U	W	15% CO_2, 5% CO_2/95% O_2, 5% CO_2/0% O_2/95% N_2	Designed to elicit mainly transient peripherally mediated response. No significant case-control differences in CO_2 response slopes; significant changes in V_T (and f in some challenges)
Nakahara, 1995	60	1	CR	NA	birth	birth	U	W/S	U	Normal response in W; flat in S
Kerbl, 1996	44	1	CR	NA	birth	8 mo	RB	W/S	U	Blunted f and arousal response to challenge
Croaker, 1998	14	5	CR	NA	birth	birth	SP: varied	W/S	U	No ventilatory response to hypercapnia
Macey, 2003	51	14	CA	NA	U	8–15 yr	D	W	5% CO_2/95% O_2, 0% CO_2/15% O_2/85% N_2	Measured fMRI global BOLD response. Gases measured in subset. Muted hypercapnic response in cases
Macey, 2004	53	12	CM	U	U	8–15 yr	D	W	5% CO_2/95% O_2, 0% CO_2/15% O_2/85% N_2	Slow/muted response. Slow f response to hypercapnia
Bajaj, 2005	7	1	CR	NPARM	pre	pre	SP: 120	S		No ventilatory response in extreme preterm with Hirschsprung disease
Chiaretti, 2005	13	3	CM	U	1–4 wk	1–3 mo	SP: 75	S		No ventilatory response
Harper, 2005	38	14	CA	U	U	8–15 yr	D	W	5% CO_2/95% O_2, 0% CO_2/15% O_2/85% N_2	Measured fMRI localized BOLD response. Most areas muted or inverse response in cases. Group differences in midline dorsal medulla, etc.
Chen, 2005	12	5	CA	U	<1 yr	mean: 21 yr	RB-13	W	5% CO_2	No ventilatory response, with normal cardiovascular response. BP response preserved
Antic, 2006	3	5	CR	20/25	varied	22–36 yr	CB, SP: 60–82	W/S		Mild phenotype in adult diagnoses (LO-CCHS) with possible antecedent symptoms
Bachetti, 2006	6	2	CR	U	birth	3 mo, <15 mo	V	N	U	No ventilatory response
Barratt, 2007	8	1	CR	20/25	32 yr?	41 yr	RB	W	U	No quantification
Diedrich, 2007	18	1	CR	20/25	U	27 yr	CB	W	U	Blunted response to challenges. No EMG response to breath hold. Reduction in some HRV measures. BP similar to control
Doherty, 2007	19	5	CR	20/25	varied	4–41 yr	RB-5	W	7% CO_2/93% O_2	LO-CCHS. Reduced response in all *PHOX2B* mutation-confirmed family members

Continued

Table 1.—*Continued*

Citation	Ref. No.	*N*	Type of Study	Genotype	Age at Onset	Age at Test	Challenge Method	State	Gas Mixtures $CO_2/O_2/N_2$	Results and Comments
Huang, 2008	40	7	CM	20/25–27	U	mean: 13 yr	V	W/N/R	U	More severe hypoventilation in N and R. Arousals in 41% of sleep trials. Summary data pooled from 7 CCHS and 2 non-CCHS with normal genotype
Lee, 2009	47	3	CU	20/25	22–30 yr	22–53 yr	RB-7	W	5% CO_2	Reduced slope response to CO_2 challenge
Fine-Goulden, 2009	24	1	CR	20/25	12 yr	12 yr	SP: >112	S		Respiratory failure after anesthesia

N, no. of subjects exposed to hypercapnic challenges. *PHOX2B*, paired-like homeobox 2B gene. Type of Study: CR, case report; CU, cohort, unmatched; CM, cohort, matched; CA, cohort, approximately matched. *PHOX2B* Genotype: NA, not available pre-2003; U, unknown; not tested; NPARM, nonpolyalanine repeat mutation; 20/25 and 20/25–27, *PHOX2B* genotype reflecting the heterozygous condition [and confirming the diagnosis of congenital central hypoventilation syndrome (CCHS)]. Nos. refer to the no. of alanines on each allele in *exon 3* of the *PHOX2B* gene. The normal individual has 20 alanines on each allele. The child with CCHS has one allele with 20 alanines and the second allele with anywhere from 24 to 33 alanines. Hence the genotype of the normal individual is 20/20, and the genotype options for CCHS patients with a polyalanine repeat expansion mutation will have a range of 20/24–20/33. Challenge Method: RB, rebreathing; SP: *x*, spontaneous hypercapnia to *x* mmHg; D, direct through ventilator, pneumotach, or mask; RB-*x*, rebreathing, with *x* liter reservoir; CB, voluntarily controlled breathing rate; V, ventilator withdrawal. Behavioral State: W, wake; S, sleep, unspecified stage; R, rapid eye movement; N, non-rapid eye movement. Gas Mixtures: U, unspecified; A, ambient room air. Specific blends of $CO_2/O_2/N_2$ are shown. Results and Comments: f, respiratory frequency; V_T, end-tidal volume; $P_{ET}_{CO_2}$, end-tidal partial pressure of CO_2; fMRI, functional magnetic resonance imaging; BOLD, blood-oxygen-level dependent; BP, blood pressure; CCHS, congenital central hypoventilation syndrome; LO-CCHS, late-onset CCHS; HRV, heart-rate variability; EMG, electromyography.

Table 2. *ROHHAD publications, including CO_2 challenge, in chronological order*

Citation	Ref. No.	*N*	Age at Onset	Age at Test	State & Challenge Method	Metrics	Results & Comments
Fishman, 1965	25	1	2.75 yr onset of obesity, 3.5 yr onset of respiratory symptoms	3.5 yr	Awake endogenous, exogenous O_2 (unspecified if awake or sleep)	Venous blood gas, $P_{ET_{CO_2}}$	pH 7.21 with P_{CO_2} of 69 Torr. $P_{ET_{CO_2}}$ was 8–10% of atmospheric pressure (normal 4.5%). Oxygen administration did not lower P_{CO_2}
Nattie, 1975	61	1	20 mo	30 mo	Awake endogenous (on presentation), sleep endogenous, awake exogenous CO_2, awake exogenous O_2	Whole body plethysmography; based on metabolic rate and box volume, the expected inspired CO_2 concentration increased ~1% every 10 min	Pa_{CO_2} ≤60 Torr and hypoxia Pa_{O_2} 65 Torr. With sleep, $P_{A_{CO_2}}$ increased to 65–75 Torr. With exogenous CO_2 via sealed box, approx. no change in V_T and small increase in f and V_E. Response diminished compared with normal (brisk increase in V_T and f). With 95% oxygen administration, $P_{A_{CO_2}}$ increased to 75 Torr (normal child remained normal at 35 Torr)
Moskowitz, 1976	59	1	7.4 yr	14.7 yr	Awake endogenous, sleep endogenous, awake exogenous: 5% CO_2 + 30% O_2, 7.7% CO_2 + 40% O_2	Arterial blood gas	Pa_{CO_2} 41 Torr. Apnea with sleep with lowest $P_{A_{O_2}}$ 41 Torr and highest $P_{A_{CO_2}}$ 57 Torr. Ventilatory response to inhaled CO_2 was in the low-normal range
				17 yr	Sleep endogenous, awake exogenous (repeated)		Apnea with sleep resulting in $P_{A_{O_2}}$ 29 Torr and Pa_{CO_2} 50 Torr. Exogenous challenge unchanged
Dunger, 1980	21	1	4.5 yr	13 yr	Endogenous (unspecified if awake or sleep), exogenous CO_2 (unspecified if awake or sleep)	Arterial blood gas, ventilatory response to CO_2 production assessed by rebreathing method	Pa_{CO_2} 60–70 Torr; unchanged after naloxone administration. No ventilatory response to $P_{ET_{CO_2}}$ of 71 Torr
Frank, 1981	29	1	5 yr onset of weight gain, 6 yr onset of respiratory symptoms	6 yr	Sleep endogenous, sleep exogenous O_2	Arterial blood gas	Sleep $P_{A_{CO_2}}$ 60 Torr and had obstructive sleep apnea + hypnoneas with persistent hypopnea after tracheostomy placement. With supplemental oxygen, $P_{A_{CO_2}}$ increased to 100 Torr
DuRivage, 1985	22	2	4 yr onset of obesity, 7.5 yr onset of respiratory symptoms	7.5 yr	Sleep endogenous, exogenous (unspecified if awake or sleep)		$P_{A_{CO_2}}$ ~70 Torr and transcutaneous P_{O_2} 49 Torr. Depressed ventilatory response to hypercarbia and hypoxia (details unavailable)
			9 yr	14 yr	Sleep endogenous	Blood gases and polygraphic monitoring	Bradypnea (to 5 beats/min) while asleep with apnea of 33 s, P_{CO_2} 64 Torr, and hypoxemia P_{O_2} 46 Torr. "Adequate ventilation when awake"
Gurewitz, 1986	35	1	4 yr	16 yr	Sleep endogenous, awake exogenous CO_2	Neuromuscular responsiveness to CO_2 by mouth occlusion pressure method (normal 0.8–3.3 cmH_2O to P_{CO_2} 42.7–51.3 Torr)	With sleep, subject had central apnea and elevated apnea index. Depressed response to CO_2 by mouth occlusion (0.8–3.2 cmH_2O pressure in response to P_{CO_2} 48–61 Torr)
Proulx, 1993	76	1	4 yr	9 yr	Sleep endogenous, exogenous CO_2 (unspecified if awake or sleep)		With sleep, P_{CO_2} increased to 56 Torr. No ventilatory response to CO_2 (details unavailable)
North, 1993	62	1 of 2	2.3 yr	3.7 yr	Awake/sleep endogenous		Subject had a seizure, which led to respiratory failure; he subsequently "continued to hypoventilate and have apneic episodes" awake and asleep. He received a tracheostomy, but suffered sudden unexpected death a few weeks after weaned from ventilator

Continued

Table 2.—*Continued*

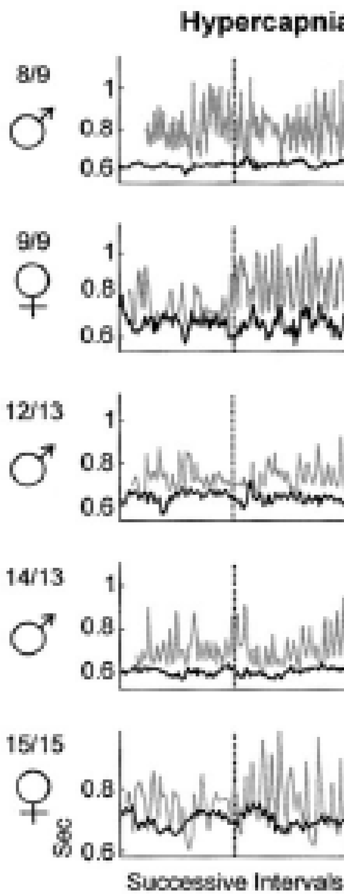
Citation	Ref. No.	*N*	Age at Onset	Age at Test	State & Challenge Method	Metrics	Results & Comments
Ouvrier, 1995	68	1	3.5 yr	3.5 yr	Sleep endogenous	Polysomnography	Central hypoventilation with frequent apneic episodes (details unavailable). After 5 mo, he died of respiratory failure
Del Carmen Sanchez, 1996	17	1 of 2	2.5 yr	3 yr	Awake/sleep endogenous	Monitoring in pediatric intensive care unit	Central sleep apnea; $P_{A_{CO_2}} > 80$ Torr and $Sa_{O_2} < 70\%$. With wakefulness, normal $P_{A_{CO_2}}$ and $P_{A_{O_2}}$
Katz, 2000	43	1	2 yr onset of obesity, 3.5 yr onset of respiratory symptoms	8 yr	Awake endogenous, sleep endogenous, awake exogenous O_2, awake exogenous CO_2	Rebreathing technique	Awake, $P_{ET_{CO_2}}$ 65 Torr and Sa_{O_2} of 98%. With sleep, $P_{ET_{CO_2}}$ increased to 76 Torr and Sa_{O_2} decreased to 81%. With supplemental oxygen, $P_{ET_{CO_2}}$ increased by ~10 Torr. No response to CO_2 (graph in reference demonstrates increase $P_{ET_{CO_2}}$ to 75 Torr without increase in $\dot{V}_E$)
Sirvent, 2002	88	1 of 2	18 mo	3.3 yr			Central and obstructive sleep apnea (details unavailable)
Gothi, 2005	31	1	8 yr	10 yr	Awake endogenous, sleep endogenous	Arterial blood gas, polysomnography	When awake, $P_{A_{CO_2}}$ 36 Torr and $P_{A_{O_2}}$ of 72 Torr. With sleep, the subject had hypopnea (no apnea) with $P_{A_{CO_2}}$ 48–59 Torr and $P_{A_{O_2}}$ 58–78 Torr
Ize-Ludlow, 2007	42	23	Median age: hypothalamic dysfunction 3 yr hypoventilation 6.17 yr		Comprehensive physiological testing for 9 patients; awake endogenous: tachypnea (34 ± 13 beats/min), $P_{ET_{CO_2}}$ 56 ± 7 Torr, SpO_2 89 ± 6%; sleep endogenous: increased $P_{ET_{CO_2}}$ 62 ± 13 Torr, no change in f or V_T; 4 of 9 patients had 24-h mechanical ventilator support	Comprehensive medical record review of 15 subjects of whom 9 subjects had comprehensive physiological testing	Alveolar hypoventilation in 15 patients; obstructive sleep apnea in 5 patients (33%); tracheostomy and mechanical ventilator (24-h/day) in 7 cases (47%) and mask ventilation (night only) in 8 cases (53%). Patients who required 24-h/day ventilation had earlier onset of respiratory manifestations, with median onset at 3.8 yr for 24-h/day vent group, compared with 7.8 yr for nighttime-only ventilation group ($P = .03$). Genetic testing negative for *PHOX2B, TRKB, BDNF*
Bougneres, 2008	10	6	Age range: obesity 1.5–4.3 yr, hypoventilation: 4.3–8.5 yr				No details of respiratory evaluation
De Pontual, 2008	16	12 of 13	0.7–9 yr		Method unknown but for 7 cases tested, response to CO_2 was abnormal (details unavailable)		Excluded subject with onset at birth. 6 of 12 patients required full-time artificial ventilation; 7/13 required ventilatory support during sleep only. Included 6 subjects also reported in Bougneres paper. Genetic testing negative for *PHOX2B, ASCL1, NECDIN*. Reported 5 autoimmune predisposing alleles on evaluation of HLA-DQ complex
Rand, 2009	78	25	2–7 yr		Challenges not conducted; aim was genetics evaluation		Genetic testing negative for *PHOX2B, HTR_{1A}, OTP*

ROHHAD, rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; $P_{ET_{O_2}}$, end-tidal partial pressure of O_2; SpO_2, oxygen saturation from pulse oximetry; Pa_{O_2}, arterial partial pressure of O_2; Pa_{CO_2}, arterial partial pressure of CO_2; $P_{A_{CO_2}}$, alveolar partial pressure of CO_2; $P_{A_{O_2}}$, alveolar partial pressure of O_2; $\dot{V}_E$, minute ventilation; Sa_{O_2}, arterial saturation of O_2; *TRKB*, tropomyosin-related kinase B; *BDNF*, brain-derived neurotrophic factor; *ASCL1*, achaete-scute complex 1; *NECDIN*, neurally differentiated embryonal carcinoma-derived protein; HLA-DQ, human leukocyte antigen-DQ; HTR_{1A}, 5-hydroxytryptamine (serotonin) receptor 1A; *OTP*, orthopedia.

Arritmia sinusal respiratoria promedio

Temporal ... y Responses to ... ital Centr...

Figure 1. Plots of successive cardiac RR (interbeat) intervals



12 CC

•Edad

10.9

10.9

Table 1. ... averaged during

	CCHS (n = 7)
Baseline	53 ± 5.7
Hypercapnia	56.4 ± 6.9
Hypoxia	52.4 ± 4.8
Hyperoxia	49.2 ± 3.3

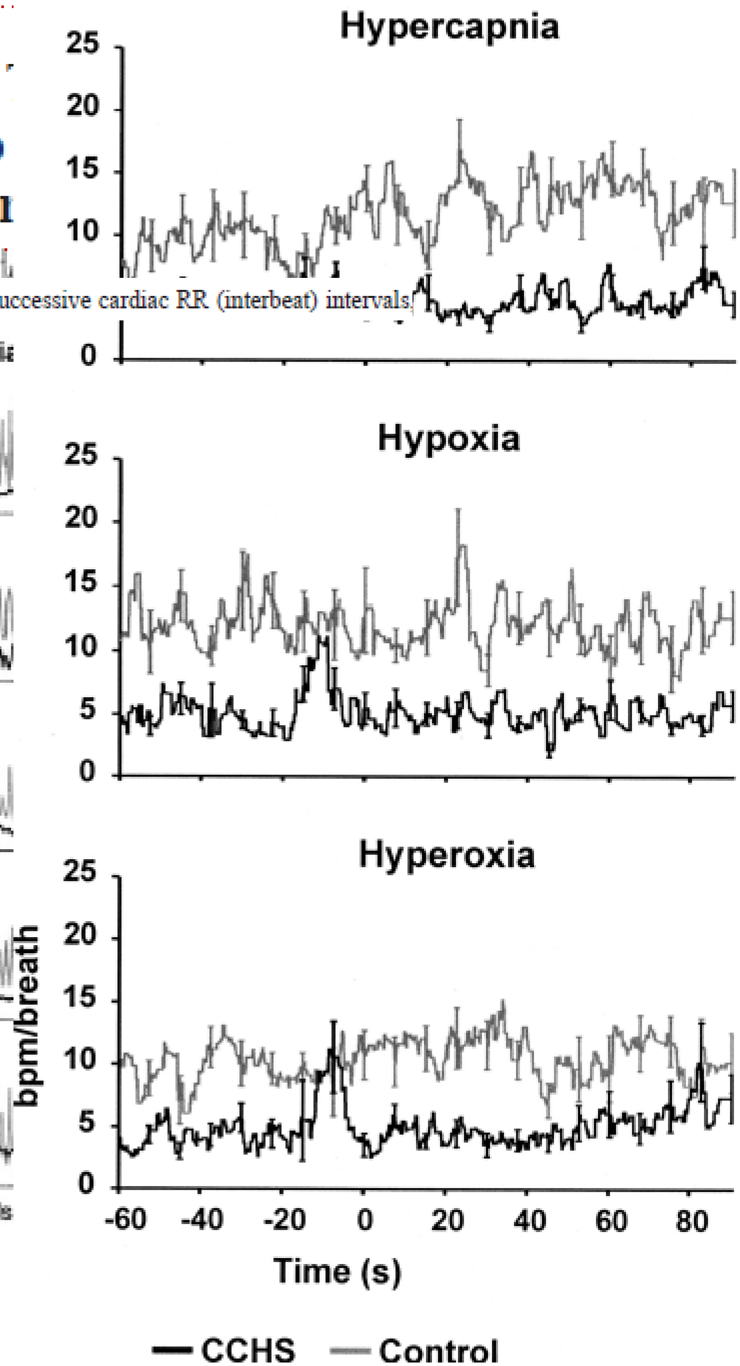
Prue

Aire a

Hiper

Hipox

Hiper



at. Pediatric Research 2004

Residual chemosensitivity to ventilatory challenges in genotyped congenital central hypoventilation syndrome

HACC genéticamente confirmados/controles: 32/15
Edad media 9 a ± 9 m (8m-29a) /23 a 8 m (18 a-26a)

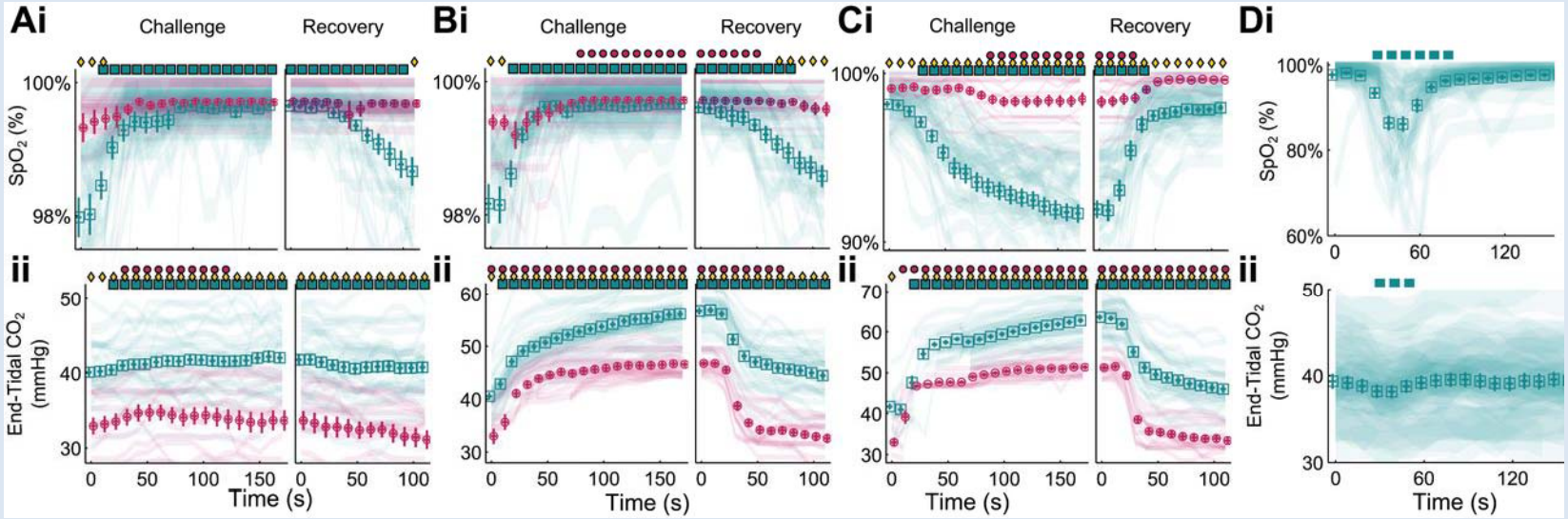
Respiratory gas measurements during ventilatory challenges and recovery for 4 different mixtures

Hiperoxia (100%O2)

Hipercapnia hiperoxica
5%CO2-95%O2

Hipercapnia hipoxica
CO2/%-14%O2

Hipoxia
N2 100%



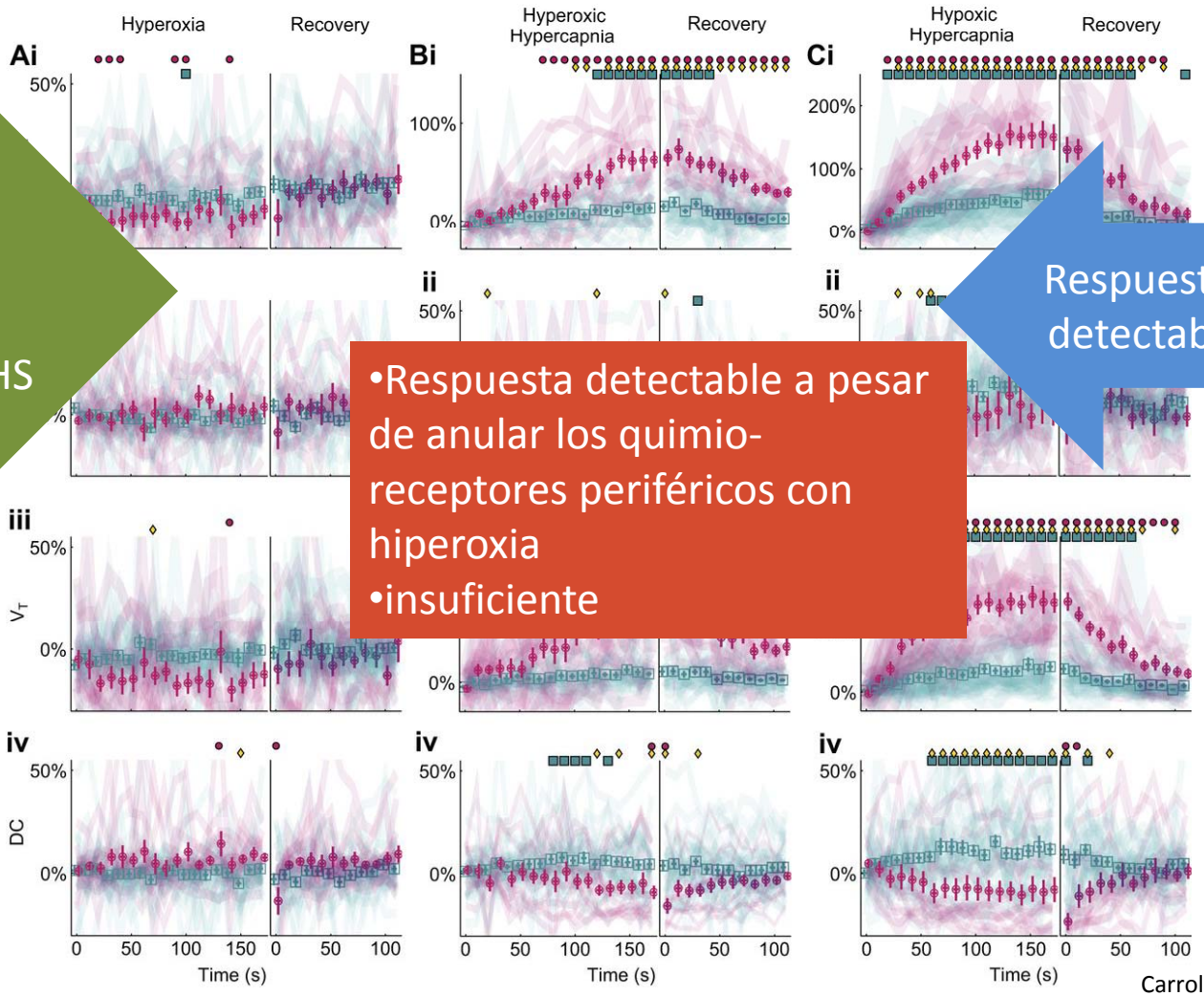
Michael S. Carroll et al. J Appl Physiol 2014

Residual chemosensitivity to ventilatory challenges in genotyped congenital central hypoventilation syndrome

Hiperoxia (100%O2)

Hipercapnia hiperoxica
5%CO2-95%O2

Hipercapnia hipoxica
CO2/%-14%O2



Ausencia de depresión ventilatoria post hiperoxia en CCHS

•Respuesta detectable a pesar de anular los quimio-receptores periféricos con hiperoxia
•insuficiente

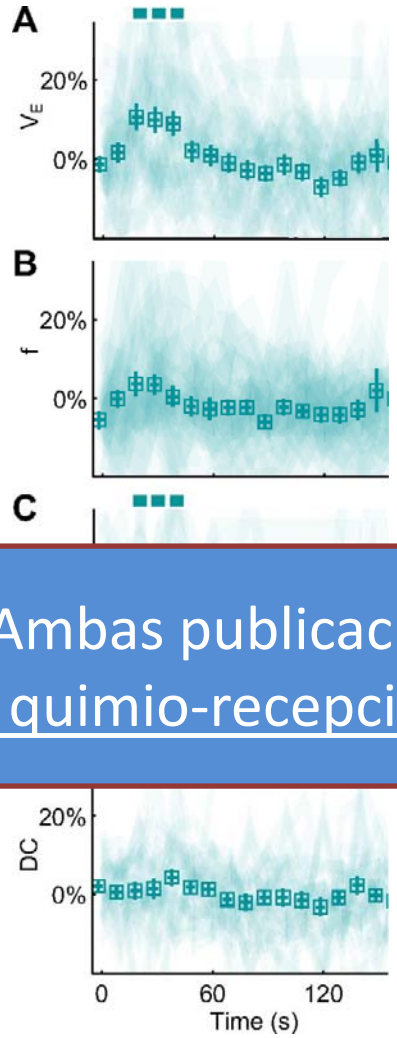
Respuesta leve pero detectable en CCHS

Carroll M et al. J Appl Physiol 2014

Residual chemosensitivity to ventilatory challenges in genotyped congenital central hypoventilation syndrome

Respuesta respiratoria a 5 o 7 VT of 1 de 100% N2 (at time = 0)

Respuesta hipoxia
Sutil pero detectable

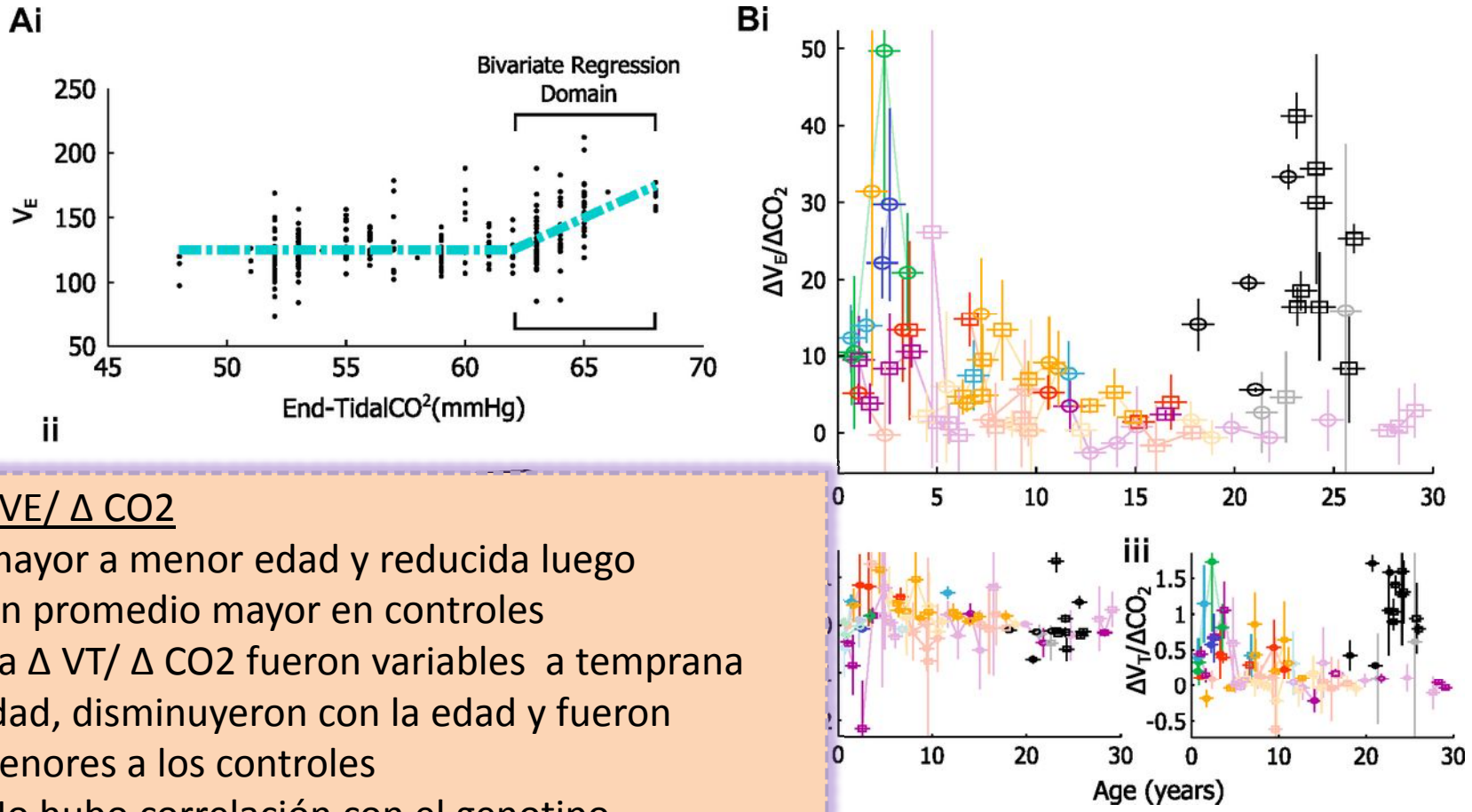


Peripheral chemoreceptor function in children with CCHS.
Gozal et al. JAP 2003
Respuestas ventilatorias a la hiperoxia similares entre 5 pacientes y controles

Ambas publicaciones
Hipótesis sobre una quimio-recepción periférica conservada

Michael S. Carroll et al. J Appl Physiol 2014;116:439-450

Ventilatory and cardio/cerebrovascular response sensitivity to gas challenge, as characterized by slope values for variables against EtCO2 during hypercapnic challenges.



Δ VE/ Δ CO2

- mayor a menor edad y reducida luego
- En promedio mayor en controles
- La Δ VT/ Δ CO2 fueron variables a temprana edad, disminuyeron con la edad y fueron menores a los controles
- No hubo correlación con el genotipo
- Punto de inflexion > CCHS (52 ± 1 vs 43,2 ± 1.7 mmHg)

Michael S. Carroll et al. J Appl Physiol 2014;116:439-450

Residual chemosensitivity to ventilatory challenges in genotyped congenital central hypoventilation syndrome

Nominally steady-state responses to ventilatory challenges in CCHS and a comparison group in ventilatory, cardiovascular, and cerebrovascular measures.

	Hyperoxia			Hyperoxic Hypercapnia			Hypoxic Hypercapnia			Hypoxia
	CCHS	Control		CCHS	Control		CCHS	Control		CCHS
Measure	Mean ± SE	Mean ± SE	Sig.	Mean ± SE	Mean ± SE	Sig.	Mean ± SE	Mean ± SE	Sig.	Mean ± SE
Ventilatory										
SpO_2	**99.5 ± 0.1**	**99.7 ± 0.1**	NS	**99.6 ± 0.1**	**99.7 ± 0.1**	NS	**93.2 ± 0.5**	**98.6 ± 0.3**	$P < 0.005$	**92.46 ± 1.08**
$EtCO_2$	**41.54 ± 0.76**	**33.98 ± 1.20**	$P < 0.005$	**53.77 ± 0.63**	**45.68 ± 0.54**	$P < 0.005$	**60.31 ± 0.57**	**50.26 ± 0.50**	$P < 0.005$	**38.21 ± 0.82**
V_E	−3.99 ± 1.98	−12.51 ± 4.14	NS	**+9.80 ± 2.44**	**+42.90 ± 7.94**	$P < 0.005$	**+44.41 ± 5.70**	**+119.94 ± 14.51**	$P < 0.005$	**+9.97 ± 2.22**
f	−1.97 ± 1.42	+1.13 ± 3.71	NS	+2.98 ± 1.66	−1.77 ± 3.80	NS	**+13.06 ± 2.94**	+0.33 ± 7.25	NS	**+7.19 ± 2.08**
V_T	−1.58 ± 1.21	−12.63 ± 4.11	NS	**+7.60 ± 2.35**	**+49.12 ± 10.56**	$P < 0.005$	**+30.60 ± 5.58**	**+123.00 ± 12.43**	$P < 0.005$	+2.60 ± 1.99
Drive	−3.44 ± 1.40	−16.48 ± 4.93	NS	+5.15 ± 2.40	**+50.03 ± 9.89**	$P < 0.005$	**+34.38 ± 6.13**	**+140.85 ± 15.61**	$P < 0.005$	**+7.51 ± 1.98**
T_I	+2.55 ± 1.13	+9.04 ± 6.21	NS	+2.62 ± 1.53	−1.67 ± 2.64	NS	−1.81 ± 1.70	−6.09 ± 4.19	NS	−3.60 ± 1.39
T_E	**+6.73 ± 3.07**	−2.04 ± 4.64	NS	−3.95 ± 2.00	+12.66 ± 5.57	$P < 0.005$	**−12.16 ± 3.17**	**+24.56 ± 10.16**	$P < 0.005$	−8.14 ± 2.89
DC	−0.73 ± 1.14	+6.18 ± 2.30	$P < 0.005$	+5.15 ± 1.64	−4.29 ± 3.05	NS	**+10.40 ± 2.75**	−8.01 ± 5.13	$P < 0.005$	+2.31 ± 1.65
Cardiovascular										
HR	**−2.71 ± 0.47**	**−6.21 ± 0.86**	$P < 0.005$	−0.14 ± 0.96	+1.04 ± 2.27	NS	**+7.41 ± 2.07**	**+15.64 ± 2.82**	NS	+2.50 ± 0.91
SDNN	**+54.62 ± 23.39**	+9.37 ± 5.67	NS	**+49.05 ± 11.72**	**+63.30 ± 19.77**	NS	**+51.33 ± 16.86**	**+63.30 ± 19.77**	NS	+0.56 ± 1.82
MBP	+1.09 ± 1.01	+0.96 ± 0.83	NS	+2.72 ± 1.38	**+7.41 ± 1.53**	NS	**+9.24 ± 2.45**	**+14.77 ± 2.46**	NS	+27.97 ± 12.28
VLF	+4.57 ± 5.32	+6.41 ± 9.26	NS	+10.37 ± 5.65	−14.53 ± 13.40	NS	−13.06 ± 5.32	−14.42 ± 16.62	NS	+19.43 ± 6.50
LF	+1.84 ± 4.31	−3.02 ± 5.09	NS	+3.11 ± 3.67	**−27.79 ± 6.01**	$P < 0.005$	−4.92 ± 4.98	**−39.43 ± 4.45**	$P < 0.005$	−0.56 ± 3.65
RF	+4.99 ± 4.07	+15.90 ± 12.08	NS	+2.75 ± 4.48	+40.24 ± 14.77	NS	+15.82 ± 6.50	**+73.39 ± 18.60**	$P < 0.005$	−1.59 ± 5.57
LF:RF	+5.53 ± 7.35	−3.44 ± 11.21	NS	+7.98 ± 5.75	**−38.95 ± 8.78**	$P < 0.005$	−8.86 ± 6.88	**−54.48 ± 8.60**	$P < 0.005$	+14.29 ± 9.17
Cerebrovascular										
cNIRS	**+8.54 ± 1.32**	**+4.58 ± 0.86**	$P < 0.005$	**+10.03 ± 1.44**	**+12.06 ± 2.09**	NS	−1.32 ± 1.00	**+3.99 ± 1.10**	$P < 0.005$	**−8.05 ± 1.43**

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Respiratory abnormalities may occur as part of a broader disease phenotype, for instance in Prader-Willi syndrome, Rett syndrome, or Riley-Day syndrome. Patients with Prader-Willi syndrome exhibit sleep-disordered breathing with apnoeas and episodes of hypoventilation [67]. Furthermore, patients with Prader-Willi syndrome have reduced ventilatory responses to hypoxia with absent peripheral chemoreceptor responses [41]. Severe blunting of carbon dioxide chemosensitivity is only an occasional finding that may be related to obesity, which is a feature of Prader-Willi syndrome [3]. Rett syndrome is characterized by an abnormal breathing pattern with episodes of hyperventilation followed by central apnoea and oxygen desaturation during wakefulness, contrasting with the absence of patent respiratory abnormalities during sleep [56]. The respiratory abnormalities emerge during early childhood [97]. Abnormalities in heart rate and baroreflex control also occur in Rett syndrome [48; 99]. Therefore, autonomic dysfunction may account for the high risk of sudden death in girls with Rett syndrome. Finally, abnormal ventilatory and cerebrovascular responses to hypoxia have been reported in patients with Riley-Day syndrome or familial dysautonomia [7].

Arens R, Gozal D, Omlin KJ, Livingston FR, Liu J, Keens TG, Ward SL (1994) Hypoxic and hypercapnic ventilatory response in Prader-Willi syndrome. J Appl Physiol 77: 2231-2236

Arens R, Gozal D, Omlin KJ, Livingston FR, Liu J, Keens TG, Ward SL (1994) Hypoxic and hypercapnic ventilatory response in Prader-Willi syndrome. J Appl Physiol 77: 2231-2236

41. Gozal D, Arens R, Omlin KJ, Davidson-Ward SL, Keens TG (1994) Absent peripheral chemosensitivity in Prader-Willi syndrome. J Appl Physiol 77: 2231-2236

67. Nixon GM, Brouillette RT (2002) Sleep and breathing in Prader-Willi syndrome. Pediatr Pulmonol 34: 209-217

CONCLUSIÓN

- El control de la ventilación depende de un controlador central, aferencias y efectores.
- Los estudios en ratones PHOX2B han demostrado que la ausencia heterocigota del gen o su mutación afectan el ritmo respiratorio y las respuestas ventilatorias
- En humanos, es claro que la mutación afecta el control central y en cierta medida periférico de la ventilación, sin embargo la detección de una sensibilidad ventilatoria residual abre puertas a tratamientos que aumenten la ganancia de estos circuitos