ΕΛΕΓΧΟΣ ΤΗΣ ΑΝΑΠΝΟΗΣ

ΚΩΣΤΗΣ ΠΟΝΤΙΚΗΣ

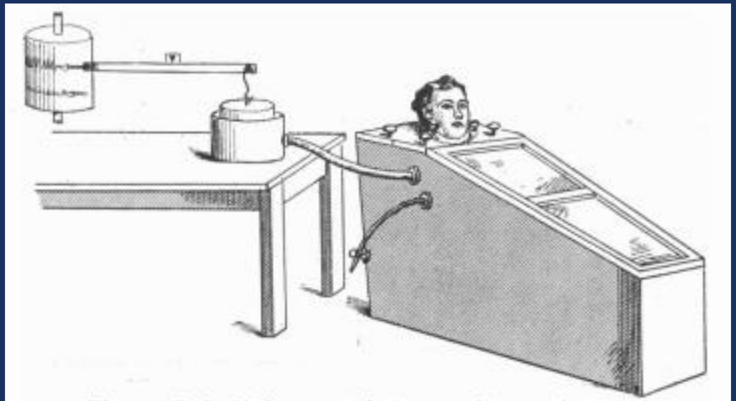


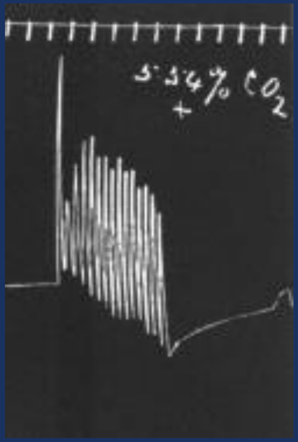
Fig. 2. Body-Plethysmograph for recording respiration.

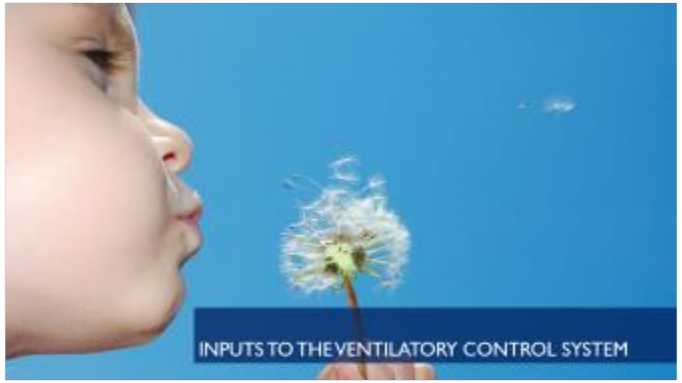
THE REGULATION OF THE LUNG-VENTILATION.

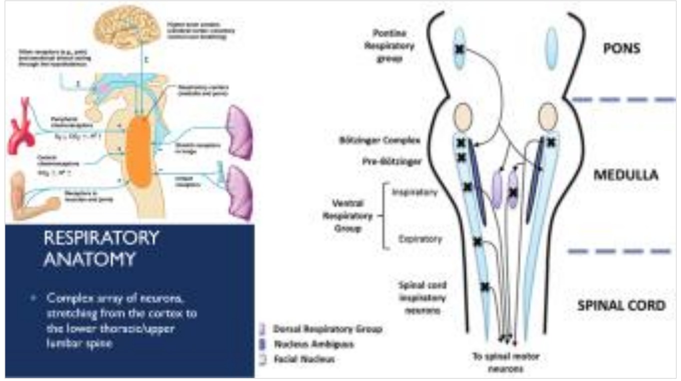
By J. S. HALDANE, M.D., F.R.S., and J. G. PRIESTLEY, B.A.
(Eleven Figures in the Text.)

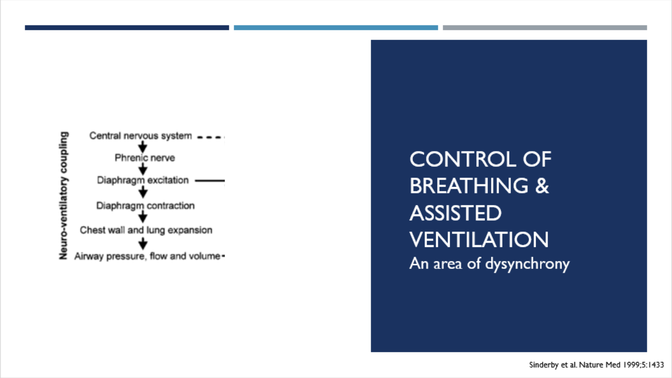
(*From the Physiological Laboratory, Oxford.*)

CONTENTS.









CONCLUSIONS

- Ventilatory control aims at achieving stable PaO2, PaCO2 and pH throughout various circumstances during life
- This task is achieved through complex neural networks, scattered throughout the CNS, but mostly in the medulla
- Three sources of input: chemoreceptors, mechanoreceptors, central command
- Different inputs predominate in different circumstances
  - Chemoreception in non-REM sleep
  - Central command in exercise and REM sleep
- High loop gain systems are unstable (instability expressed as periods of hypoventilation and periods of hyperventilation)
- Control of breathing is active during assisted mechanical ventilation and necessitate patient-ventilator synchrony (operator's mind)
- Novel technologies in the area of patient-ventilator synchrony are promising

PURPOSE OF VENTILATORY CONTROL SYSTEM

PURPOSE OF VENTILATORY CONTROL SYSTEM

- Regulation of exchange of respiratory and blood gases, particularly arterial $PaCO_2$, and maintenance of acid-base status within a relatively narrow range

Table 2
Normative arterial blood gas values

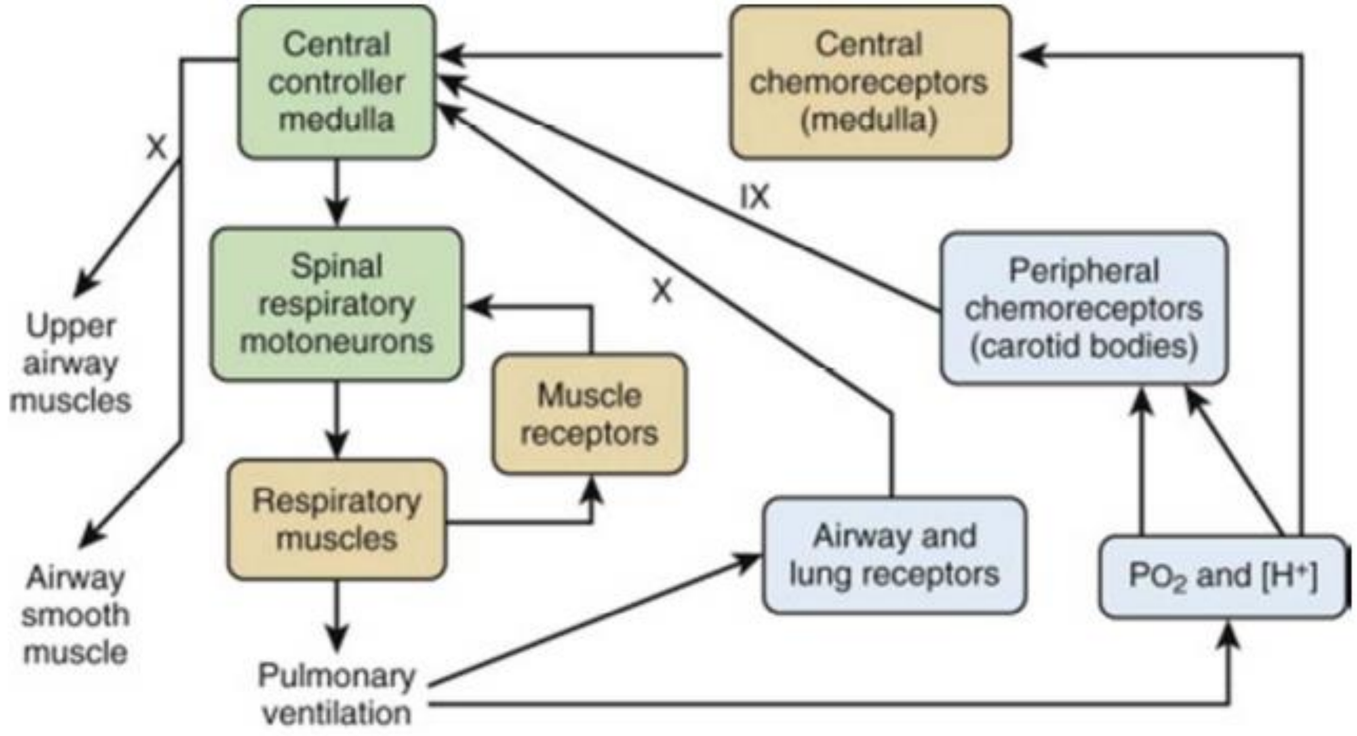
Blood Gas Analyte	Normal Ranges	Value Meaning and Interpretation
Arterial carbon dioxide partial pressure ($Paco_2$)	35–45 mm Hg	An indicator of metabolic production of CO_2. Hypercapnia refers to an elevated $Paco_2$ owing to hypoventilation. Hypocapnia refers to a reduced $Paco_2$ owing to hyperventilation.
Arterial oxygen partial pressure (Pao_2)	75–100 mm Hg	Intermittent or sustained reductions in Pao_2 indicate poor oxygenation or hypoxemia.
pH	7.34–7.44	Hydrogen ion concentration [H^+]. Increased levels result in alkalemia (pH>7.45). Decreased levels result in acidemia (pH<7.35).
H^+	35–45 nmol/L	H^+ >45: acidemic or H^+ <35: Alkalemic.
HCO_3^-	22–26 mEq/L	Bicarbonate ion (HCO_3^-) is a blood CO_2-buffering electrolyte. Low HCO_3^- results in metabolic acidosis. High HCO_3^- results in metabolic alkalosis.

- while minimizing the work & metabolic cost of each breath

Sowho et al. Clin Chest Med 2014; 35:469
Dempsey. ERJ 2014; 44:495

OVERVIEW OF THE VENTILATORY CONTROL SYSTEM

- Simple purpose: Control of
  - pH
  - pCO2
  - pO2
- Complex process
- Central & peripheral chemoreceptors
- Proprioceptive information (Peripheral pulmonary stretch receptors)
- Central command (not depicted)



Howell & Newman. Muscle Nerve 2017;56:197

PRE-REQUISITES OF AN EFFECTIVE VENTILATORY CONTROL SYSTEM

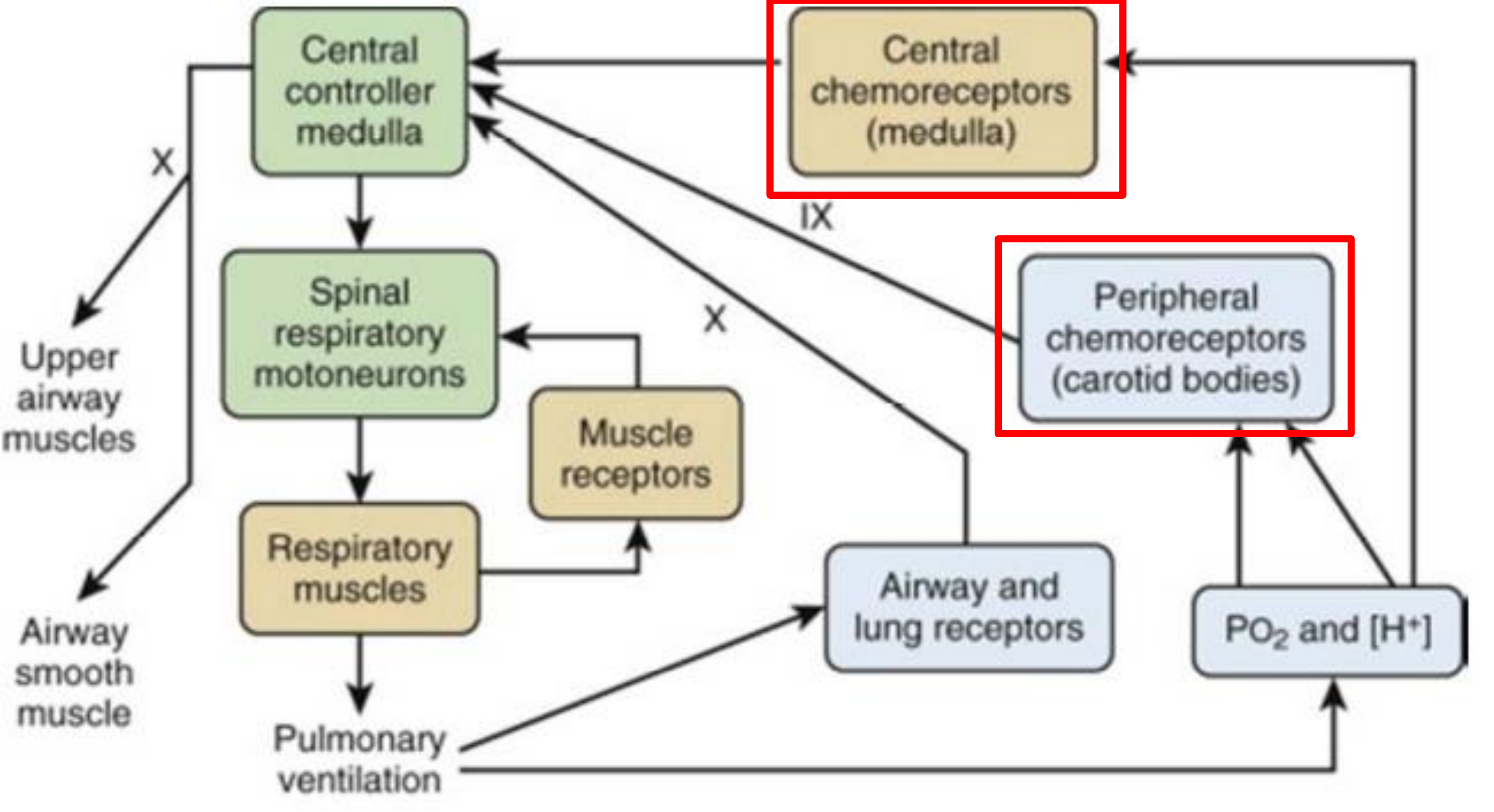
(central medullary) rhythm/pattern generator & integrator

extensive sensory inputs to the central integrator

precise synchronous distribution of motor output

- respiratory musculature of upper airways
- chest & abdominal wall musculature

Dempsey. ERJ 2014; 44:495



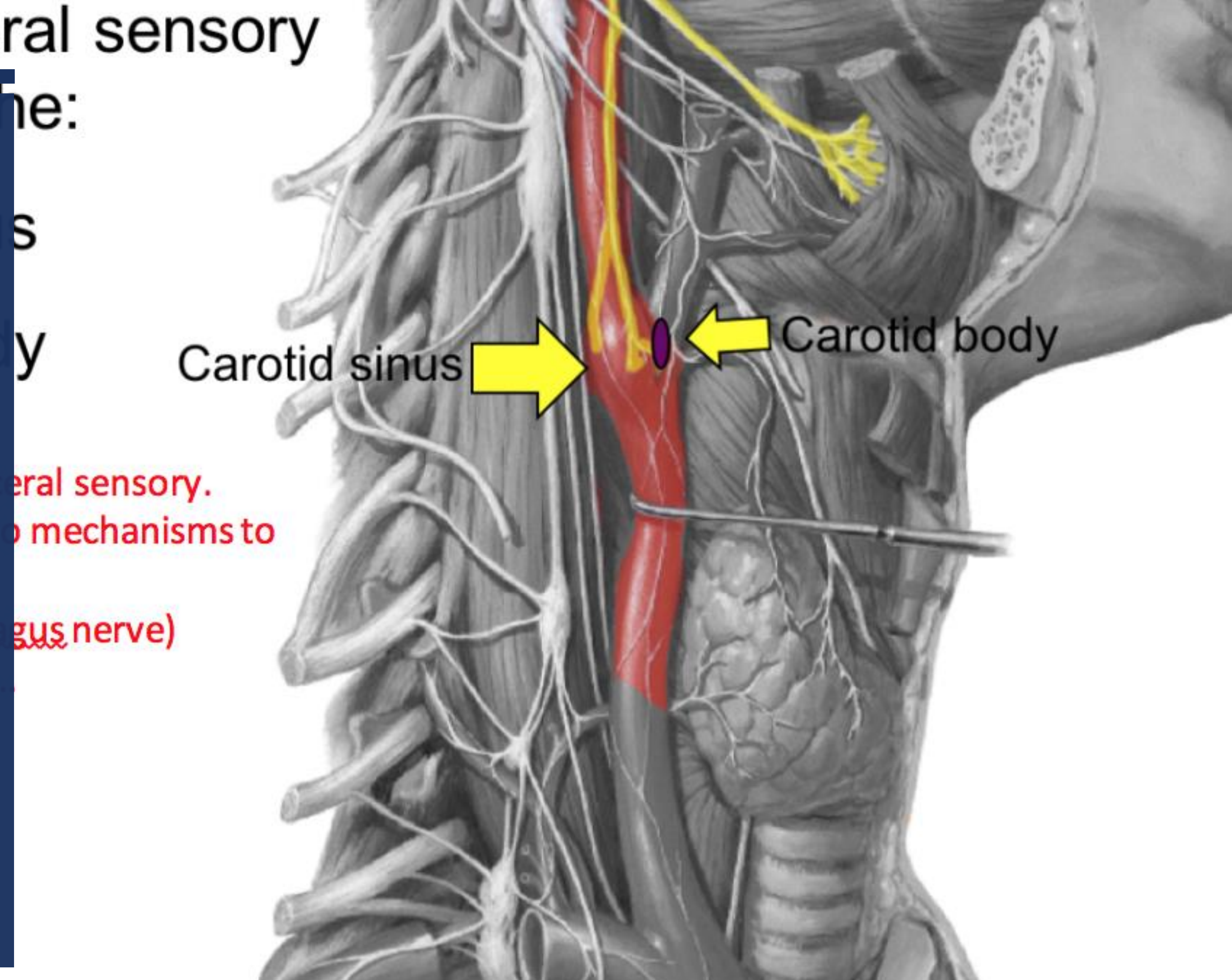
Central controller medulla
Central chemoreceptors (medulla)
Spinal respiratory motoneurons
Muscle receptors
Respiratory muscles
Peripheral chemoreceptors (carotid bodies)
Airway and lung receptors
PO2 and [H+]
Upper airway muscles
Airway smooth muscle
Pulmonary ventilation
X
X
IX

INPUTS TO THE VENTILATORY CONTROL SYSTEM

Corneille Heymans (1892-1968)

CAROTID BODY

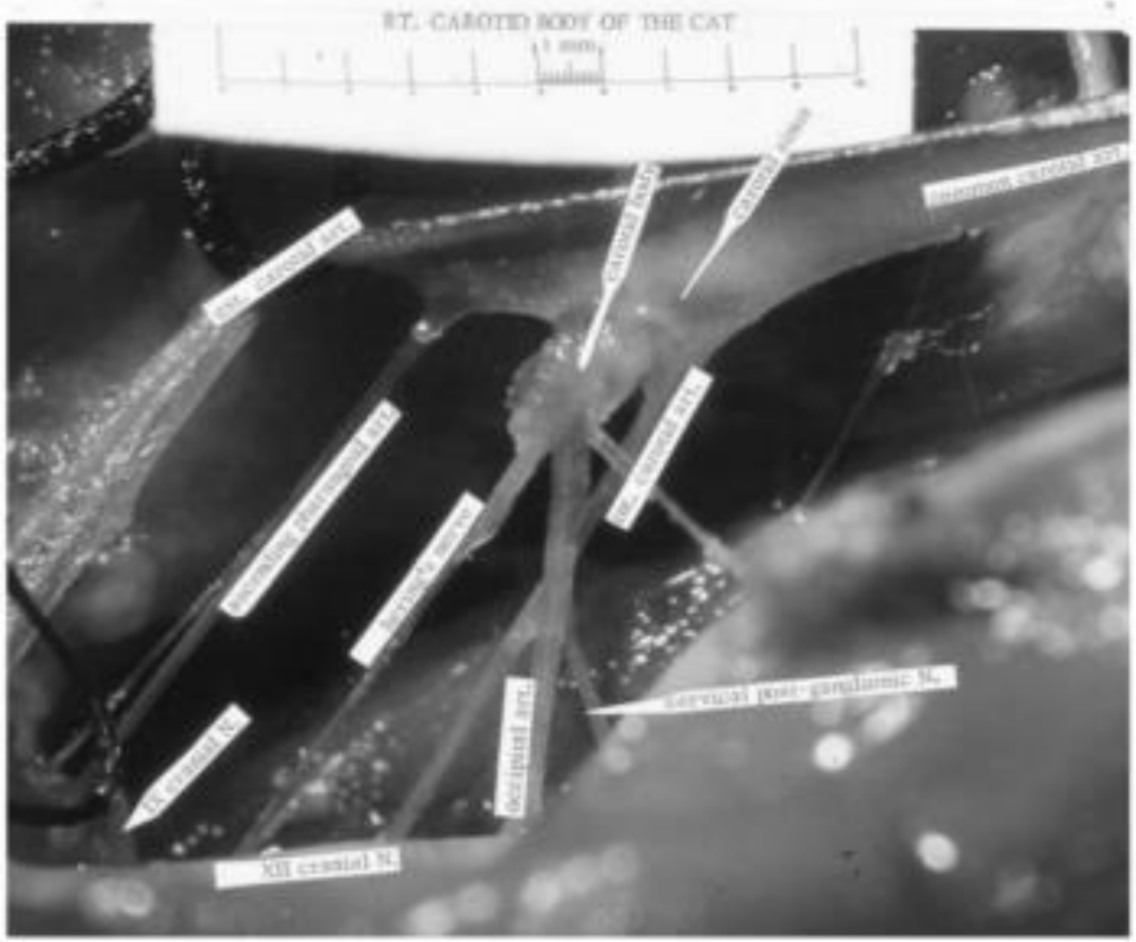
- Located in bifurcation of carotid artery
- Highly vascular
- Highly sensitive to PaO_2, $PaCO_2$ and pH glomus cells
- Interconnected with central chemoreceptors



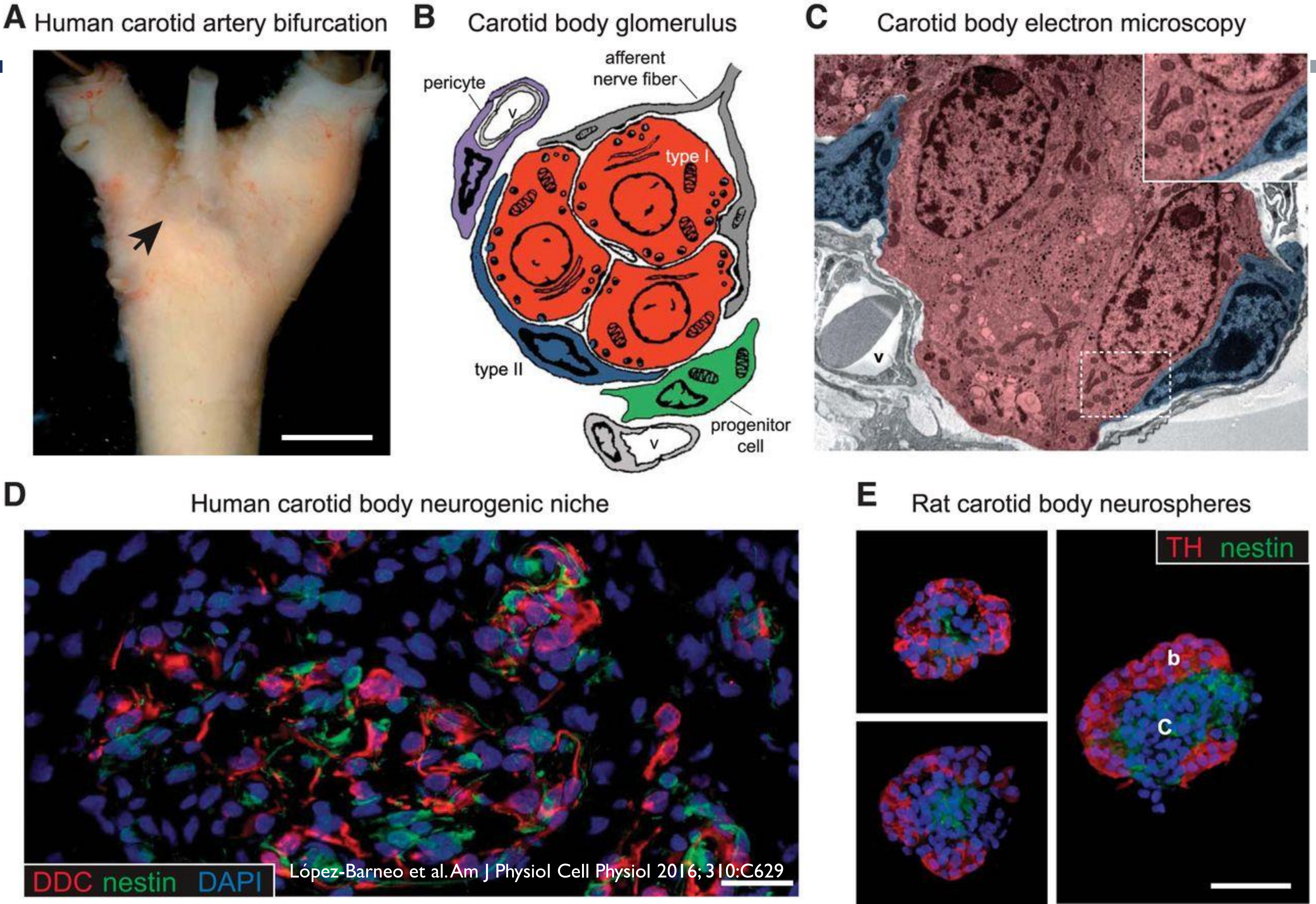
Sowho et al. Clin Chest Med 2014; 35:469
Chowdhuri & Badr. Chest 2017;151:917

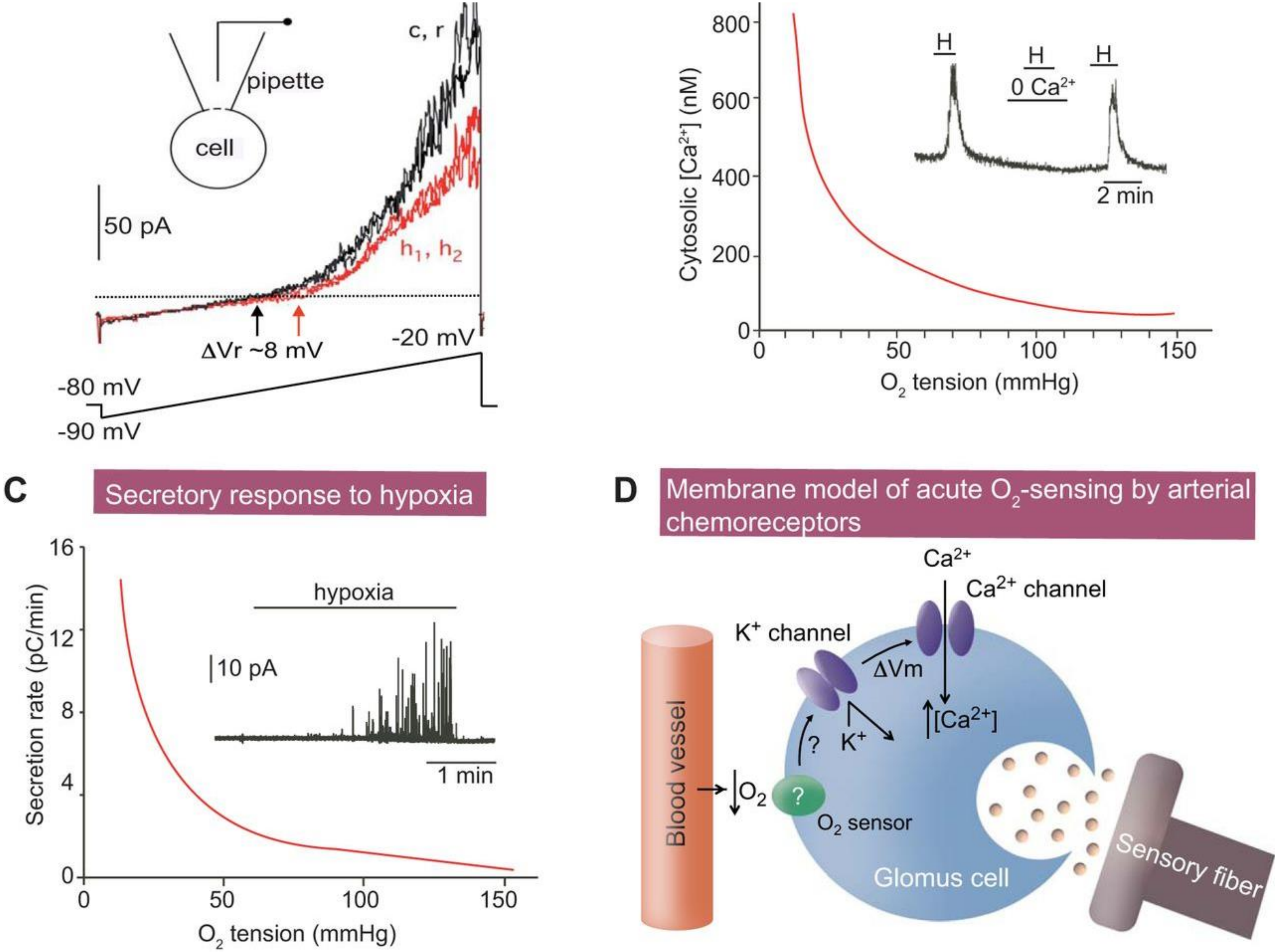
CAROTID BODY CHEMORECEPTION

- Polymodal receptors
  - O_2
  - CO_2
  - H^+
  - K^+
  - norepinephrine
  - temperature
  - osmolarity
  - glucose/insulin
  - blood flow
- Effectors of
  - Ventilation
  - Sympathetic vasoconstrictor outflow



Dempsey. ERJ 2014; 44:495


A Human carotid artery bifurcation
B Carotid body glomerulus
pericyte
afferent nerve fiber
v
type I
type II
progenitor cell
C Carotid body electron microscopy
v
D Human carotid body neurogenic niche
DDC nestin DAPI
E Rat carotid body neurospheres
TH nestin
b
c
López-Barneo et al. Am J Physiol Cell Physiol 2016; 310:C629



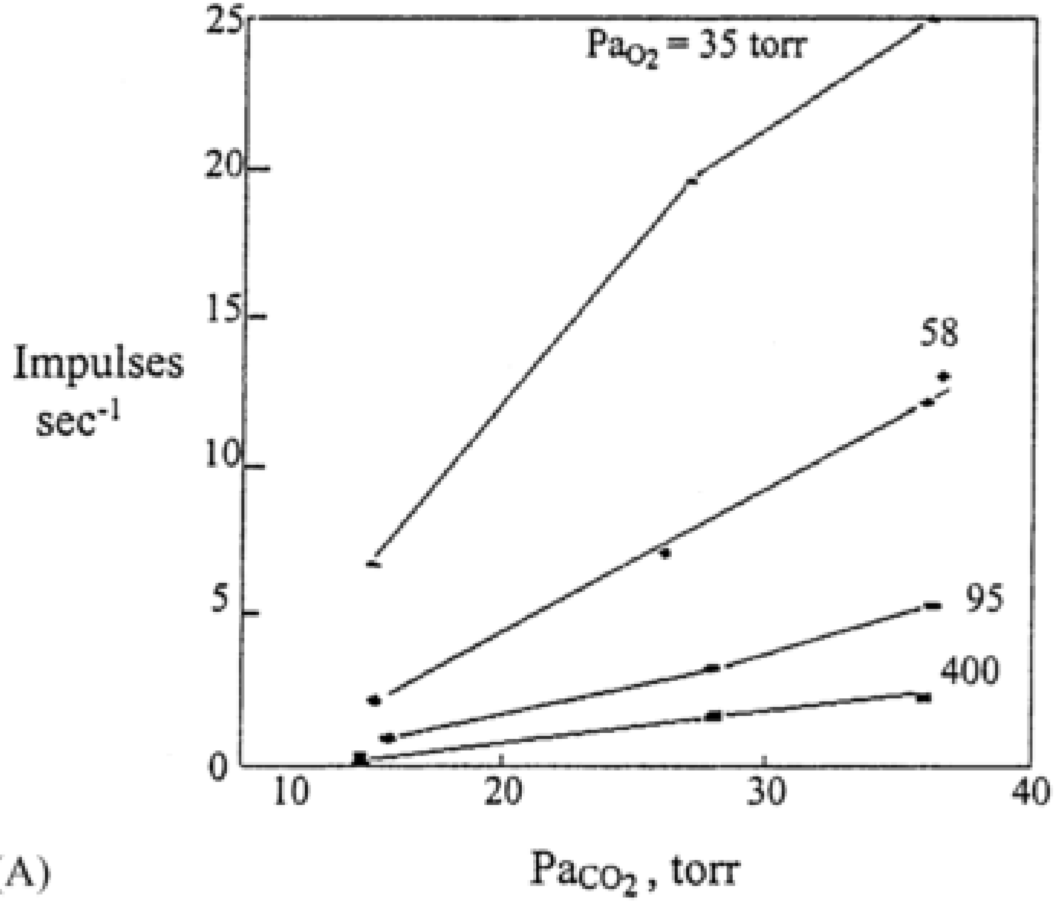
CAROTID BODY FUNCTION

OXYGEN SENSING

López-Barneo et al. Am J Physiol Cell Physiol 2016; 310:C629

CAROTID BODY FUNCTION

RESPONSE TO CO_2



(A)

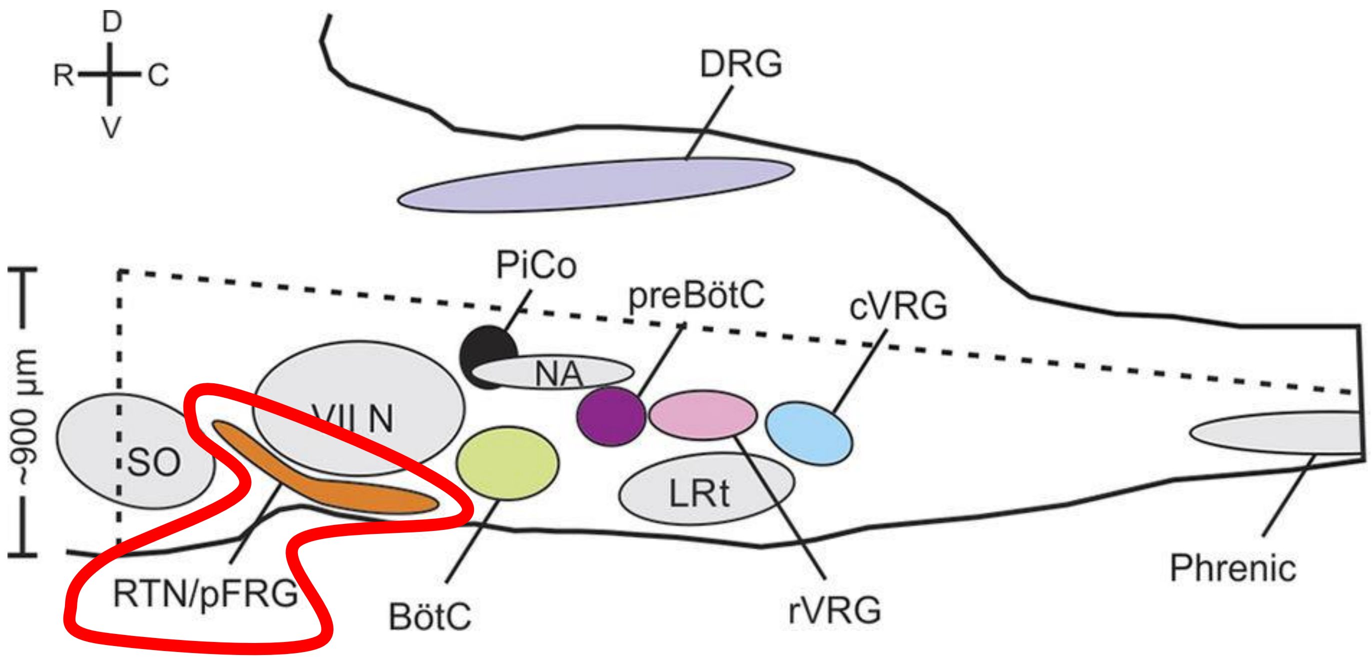
Modified from *Respir. Physiol.* 24, 249-266, 1975.

Effects on carotid chemoreceptors activities of $PaCO_2$ changes, at given levels of PaO_2

Lahiri & Forster. Int J Biochem Cell Biol 2003; 35:1413

CENTRAL CHEMORECEPTION

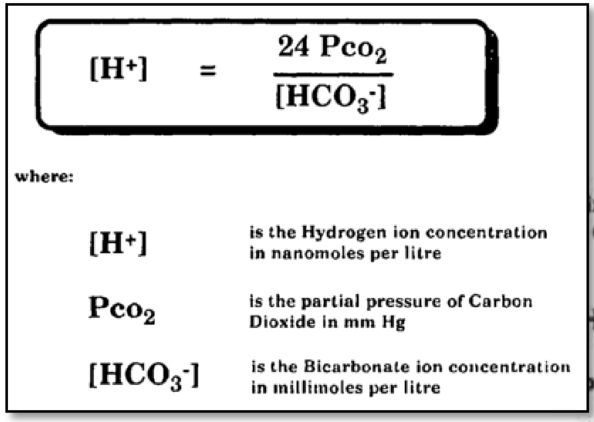
- **Retrotrapezoid nucleus/parafacial region** (central chemoreceptors)
- **Botzinger complex** (expiratory neurons that modulate respiratory rhythm)
- **Pre-BotC** (core respiratory rhythm-generating circuit)
- **Rostral VRG** (inspiratory activities control)
- **Caudal VRG** (expiratory activities control)



Moreira & Mulkey. J Physiol 2015; 593: 1065
Anderson et al. Nature 2016; 536:76

RETROTRAPEZOID NUCLEUS pH SENSING

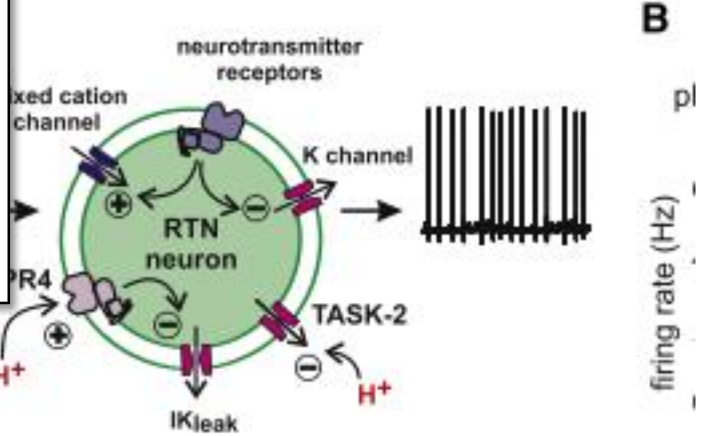
- $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3$
- effects of CO_2 on breathing are presumably mediated via changes in $[H^+]$
- (at least) two molecular proton detectors:
  - TASK-2
  - GPR4

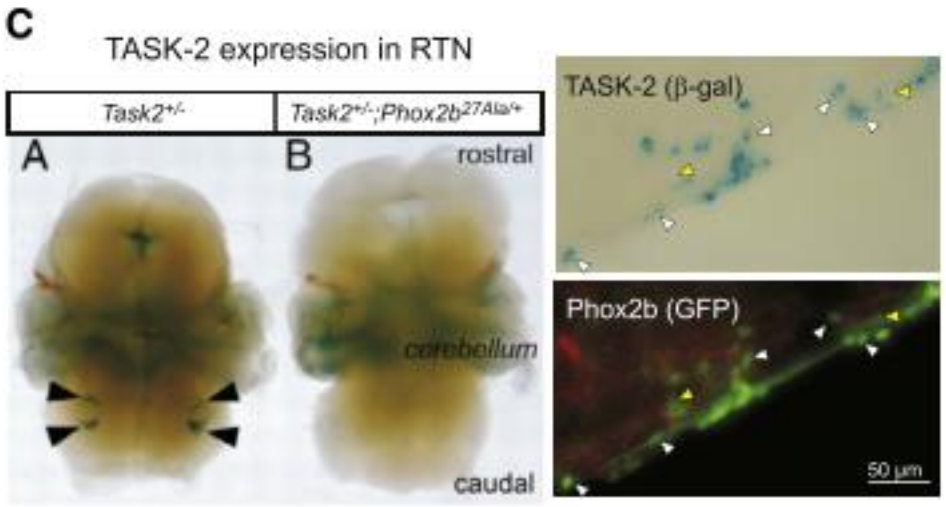


$$[H^+] = \frac{24\ Pco_2}{[HCO_3^-]}$$

where:

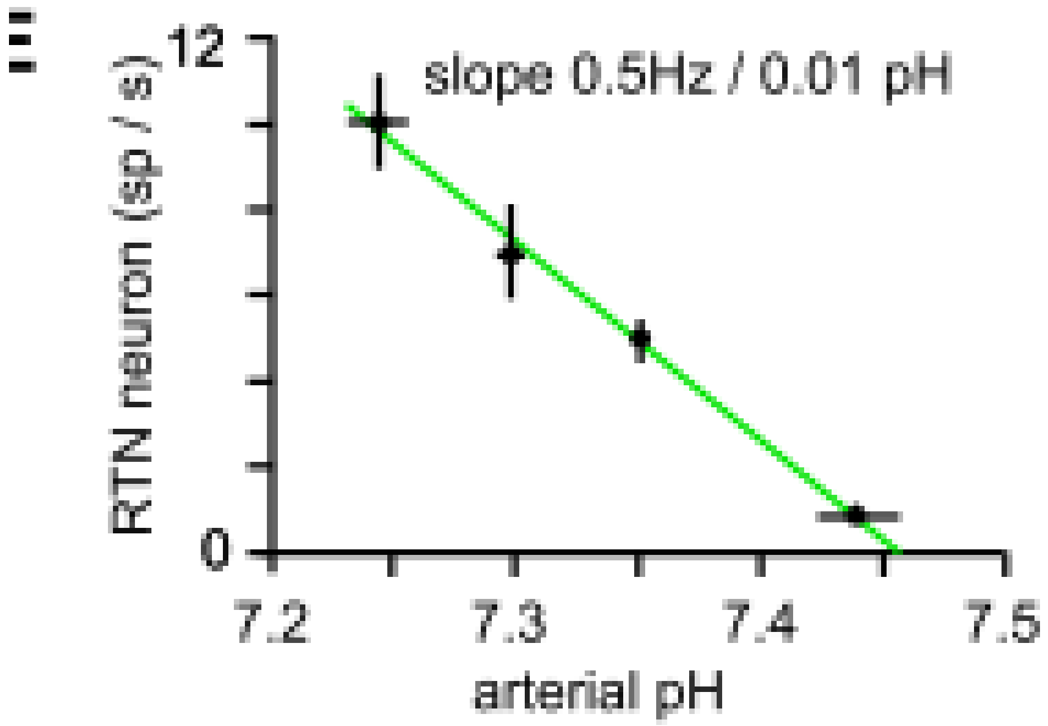
$[H^+]$	is the Hydrogen ion concentration in nanomoles per litre
Pco_2	is the partial pressure of Carbon Dioxide in mm Hg
$[HCO_3^-]$	is the Bicarbonate ion concentration in millimoles per litre





Guyenet & Bayliss. Neuron 2015; 87:946
Duffin. Can J Anaesthesia 1990;37:933

RETROTRAPEZOID NUCLEUS



- This picture shows the current generated by RTN neurons according to pH (Low pH → High current)

Guyenet & Bayliss. Neuron 2015; 87:946

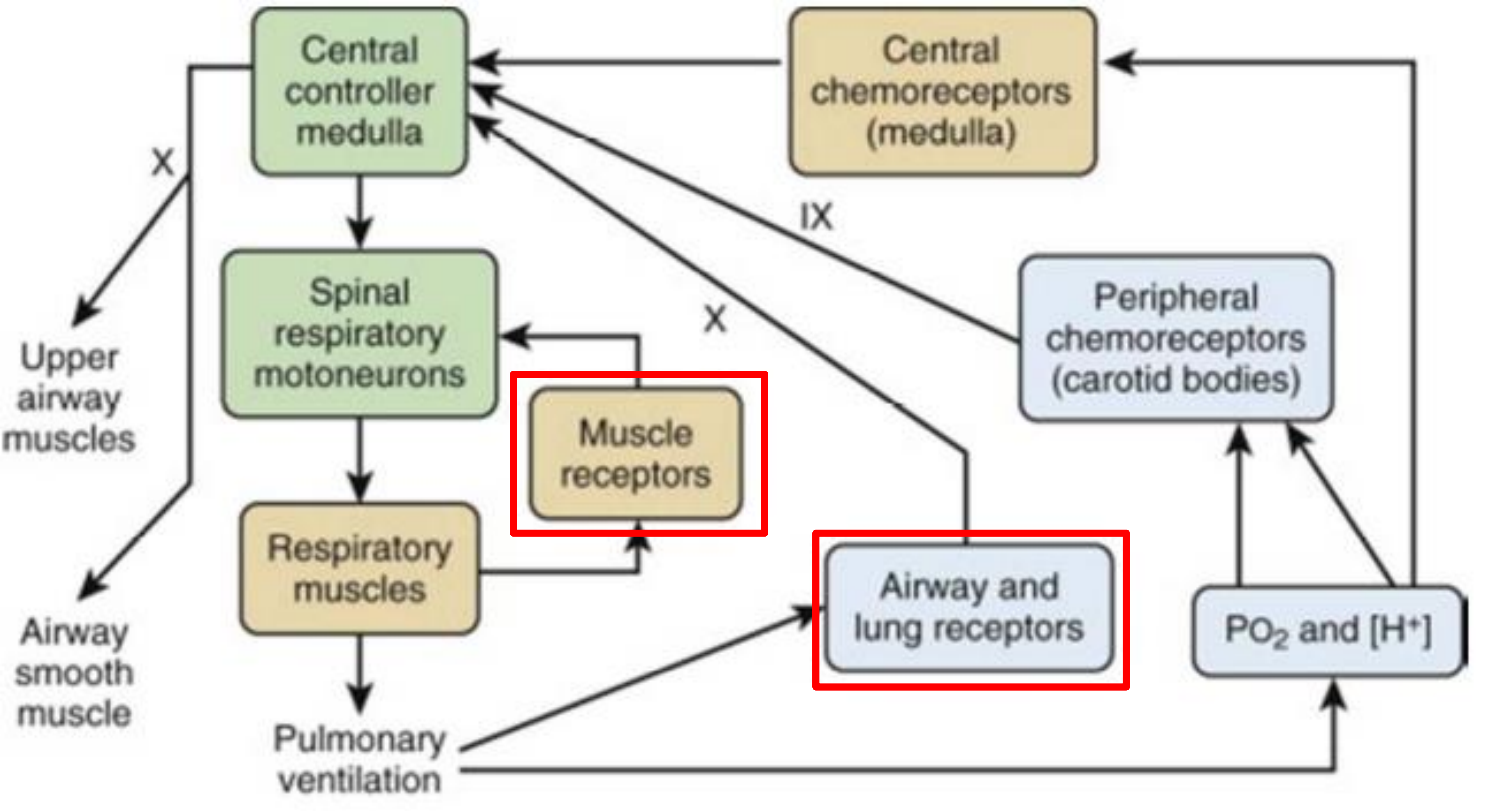

Central controller medulla
Central chemoreceptors (medulla)
X
IX
X
Spinal respiratory motoneurons
Peripheral chemoreceptors (carotid bodies)
Upper airway muscles
Muscle receptors
Respiratory muscles
Airway and lung receptors
PO2 and [H+]
Airway smooth muscle
Pulmonary ventilation

Table 3
Chemoreceptors and mechanoreceptors of the respiratory system

	Sensor Type	Location	Action
Chemoreceptors			
Central	pH-sensitive membrane bound proteins	Ventrolateral medulla	Signal respiratory efferent neurons for control of eupneic breathing; contribute to ~75% of the ventilatory response to small change in Pa_{CO_2}
Peripheral	Glomus cells sensitive to Pa_{O_2}, pH, and Pa_{CO_2} sensitive	Carotid body, aortic body	Combined ~25% of the chemical control of ventilation; afferent signal of glossopharyngeal and vagus nerves
Lung and airway mechanoreceptors			
Stretch	Myelinated afferent fibers sensitive to pressure	Airway smooth muscle and extrapulmonary airway	Increased firing by elevated bronchial transmural pressure; afferent transmission via vagus nerve
Irritant	Myelinated afferent fibers stimulated chemically by nitrogen dioxide, sulfur dioxide, ammonia, inhaled antigens	Airway epithelial cells	Cough, bronchoconstriction, apnea and glottal closure
Unmyelinated C fibers	Unmyelinated afferent fibers and local receptors stimulated by chemical irritants	Lung interstitium and alveolar walls	Vagal afferent signal causing irritation, burning and choking sensations; localized vasodilation and mucosal swelling
Chest wall mechanoreceptors			
Joint	Receptors responding to deep pressure, stress or change in position	Joint capsules and associated ligaments	Proprioception of rib movement during inspiration and expiration
Muscle spindle	Stretch-sensitive nerve fibers imbedded in muscles	Muscle fibers of intercostal and abdominal wall muscles	Spindle afferent fibers project to the cerebral cortex; posture and rib cage stabilization response to increases in airway resistance or by decreases in lung compliance
Tendon organs	Branched nerve endings respond to stretch	Tendons	Response proportion to stimulus; causes relaxation of the attached muscle

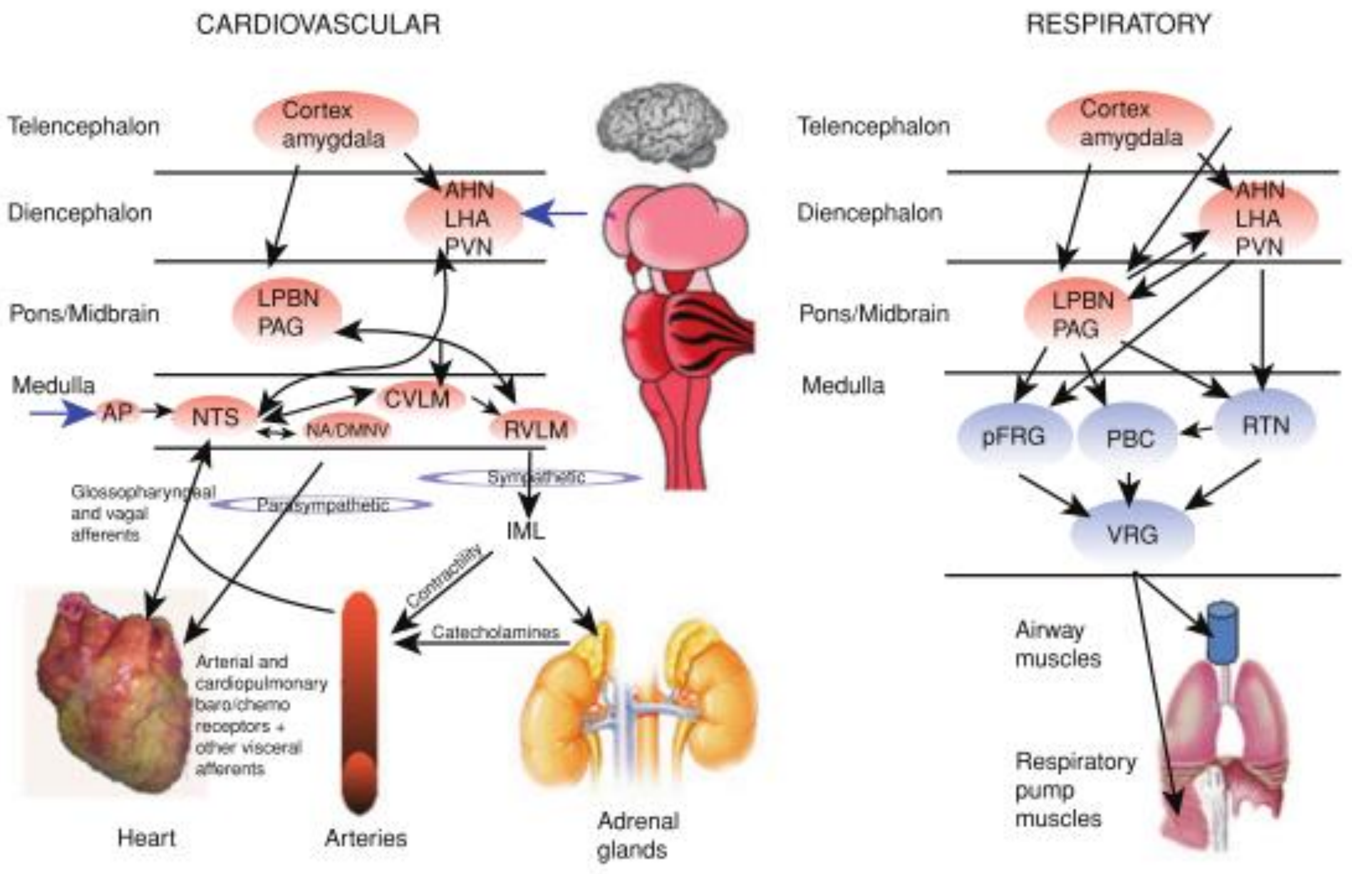
RECEPTORS OF THE RESPIRATORY SYSTEM

- 3 types of (mechanosensors):
  - C-fiber receptors
  - Rapidly Adapting Receptors (RARs, sustained activation to irritants)
  - Slowly Adapting Receptors (SARs, responsible for iHBr)
- Hering-Breuer reflex (1868): Lung inflation suppresses inspiratory activity and promotes expiration (Hering-Breuer inflation reflex, iHBr), where lung deflation stimulates inspiratory efforts by increasing respiratory rate and inspiratory force (Hering-Breuer deflation reflex, dHBr)
- Mediation via the vagal myelinated pathway

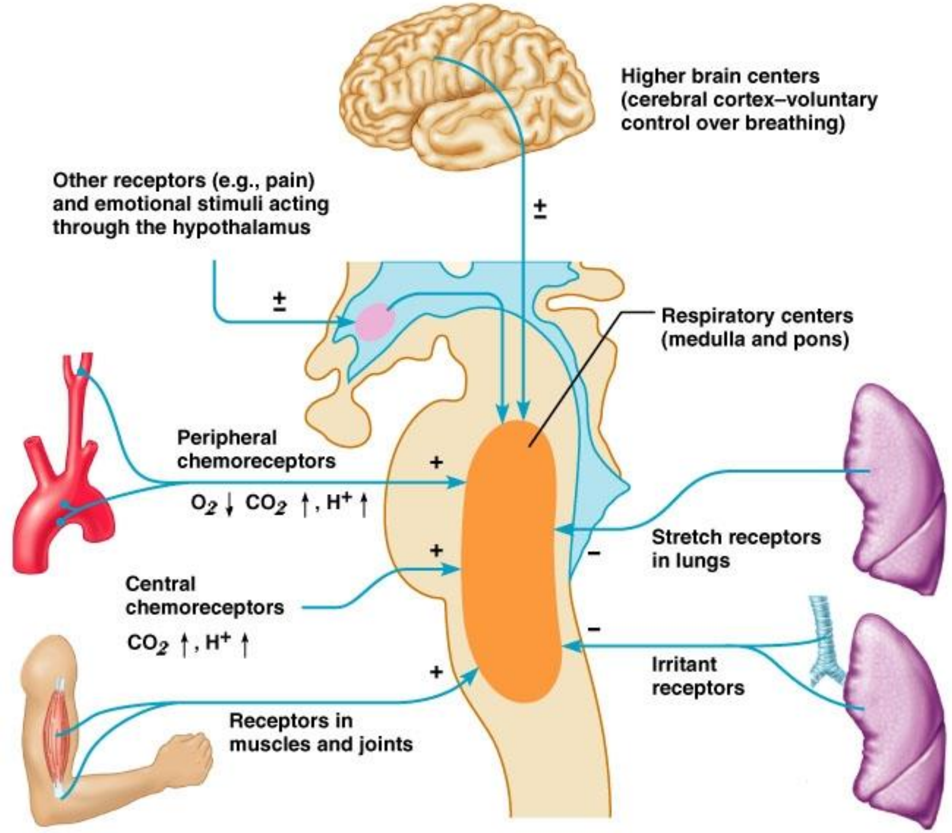
Sowho et al. Clin Chest Med 2014; 35:469
Yu. J Appl Physiol 2016;121:1041
Alheid & McCrimmon. Resp Physiol Neurobiol 2008;164:3

CENTRAL COMMAND

- Central command refers to the influence of brain structures involved in locomotion on the respiratory network

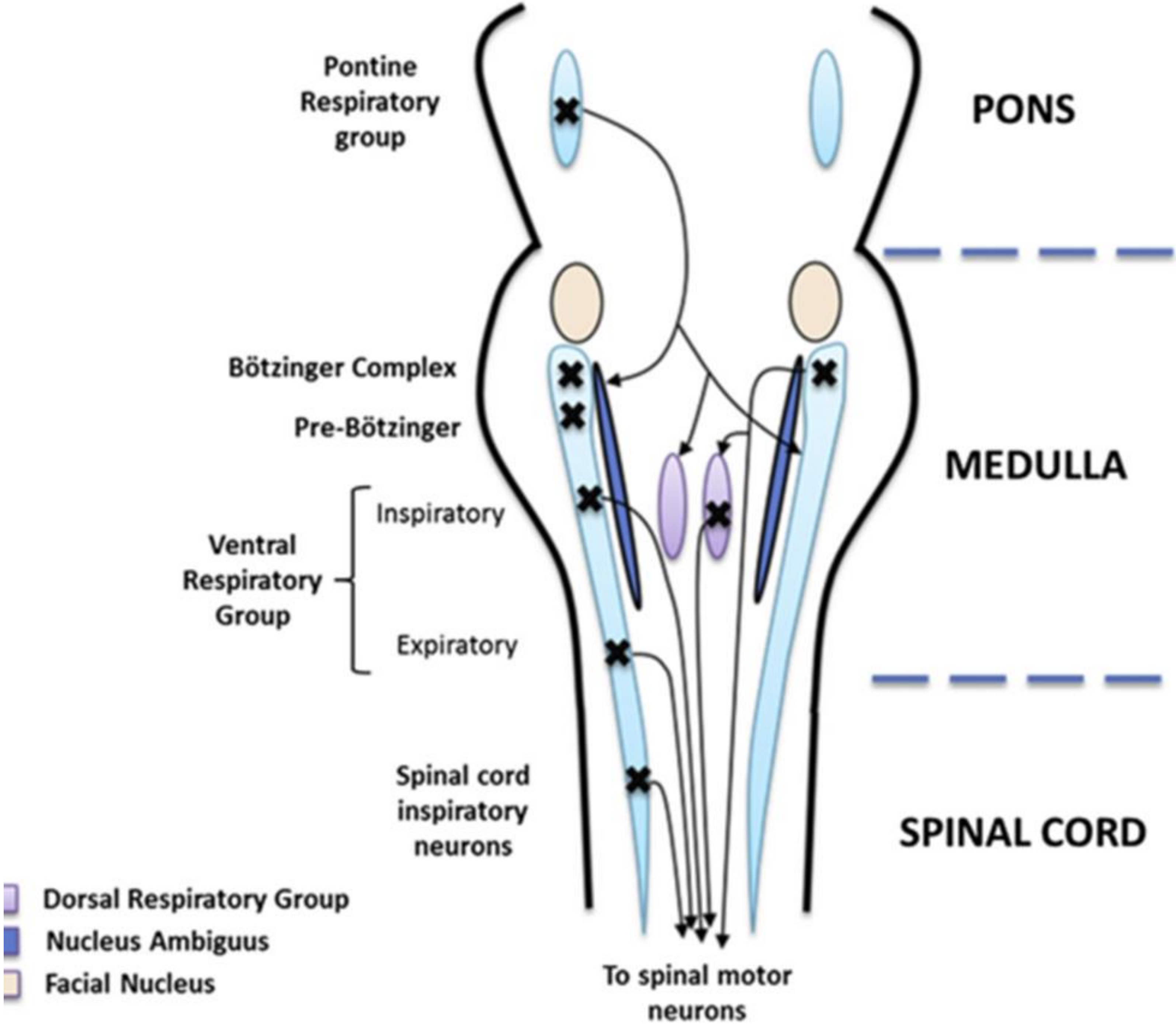


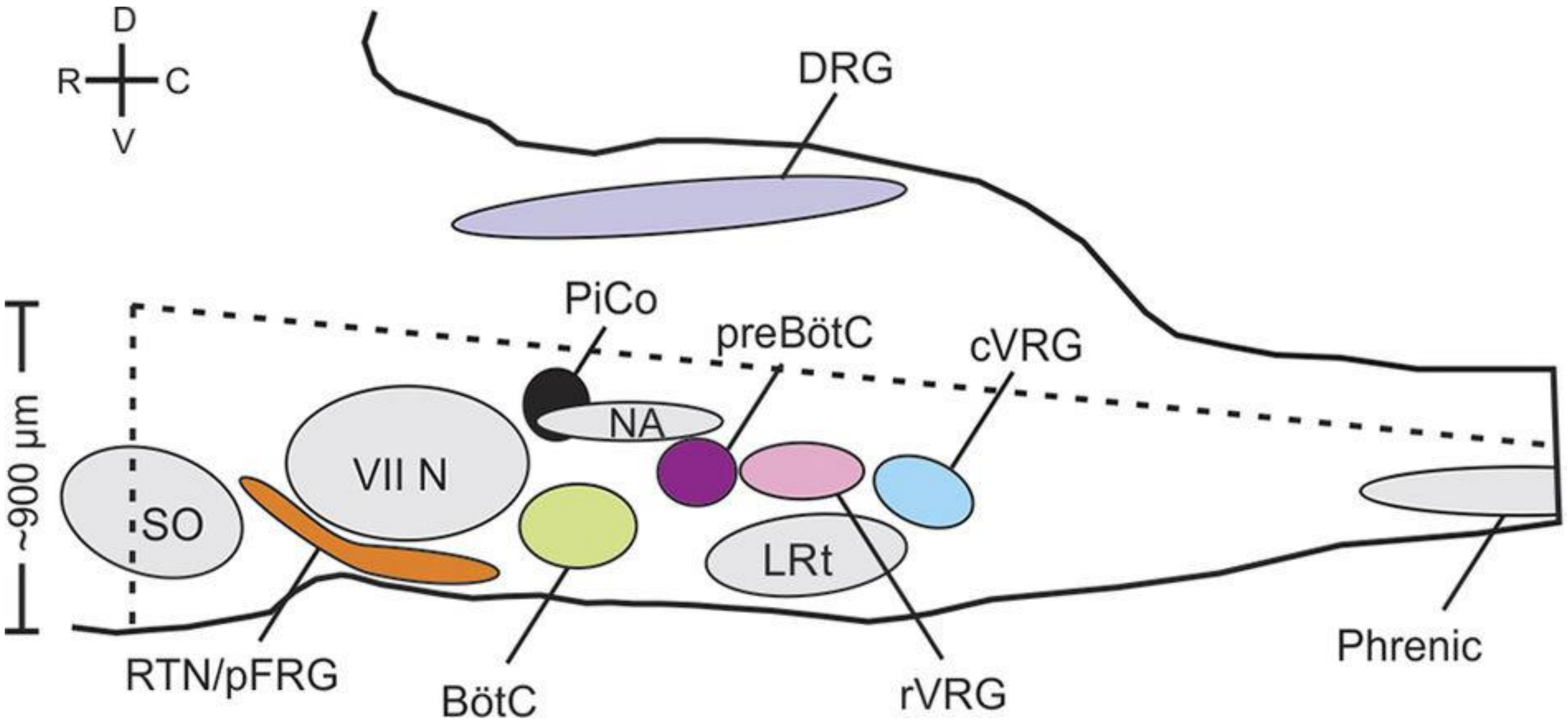
Forster et al. Compr Physiol;2:743



RESPIRATORY ANATOMY

- Complex array of neurons, stretching from the cortex to the lower thoracic/upper lumbar spine



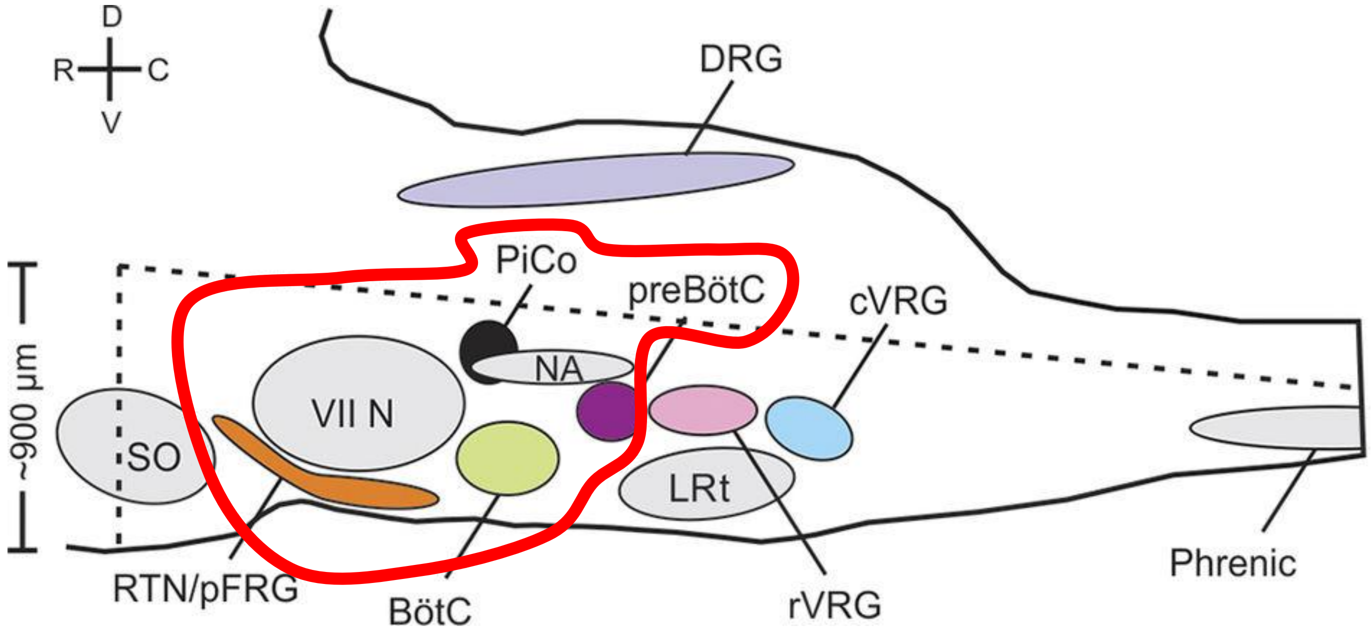


Various types of inspiratory and expiratory neurons

VENTRAL RESPIRATORY COLUMN (VRC)

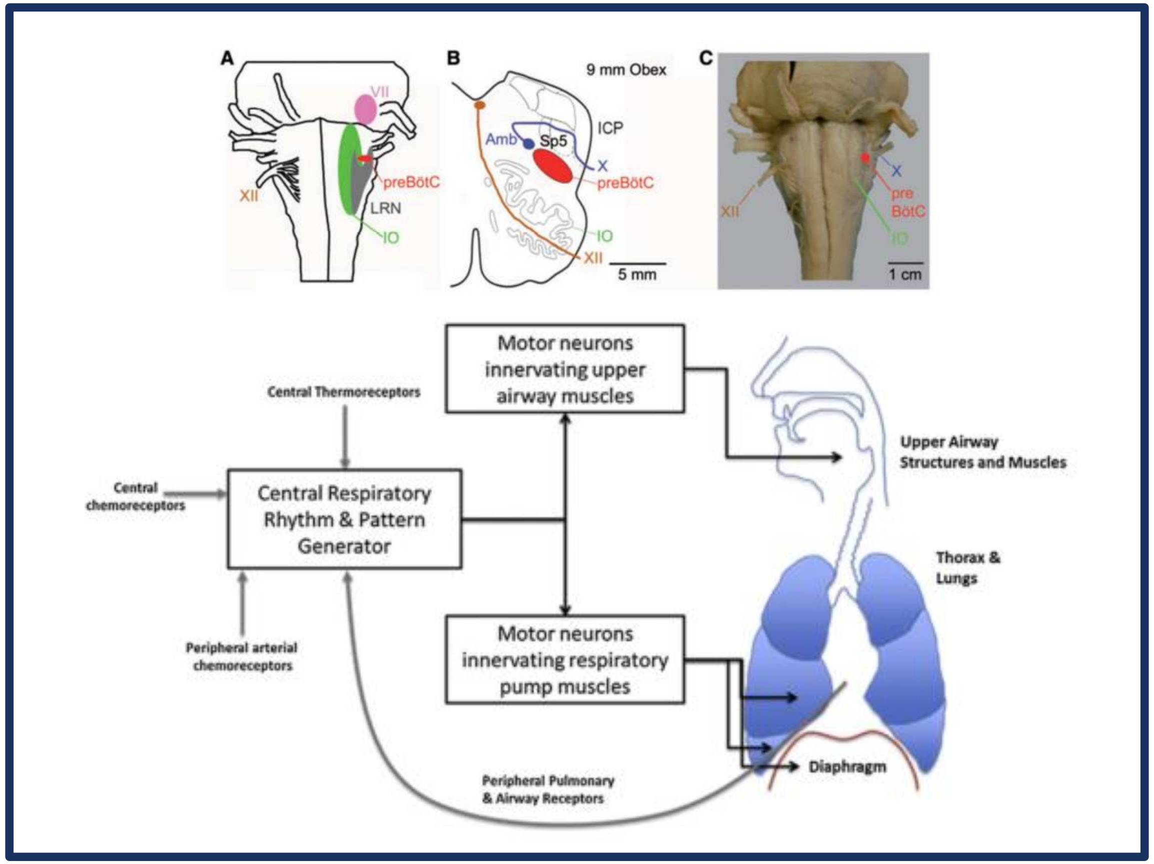
ROSTRAL VENTRAL RESPIRATORY COLUMN

- **Retrotrapezoidal nucleus**
  - **Central chemoreception**
- **Botzinger complex**
  - expiratory neurons that modulate respiratory rhythm
- **Pre-Botzinger Complex**
  - core respiratory rhythm-generating circuit
- **Parafacial Respiratory Group**
  - Expiratory rhythm generator



Moreira & Mulkey. J Physiol 2015; 593: 1065
Anderson et al. Nature 2016; 536:76
Alheid & McCrimmon. Resp Phys Neurobiol 2008;164:3

(OSCILLATING) CENTRAL RESPIRATORY GENERATOR

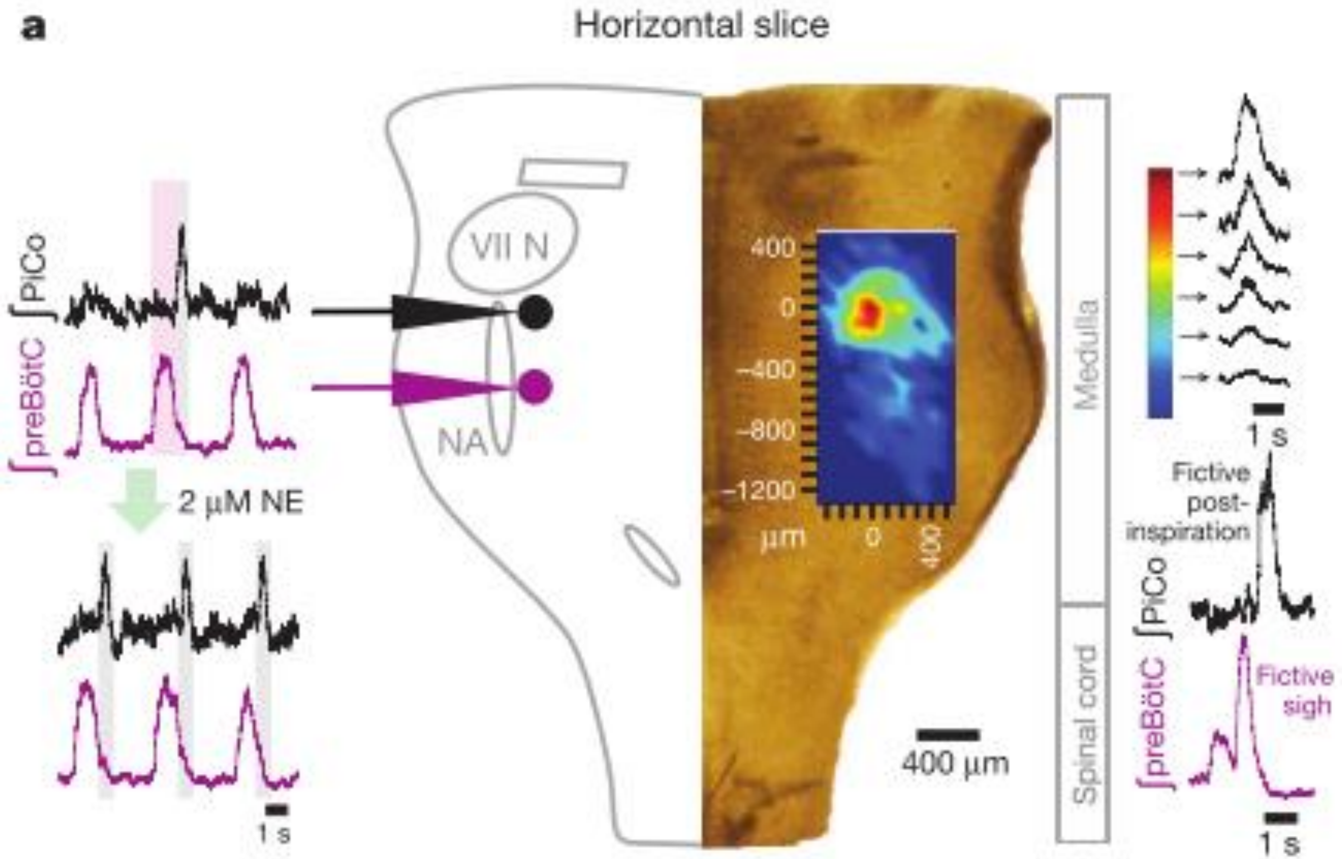


- Pre-Botzinger complex (Smith, 1991)
  - spontaneous inspiratory rhythm generator
- (respiratory) Parafacial respiratory group (Onimanu & Homma, 2003)
  - likely rhythm generator for active expiration
- Produces:
  - Respiratory drive (tonic activity)
    - based on peripheral & central chemoreception
  - Respiratory rhythm (phasic activity)
    - Inspiratory premotor VRG & DRG neurons → phrenic and intercostal neurons
- Inspiration termination: Projections from the Botzinger complex
- During expiration, pharyngeal muscles receive tonic projections from reticular formation

Sowho et al. Clin Chest Med 2014; 35:469
Howell & Newman. Muscle Nerve 2017;56:197

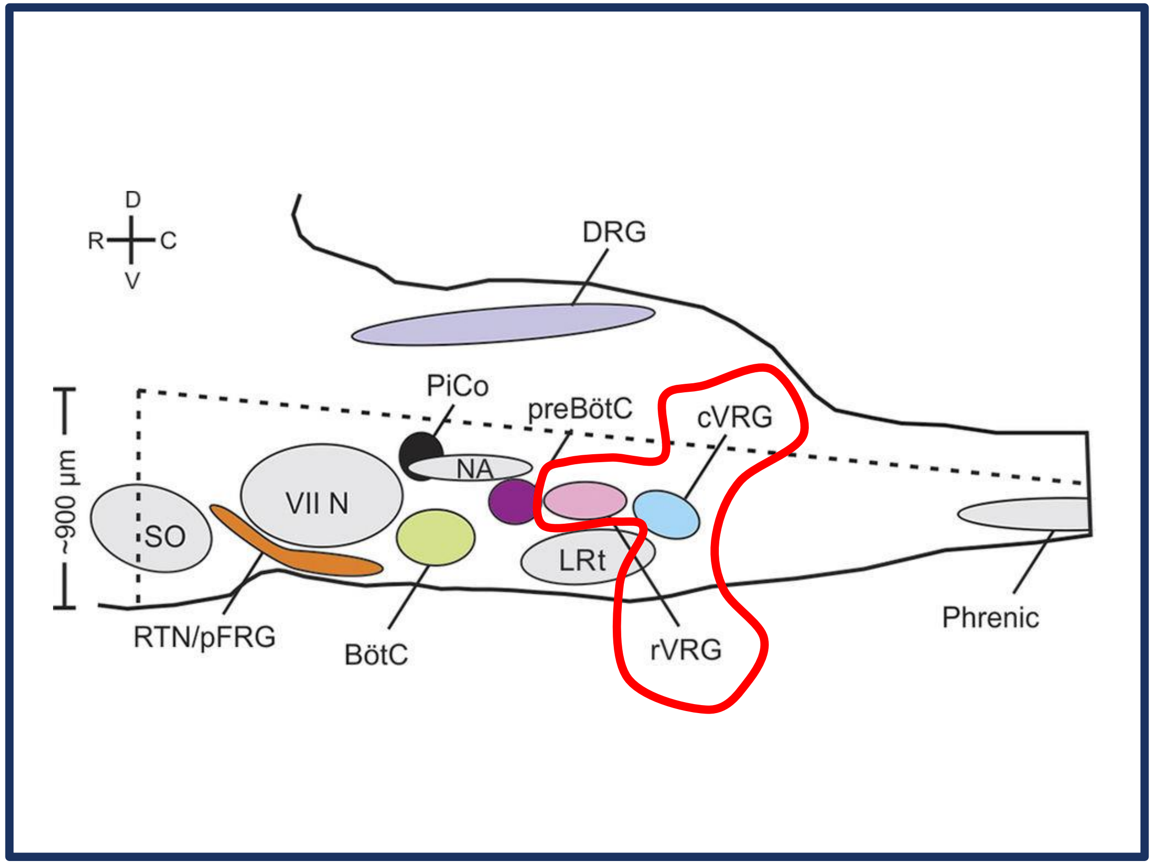
CONTROL OF POST-INSPIRATORY ACTIVITY

- Post-inspiratory Complex (PiCO)
- excitatory and rhythmogenic neuronal population that is specifically active during postinspiration
- might also contribute to the generation of other postinspiratory behaviours such as swallowing and vocalization



Anderson et al. Nature 2016; 536:76

CAUDAL VENTRAL RESPIRATORY COLUMN

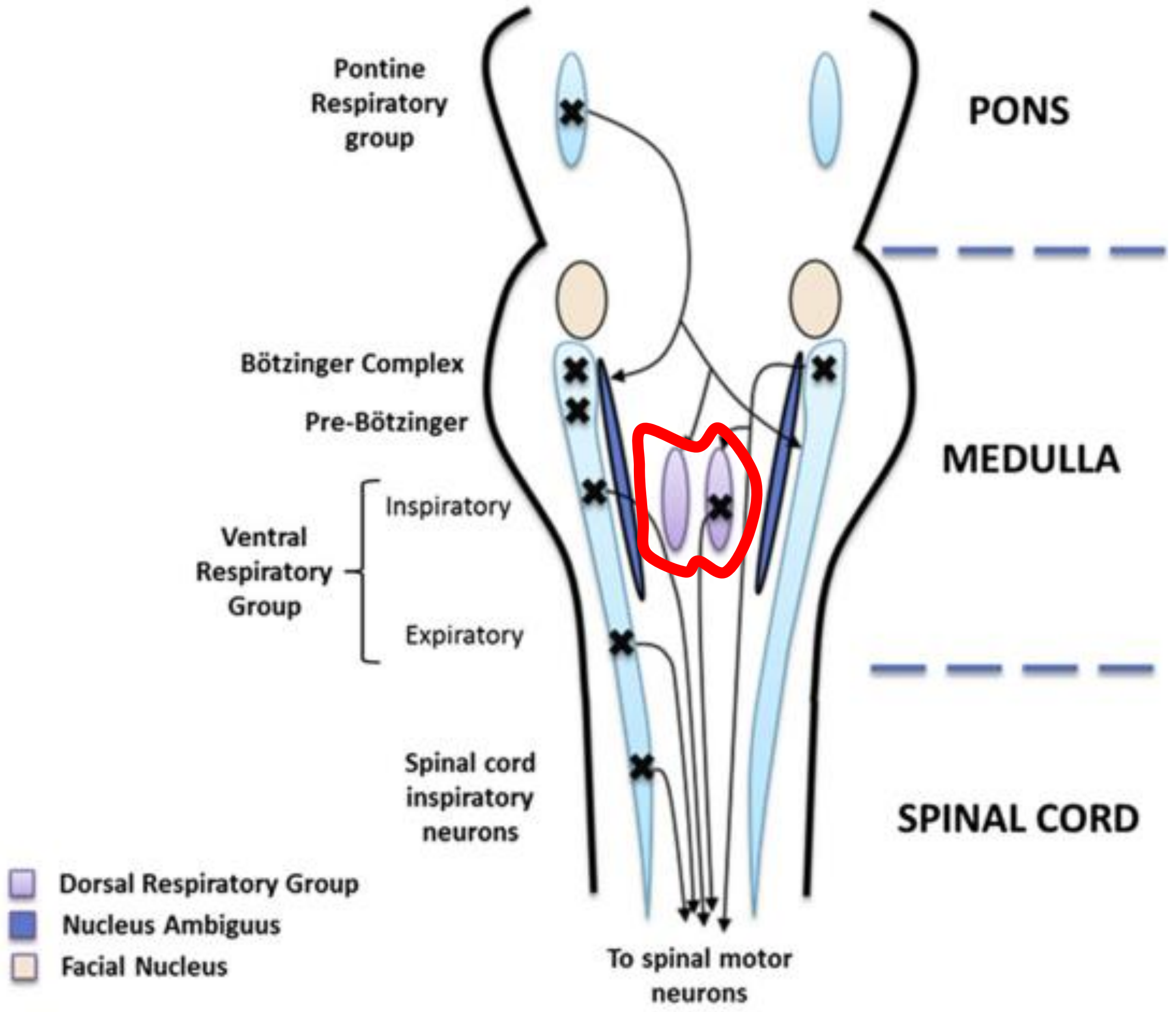


- Ventral Respiratory Group (VRG)
  - Rostral VRG: inspiratory neurons
    - Projections to phrenic nucleus and the cervical spine group
  - Caudal VRG: expiratory neurons
    - innervation of abdominal and expiratory internal intercostal notoneurons

Alheid & McCrimmon. Resp Phys Neurobiol 2008;164:3
Anderson et al. Nature 2016; 536:76

DORSAL RESPIRATORY GROUP

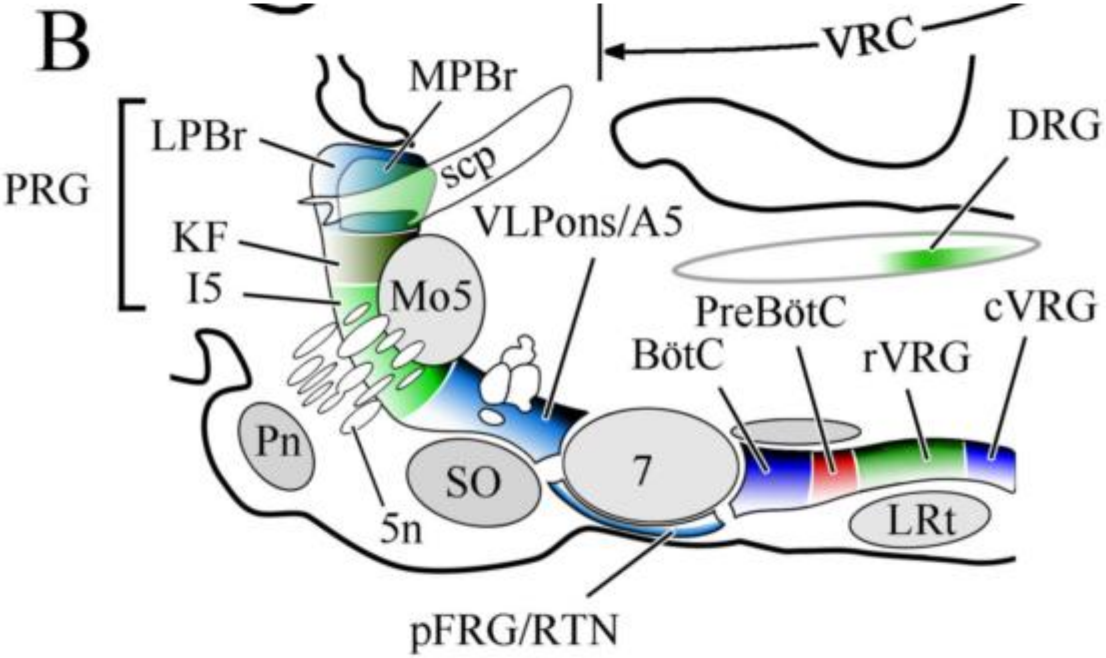
- Caudal third of the nucleus of the solitary tract (cNTS)
- Principal site of termination for sensory afferents
- First step in brain's processing of info from the periphery
- Mostly inspiratory neurons
- Connected with phrenic nucleus



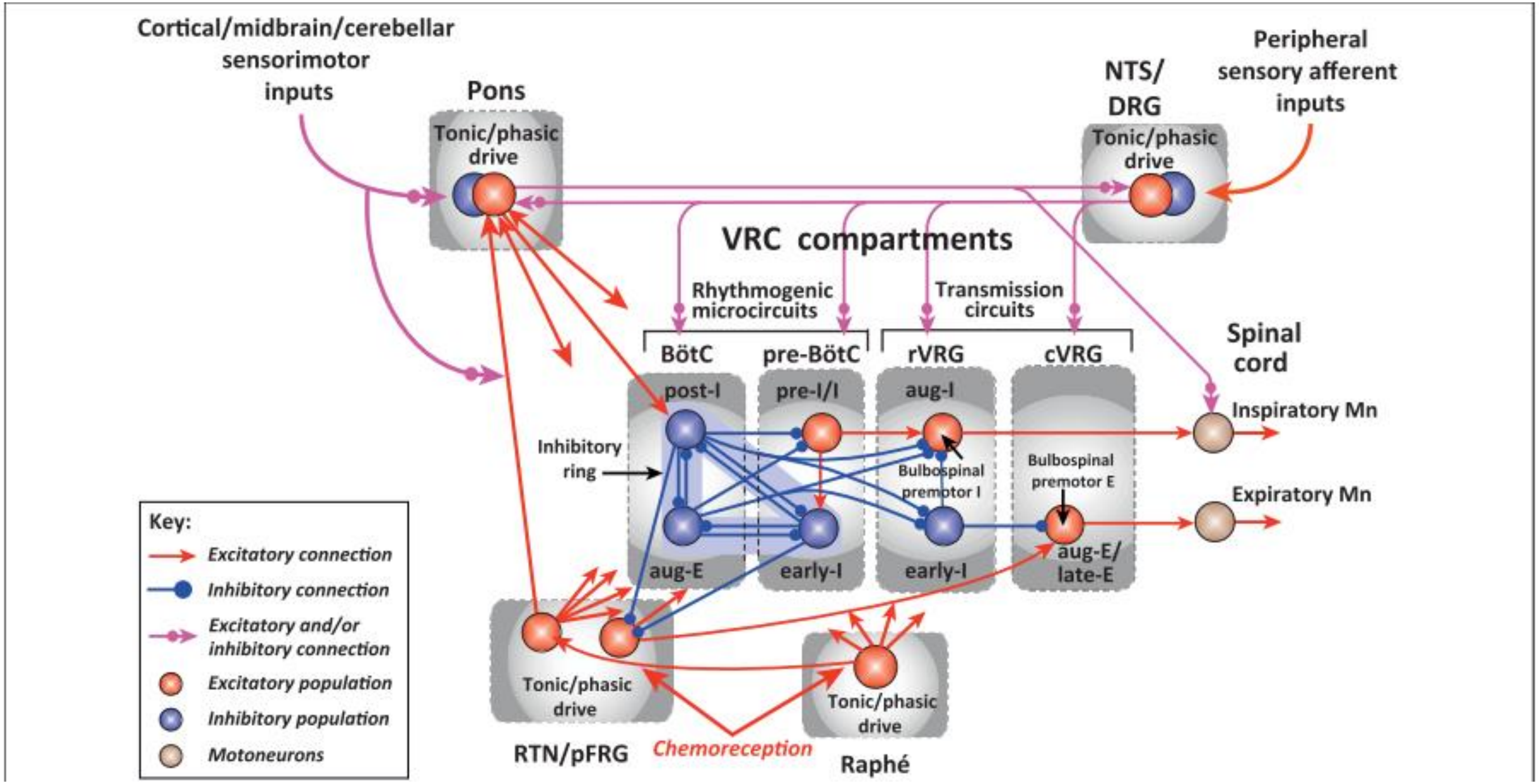
Sowho et al. Clin Chest Med 2014;35:469
Alheid & McCrimmon. Resp Phys Neurobiol 2008;164:3

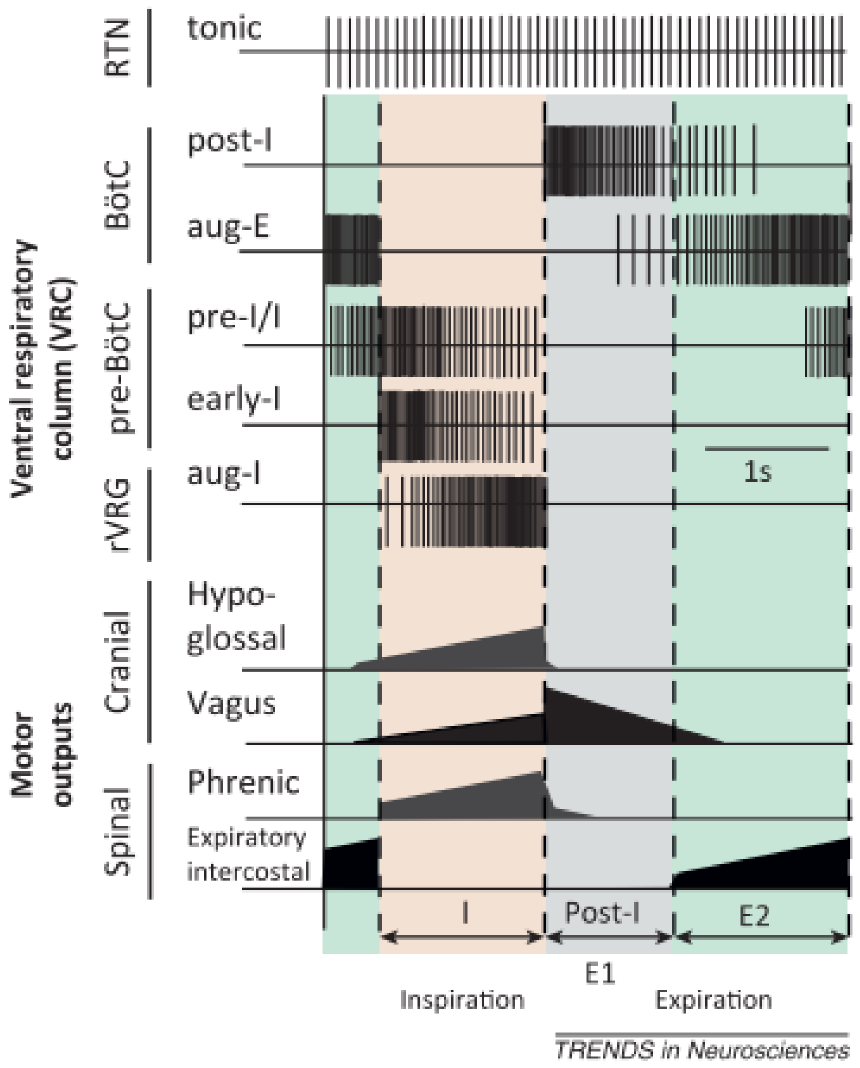
PONTINE RESPIRATORY GROUP

- Kolliker-Fuse & parabrachial nuclei
- Regulation of airway resistance (Kolliker-Fuse nucleus)
- Termination of RTN neurons
- Reflex and higher order CNS control of breathing
- Inspiratory-expiratory phase transition (KF)
- Dynamic control of airway patency (KF)
- Vagal and glossopharyngeal afferent inputs



Chowdhuri & Badr. Chest 2017;151:917


Cortical/midbrain/cerebellar sensorimotor inputs
Pons
Tonic/phasic drive
NTS/ DRG
Peripheral sensory afferent inputs
Tonic/phasic drive
VRC compartments
Rhythmogenic microcircuits
Transmission circuits
BötC
pre-BötC
rVRG
cVRG
Spinal cord
post-I
pre-I/I
aug-I
Inspiratory Mn
Inhibitory ring
Bulbospinal premotor I
Bulbospinal premotor E
Expiratory Mn
aug-E
early-I
early-I
aug-E/ late-E
Key:
Excitatory connection
Inhibitory connection
Excitatory and/or inhibitory connection
Excitatory population
Inhibitory population
Motoneurons
Tonic/phasic drive
Tonic/phasic drive
RTN/pFRG
Chemoreception
Raphé



Smith et al. Trends Neurosci 2013;36:152

BREATHING CONTROL IN EXERCISE & SLEEP

TRIGGERING OF EXERCISE HYPERPNEA

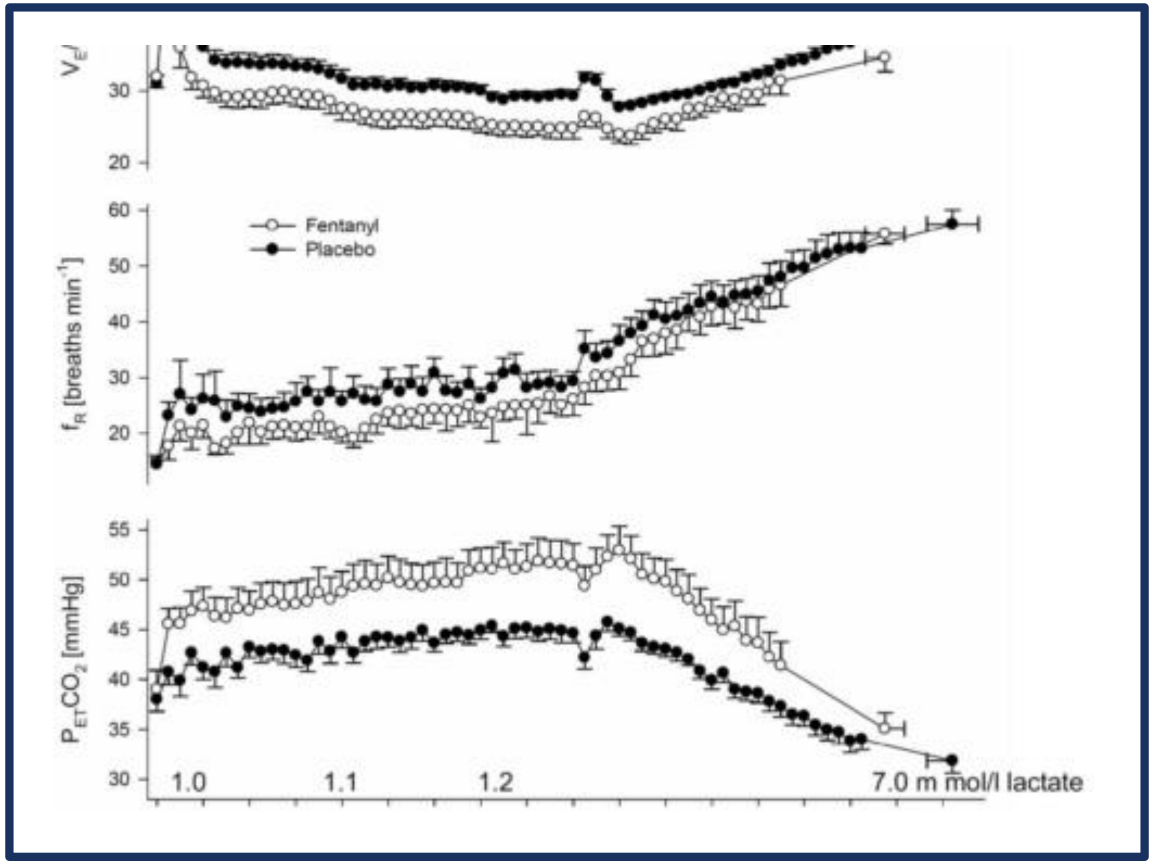
- Evidence of **central command** feedforward stimulus
  - Anticipatory hyperventilation
  - Immediate ventilatory increase at exercise onset
  - Hyperventilation responses in hypnotized humans with ‘suggested exercise’
  - increased ‘locomotor’ drive accompanied by increased ventilatory responses

THE REGULATION OF RESPIRATION AND CIRCULATION DURING THE INITIAL STAGES OF MUSCULAR WORK. BY A. KROGH AND J. LINDHARD.

(From the Laboratory of Zoophysiology, University of Copenhagen.)

IN the present paper we propose to describe the changes in ventilation, blood flow, pulse rate, respiratory exchange and alveolar CO_2 tension taking place in man during the first few minutes of light or heavy work and we shall attempt further an inquiry into the mechanism of these changes. The experiments have been made by means of the bicycle ergometer and respiration apparatus described in another paper[1] in which also the main parts of the technique employed have been set forth in detail.

EXERCISE HYPERPNEA



Muscle afferent feedback

- Thinly myelinated afferents (mechanical distortion and/or metabolite accumulation)
- Dorsal horn of spinal cord → Solitary Tract Nucleus → Ventral Respiratory Column

Dempsey. ERJ 2014;44:495

VENTILATION CONTROL DURING SLEEP

BREATHING CONTROL DURING SLEEP (NON-REM)

Ventilation becomes dependent on chemoreceptor and mechanoreceptor stimuli

Reduced activity of upper airway dilators → upper airway narrowing

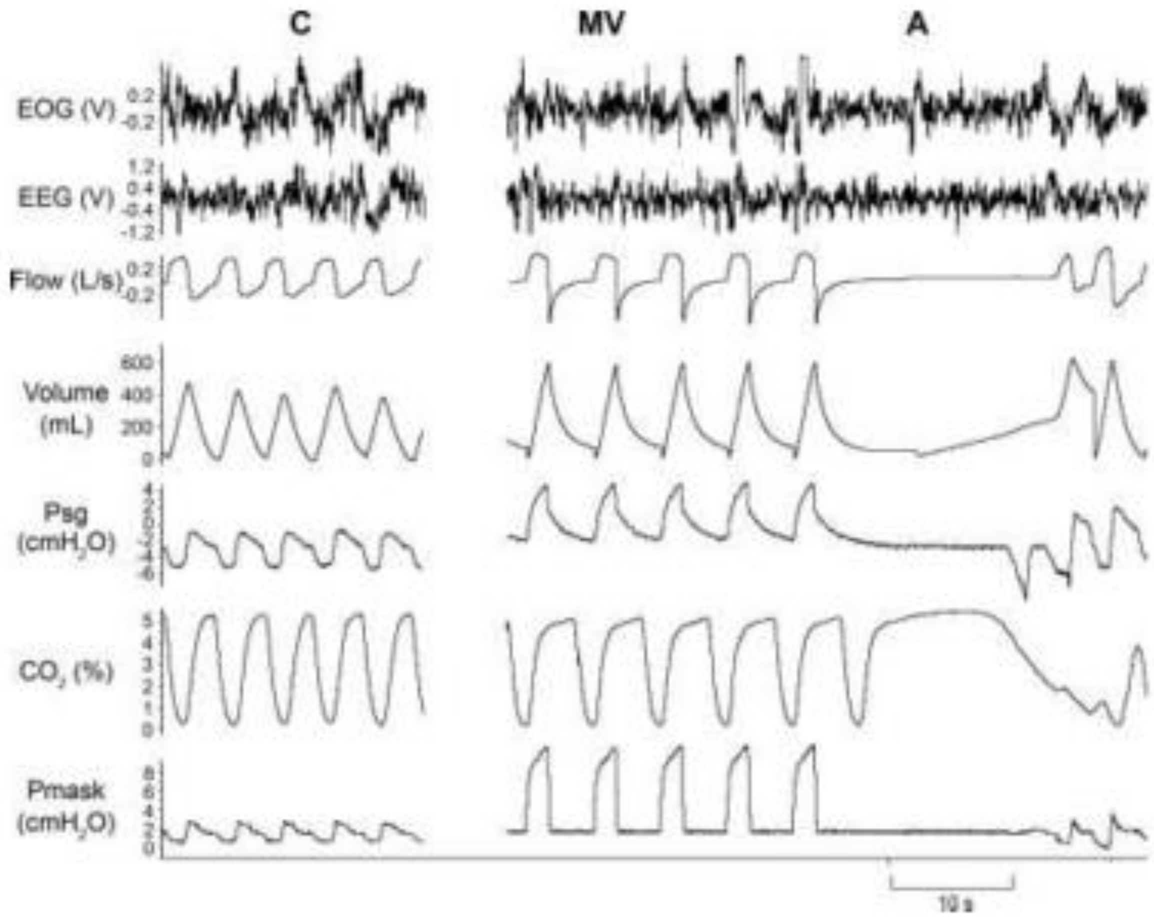
Absence of load compensation

Ventilation decrease - $PaCO_2$ increased

Chowdhuri & Basr. Chest 2017;151:917

APNEA THRESHOLD

- *CO2 Reserve: Eupneic $PaCO_2$ – Apnea Threshold*



Chowdhuri & Badr. Chest 2017; 151:917

BREATHING CONTROL DURING SLEEP (REM)

- Ventilation is under predominantly behavioral rather than metabolic control (insensitive to $PaCO_2$ changes)
  - Central sleep apnea uncommon
- Retrotrapezoid nucleus no longer controls breathing frequency during REM sleep (controls Tidal Volume, however)

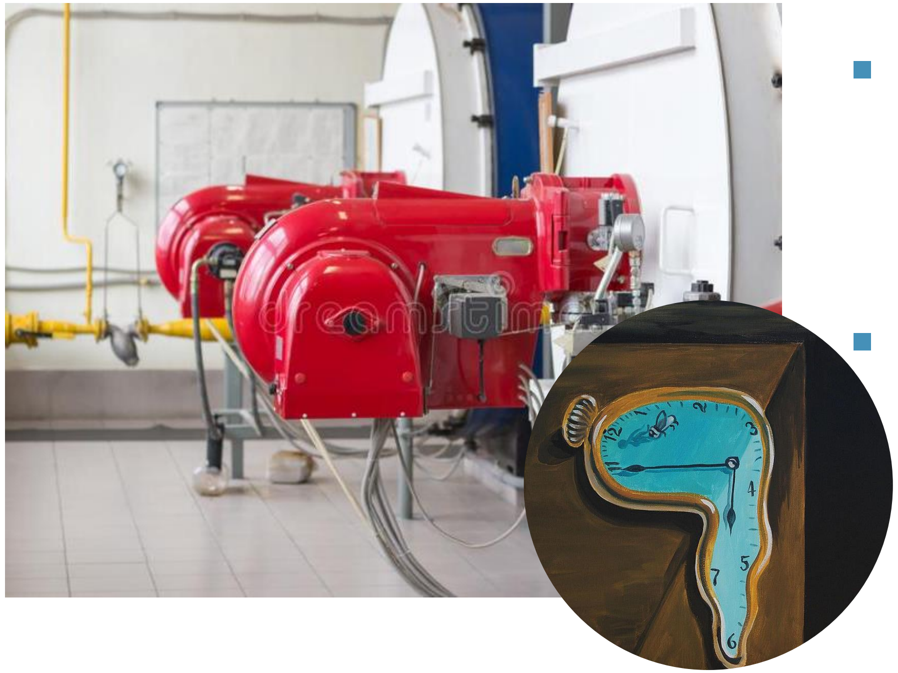
Chowdhuri & Basr. Chest 2017;151:917

THE CHEMOREFLEXES: AN ENGINEERING APPROACH


I'M CO


ΑΝ Η ΘΕΡΜΟΚΡΑΣΙΑ ΠΕΣΕΙ ΣΤΟΥΣ 24° C ➔ ΚΑΥΣΤΗΡΑΣ ΣΤΟ ON ΓΙΑ 2 ΩΡΕΣ

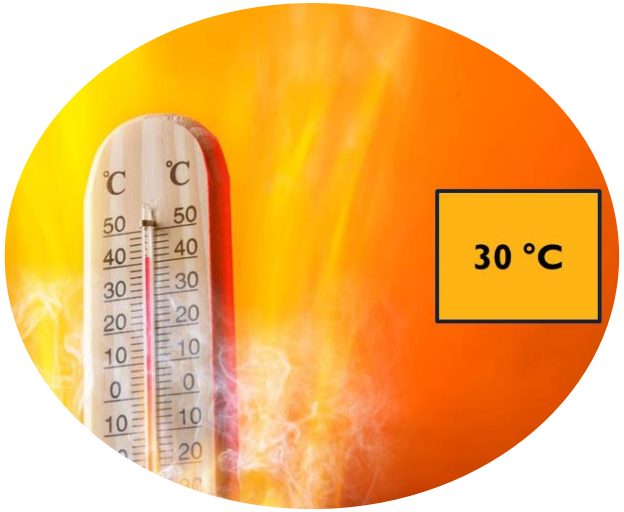
ΚΥΚΛΟΦΟΡΗΤΗΣ ΤΗΣ ΠΛΑΚΑΣ



- Την ικανότητα του καλοριφέρ να θερμαίνει το σπίτι την ονομάζουμε Plant Gain
  - Την ιδιότητα του καλοριφέρ να ανεβάζει πολύ τη θερμοκρασία θα την ονομάσουμε High Plant Gain
- Την ικανότητα του θερμοστάτη να ανταποκρίνεται στην πτώση της θερμοκρασία θα την ονομάσουμε Controller Gain
  - Την ιδιότητα του καυστήρα να δουλεύει έντονα (& για πολύ ώρα) όταν η θερμοκρασία πέσει στους 24 θα την ονομάσουμε High Controller Gain
- Το συνδυασμό αυτών των δύο θα τον ονομάσουμε High Loop Gain

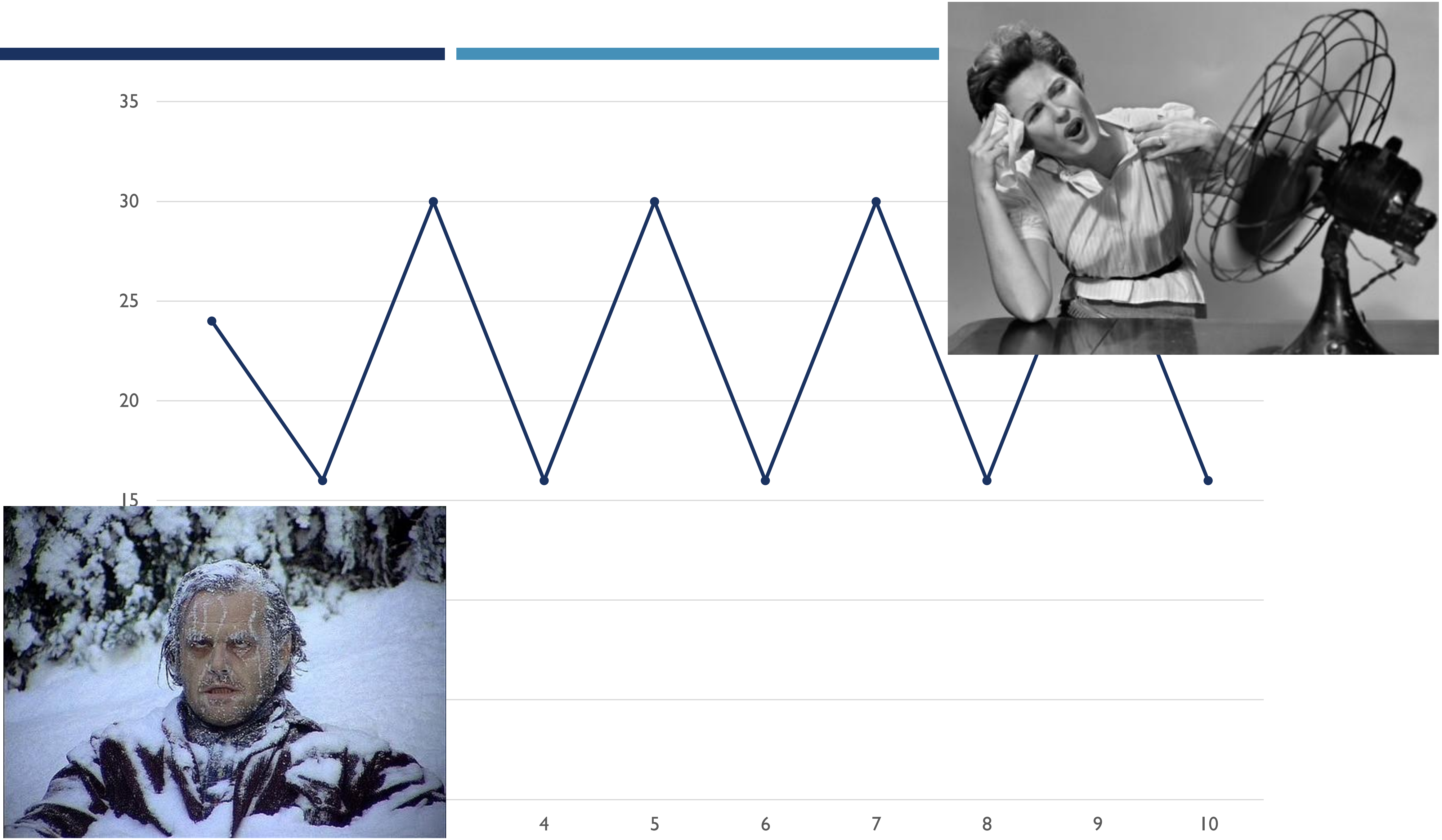

Warmup
tue 20 apr | 09:48 | 22.5 floor
21.5 °C air
22.0 until 12:30
17.5
WILO
WILO

16 °C


30 °C


°C °F
Warmup
tue 20 apr | 09:48 | 22.5 floor
21.5 °C air
22.0 until 12:30
17.5
WILO
WILO

16 °C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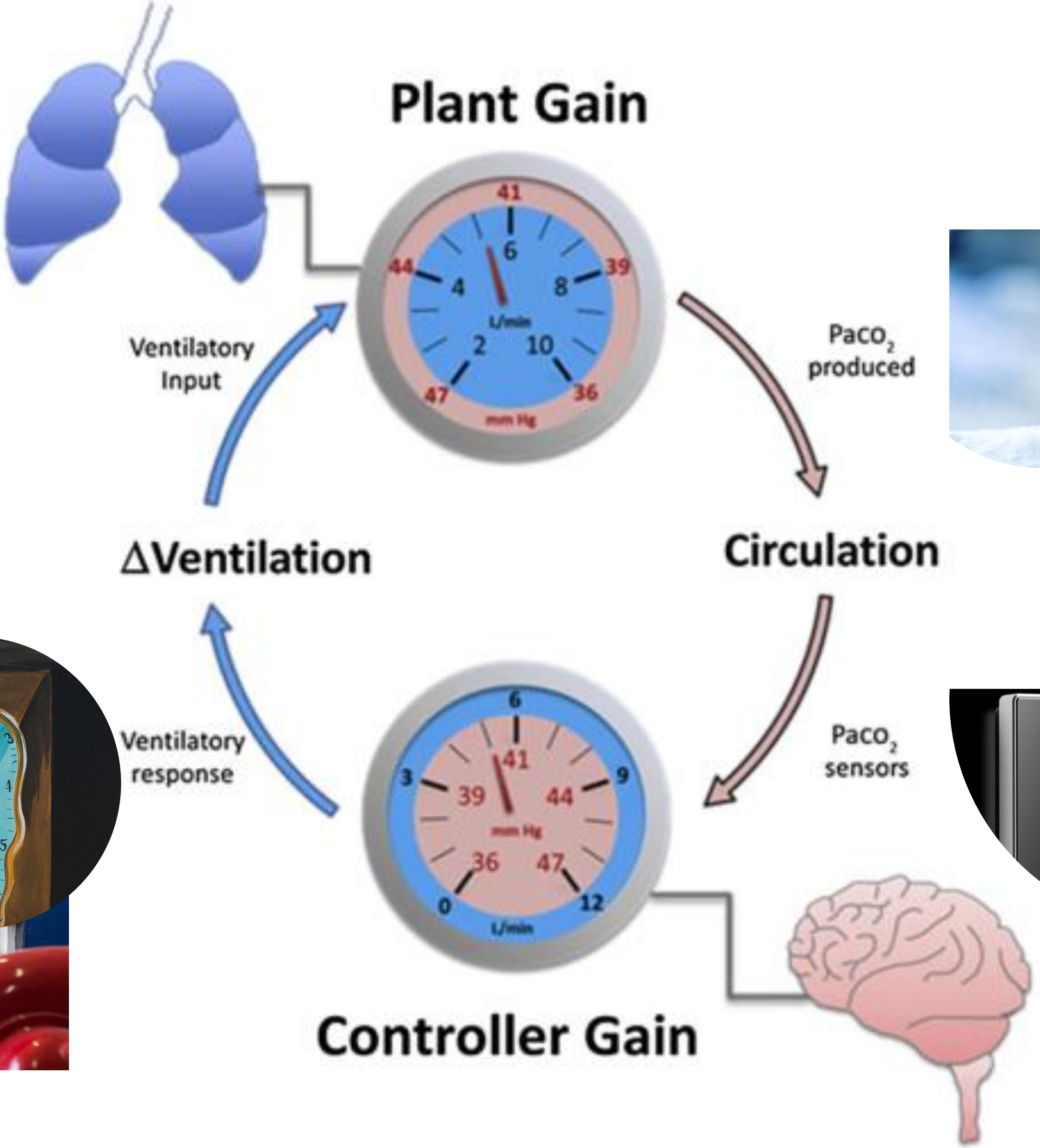
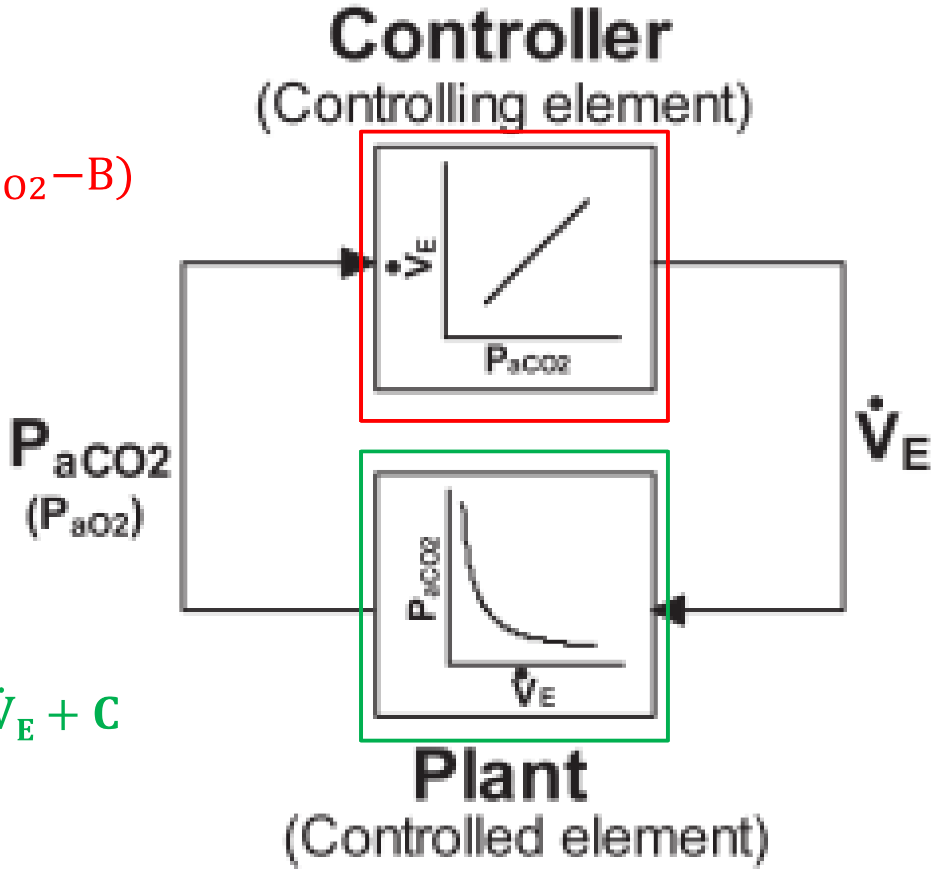


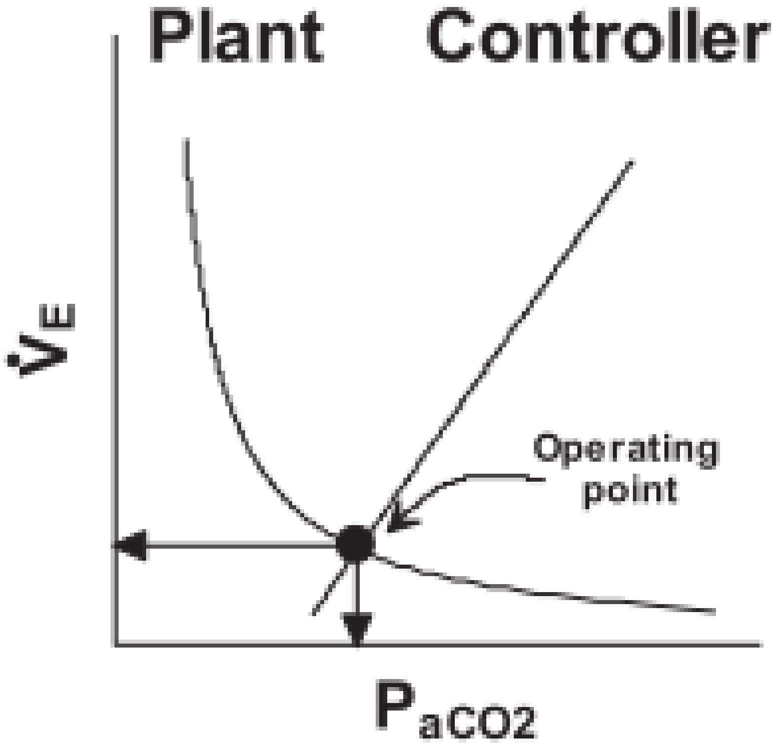
Sowho et al. Clin Chest Med 2014; 35:469

EQUILIBRIUM DIAGRAM MODEL OF THE RESPIRATORY CHEMOREFLEX FEEDBACK SYSTEM (PROVIDED OXYGEN IS KEPT HIGH)

$\dot{V}_E = S \times (P_{aCO2} - B)$



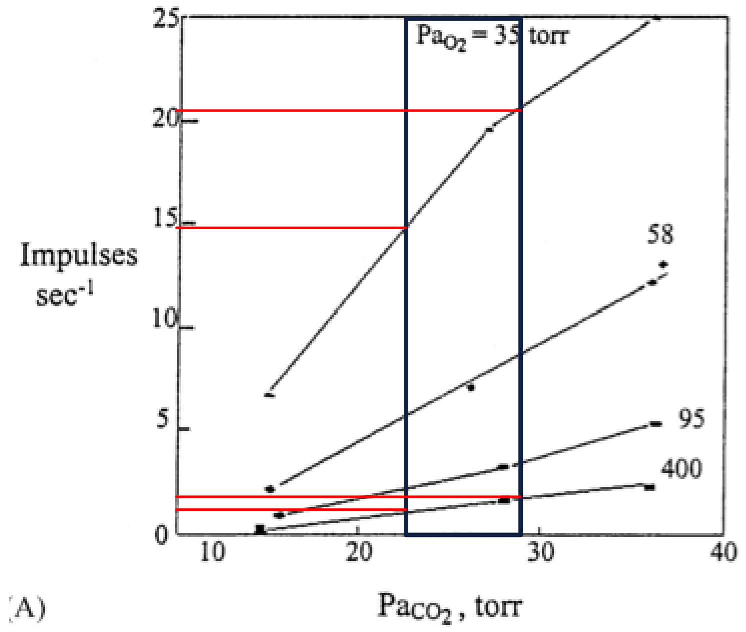
$P_{aCO2} = {}^{A}/_{\dot{V}_E} + C$



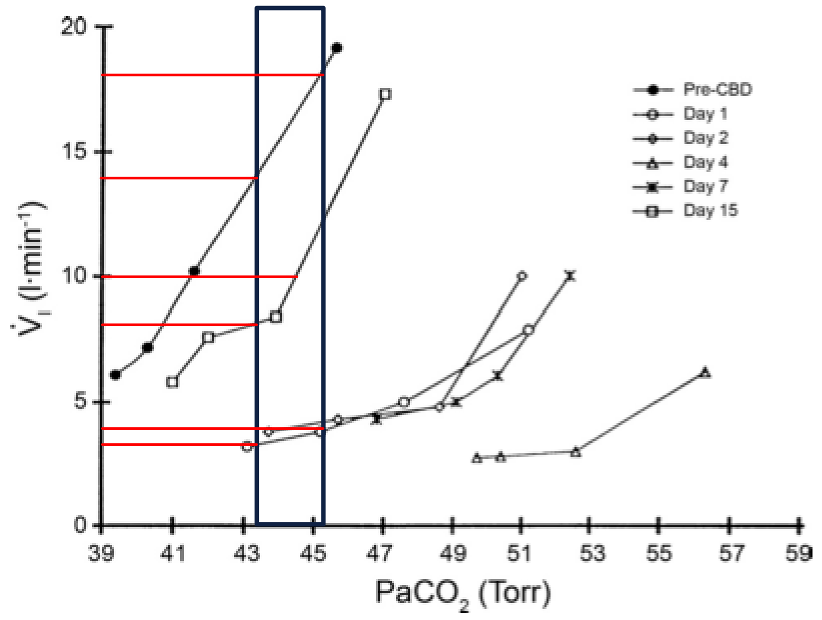
A = 0.863 × α / (1 - VD/VT) α is the scaling factor reflecting VCO2 unrelated to work of breathing

C = 0.863 × β / (1 - VD/VT) β is that reflecting VCO2 related to work of breathing

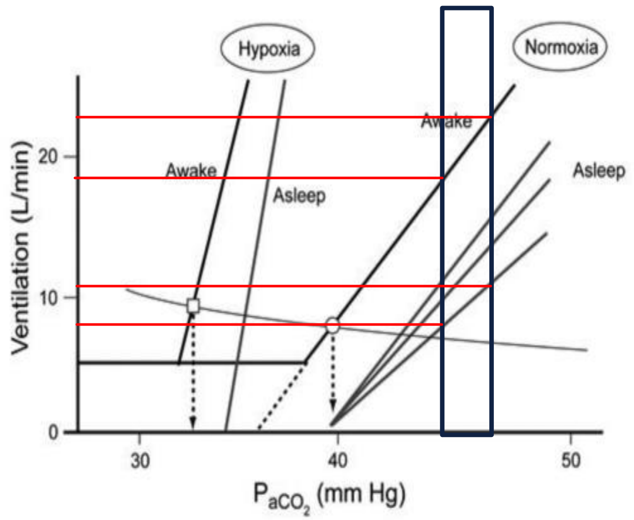
Miyamoto. J Phys Fit Sport Med 2016;5:329



Hypoxemia



Excision of carotid body



Sleep

CONTROLLER GAIN

How much is ventilation increased for a given change in PaCO$_2$

Miyamoto. J Phys Fit Sport Med 2016;5:329

PLANT GAIN
How much is $PaCO_2$ changed for a given change in ventilation

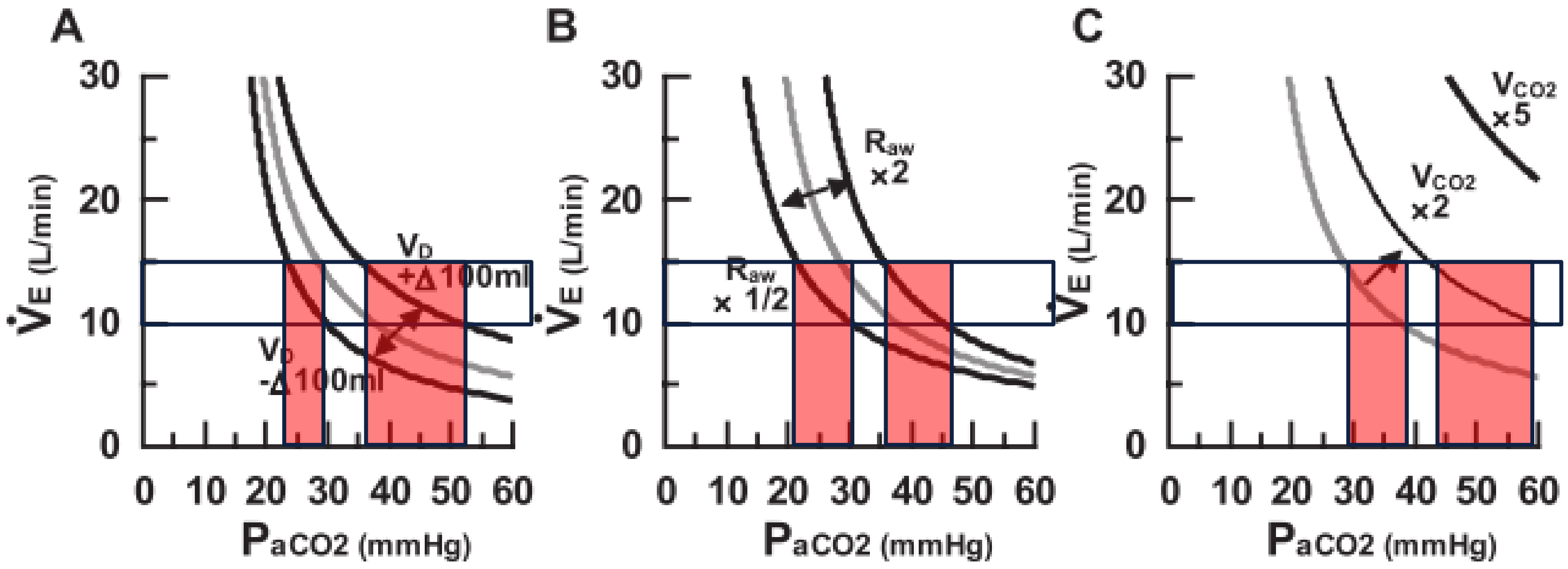


Fig. 5 Simulation of gas exchange dynamics of the plant subsystem element ($\dot{V}_E \rightarrow P_{aCO2}$ input-output relationship) within the respiratory control system. $\dot{V}_D$: deadspace, R_{aw}: airway resistance, V_{CO2}: carbon dioxide output.

Miyamoto. J Phys Fit Sport Med 2016;5:329

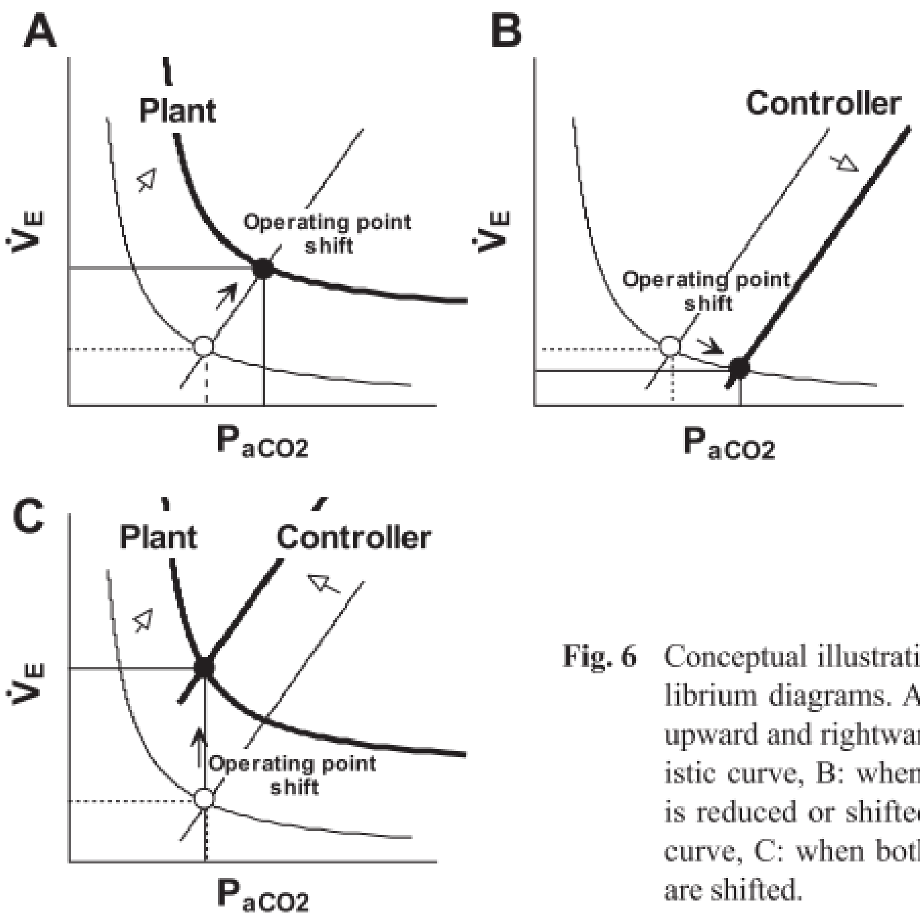


Fig. 6 Conceptual illustration of analytical approach using respiratory equilibrium diagrams. A: when the plant characteristics curve is shifted upward and rightward without any change in the controller characteristic curve, B: when the slope of the controller characteristics curve is reduced or shifted without any change in the plant characteristic curve, C: when both the controller and plant characteristics curves are shifted.

EQUILIBRIUM DIAGRAM ANALYSIS

Miyamoto. J Phys Fit Sport Med 2016;5:329

CONCEPT OF LOOP GAIN

Loop Gain

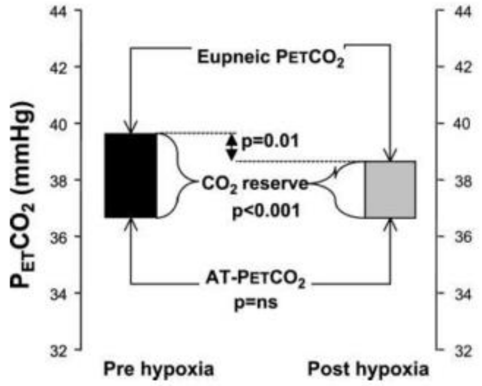
- Controller gain
  - Chemoresponsiveness ($\Delta Vi/\Delta PaCO2$)
- Plant gain
  - Change in PaCO2 for a given ventilation change ($\Delta PaCO2/\Delta Vi$)
- Delay, dilution & diffusion inherent in transferring the signal

Increased controller gain:

- Sustained hypoxia
- Acute intermittent hypoxia
- Heart failure

Increased plant gain:

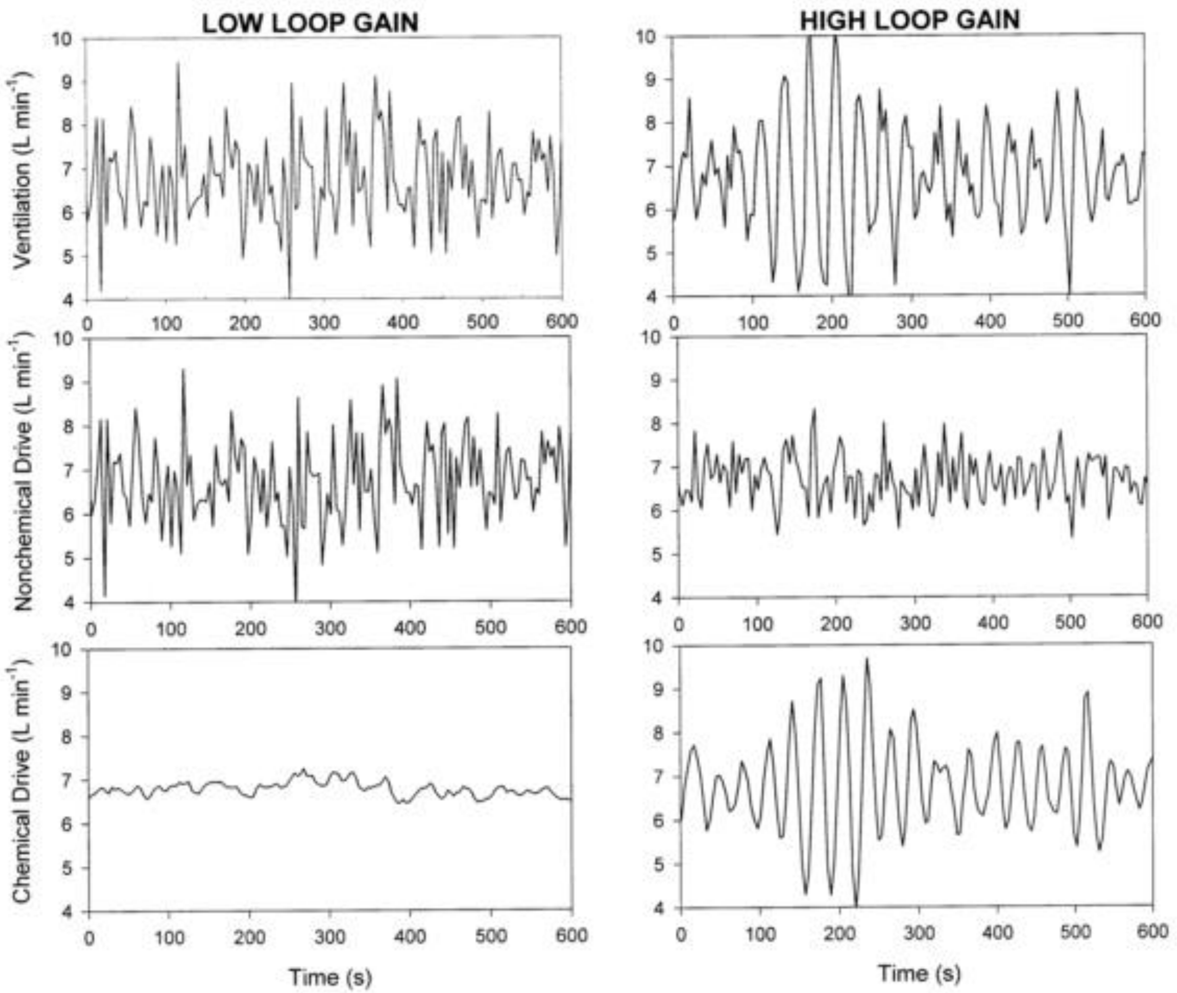
- Metabolic alkalosis
- Disorders of hypoventilation



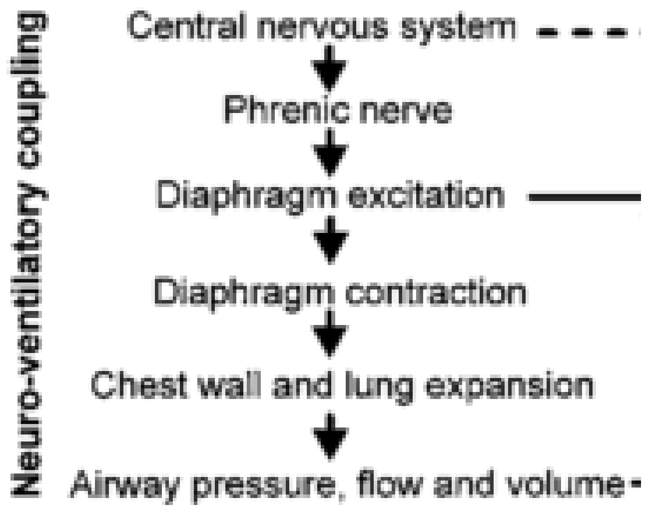
Increase in loop gain leads to respiratory instability

Chowdhuri & Badr. Chest 2017;151:917

IMPACT OF LOOP GAIN ON BREATHING STABILITY



Khoo. Respir Physiol 2000;122:167

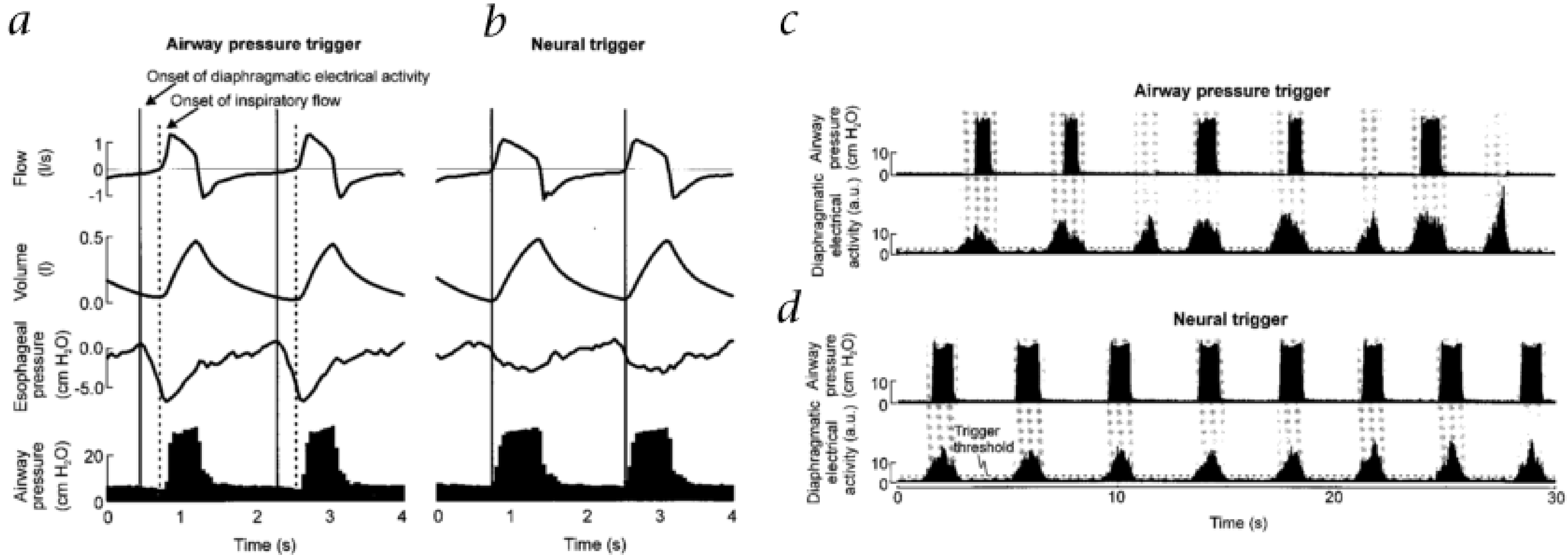


CONTROL OF BREATHING & ASSISTED VENTILATION

An area of dysynchrony

Sinderby et al. Nature Med 1999;5:1433

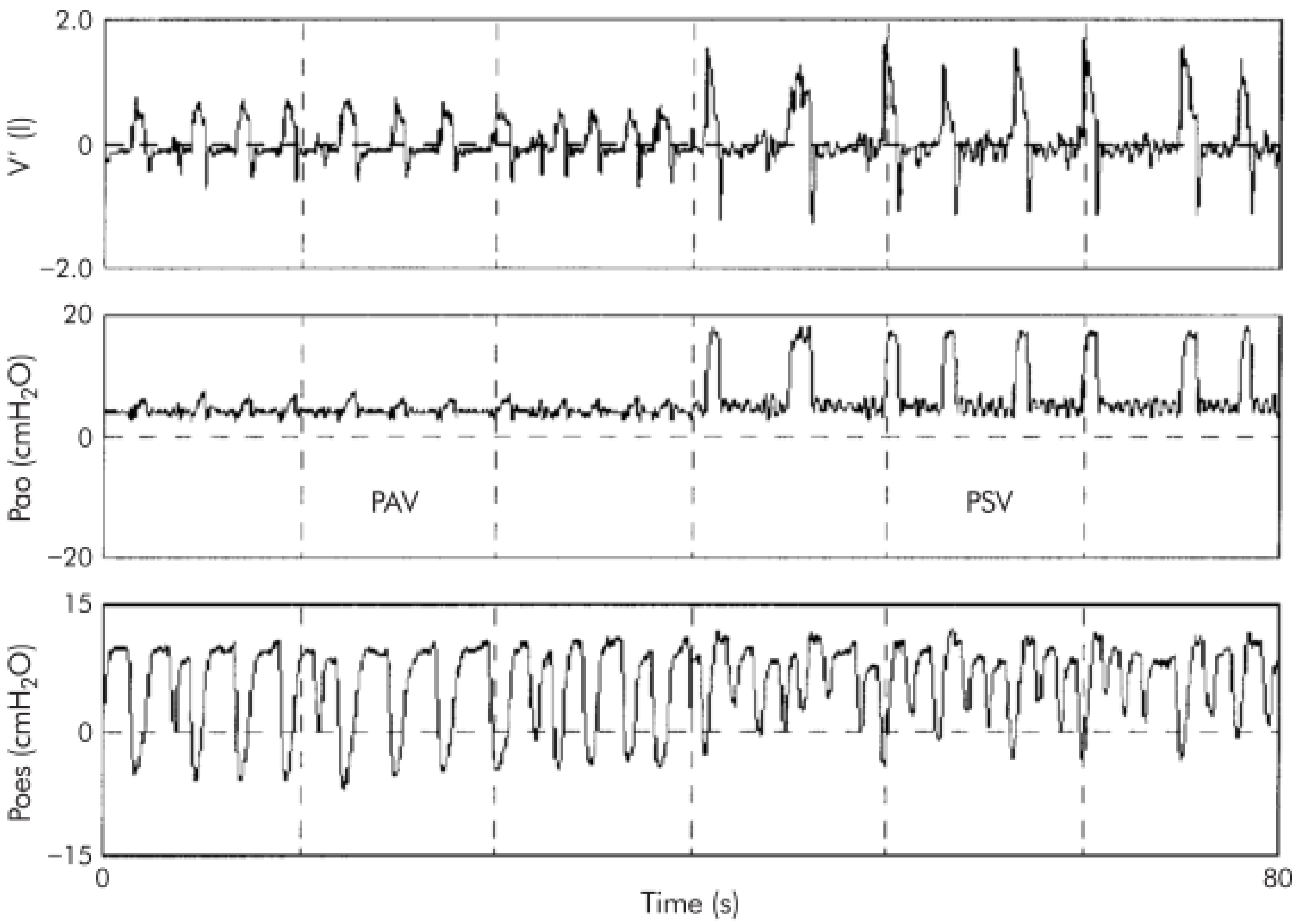
NEURAL TRIGGERING (NEURALLY ADJUSTED VENTILATORY ASSIST)



Sinderby et al. Nature Med 1999;5:1433

PROPORTIONAL ASSIST VENTILATION (PAV)

- Synchronized partial ventilatory assistance
- 'The more the patient pulls, the more pressure the machine generates'
- Allowance of the patient to attain whatever ventilation and breathing pattern seems to fit the ventilatory control system
- Automatic measurement of compliance & resistance every 4-10 breaths
- Then share the work of breathing between the patient and the machine



http://www.medtronic.com/content/dam/covidien/library/us/en/legacyimport/patientmonitoringrecovery/rms/3/pav-plus-software-resources.pdf

Ambrosino & Rossi. Thorax 2002;57:272

CONCLUSIONS

- Ventilatory control aims at achieving stable PaO_2, $PaCO_2$ and pH throughout various circumstances during life
- This task is achieved through complex neural networks, scattered throughout the CNS, but mostly in the medulla
- Three sources of input: chemoreceptors, mechanoreceptors, central command
- Different inputs predominate in different circumstances
  - Chemoreception in non-REM sleep
  - Central command in exercise and REM sleep
- High loop gain systems are unstable (instability expressed as periods of hypoventilation and periods of hyperventilation)
- Control of breathing is active during assisted mechanical ventilation and necessitate patient-ventilator synchrony (operator's mind)
- Novel technologies in the area of patient-ventilator synchrony are promising