Children's Hospital LOS ANGELES
DIVISION OF PEDIATRIC PULMONOLOGY AND SLEEP MEDICINE

CCHS NETWORK
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Tracing the History of Congenital Central Hypoventilation Syndrome

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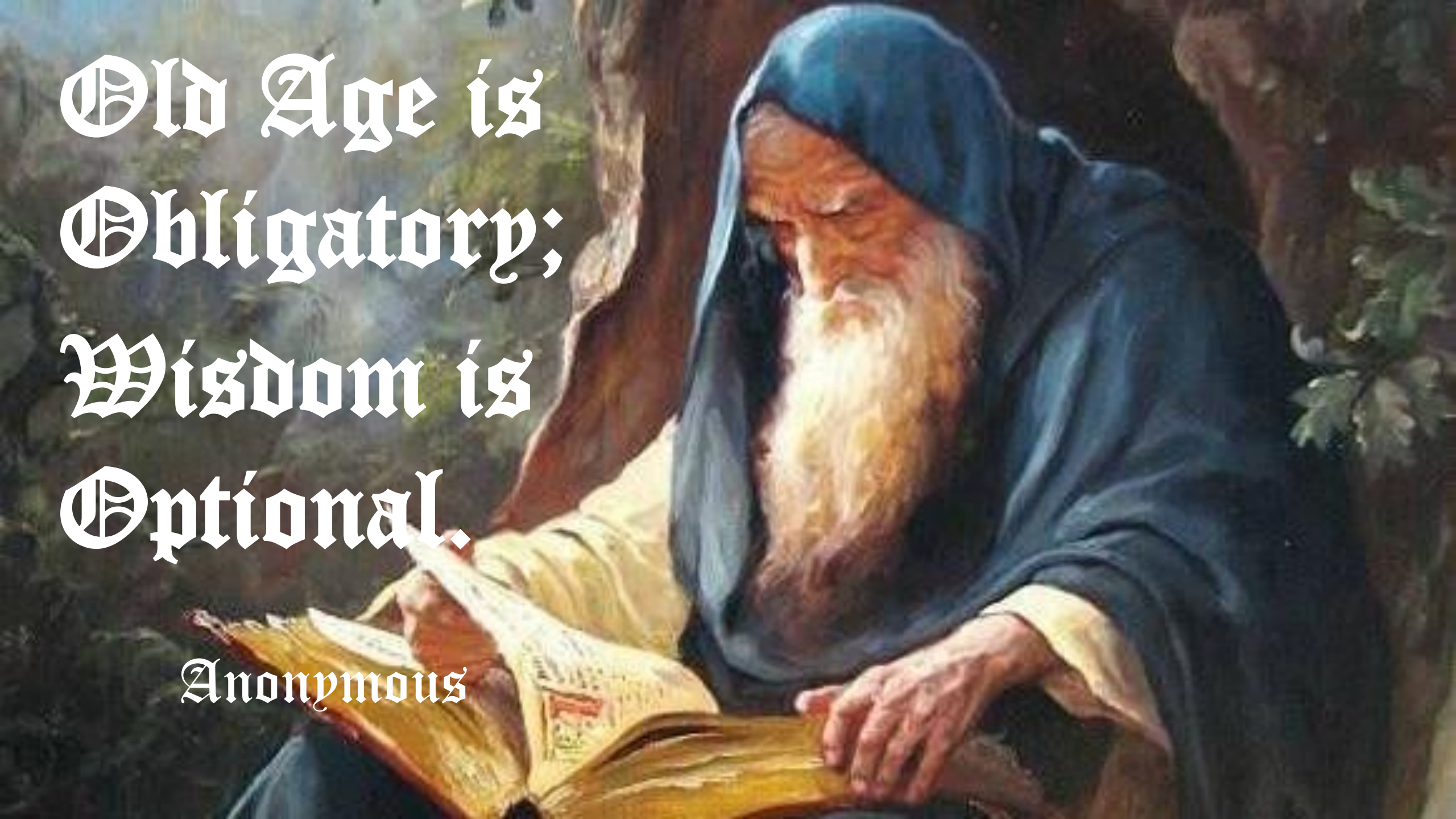
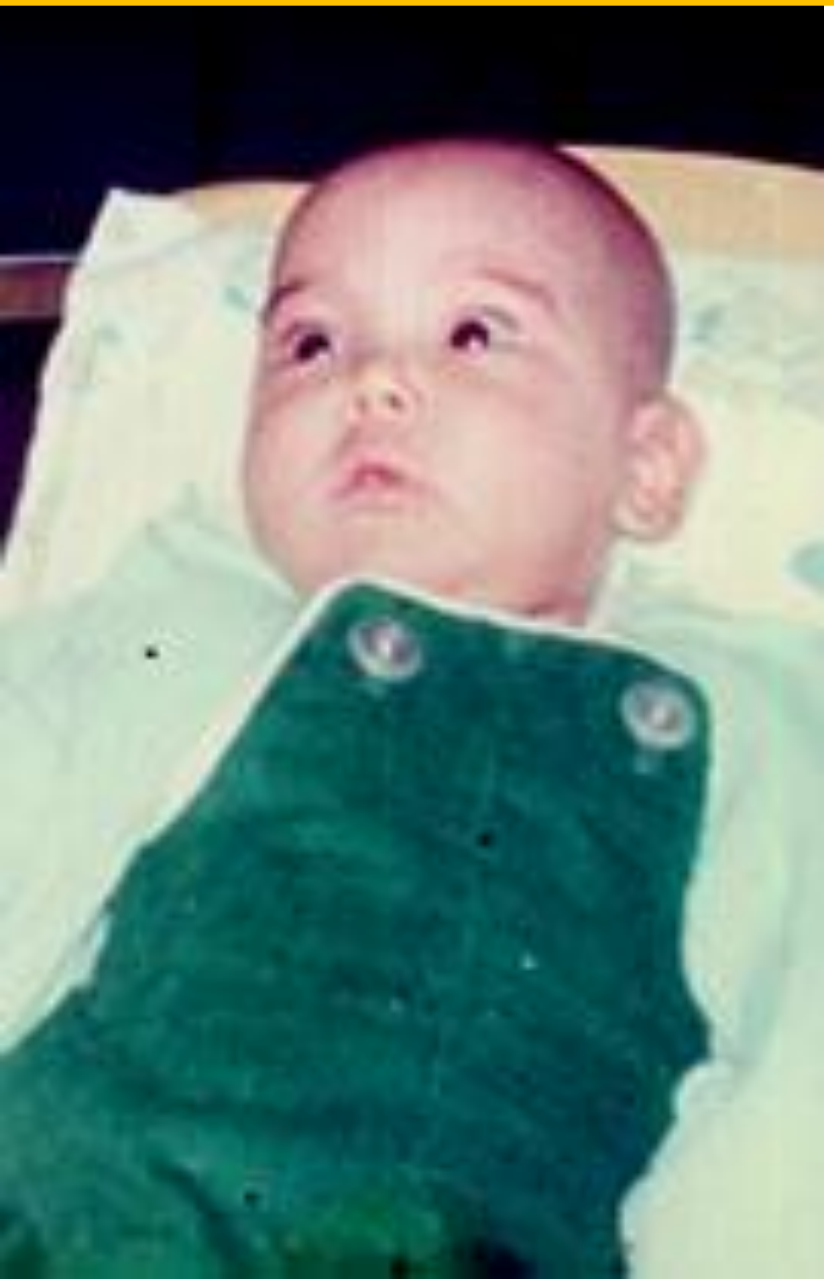
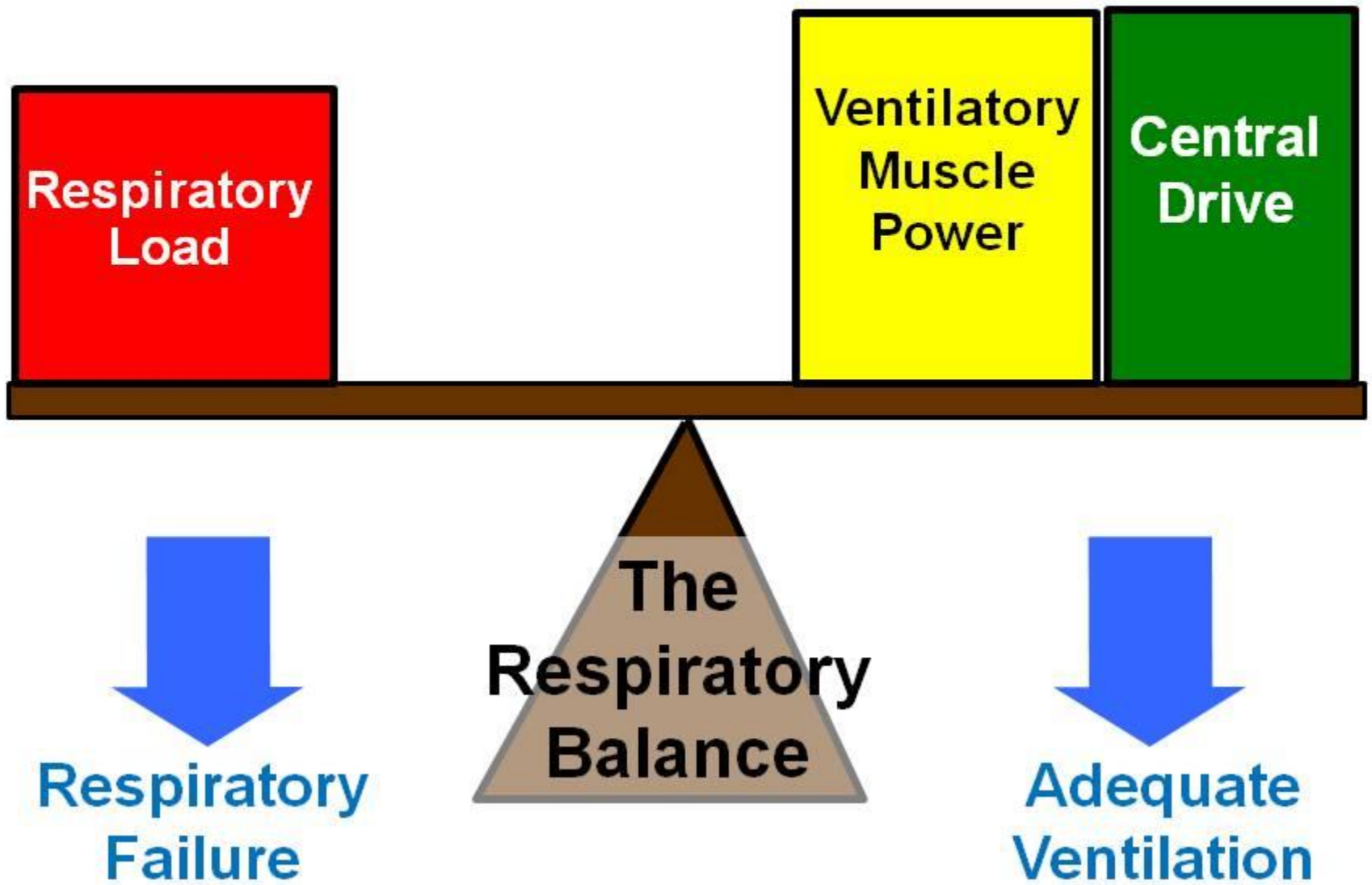
No Conflicts of Interest to Disclose

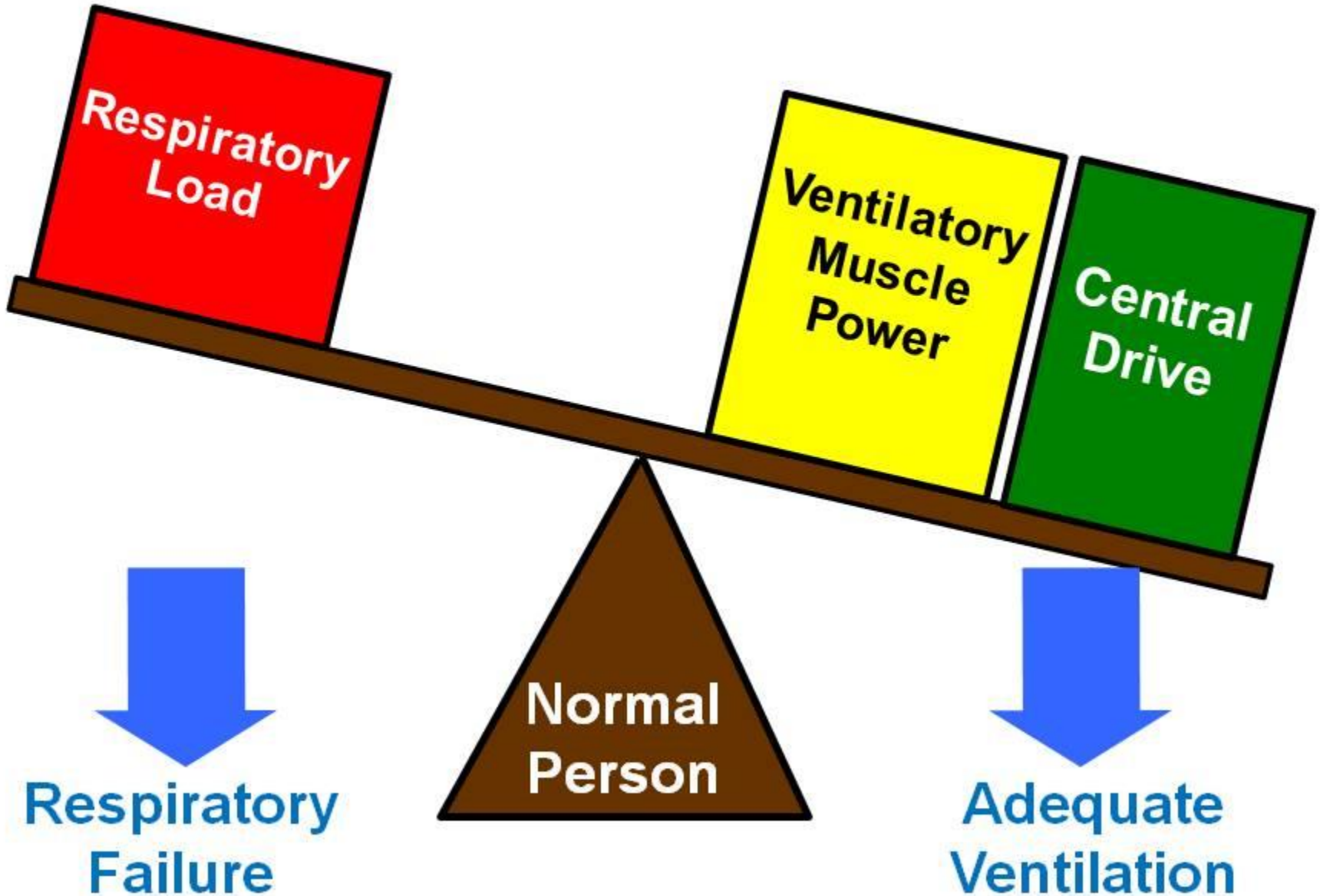

Old Age is Obligatory; Wisdom is Optional.
Anonymous

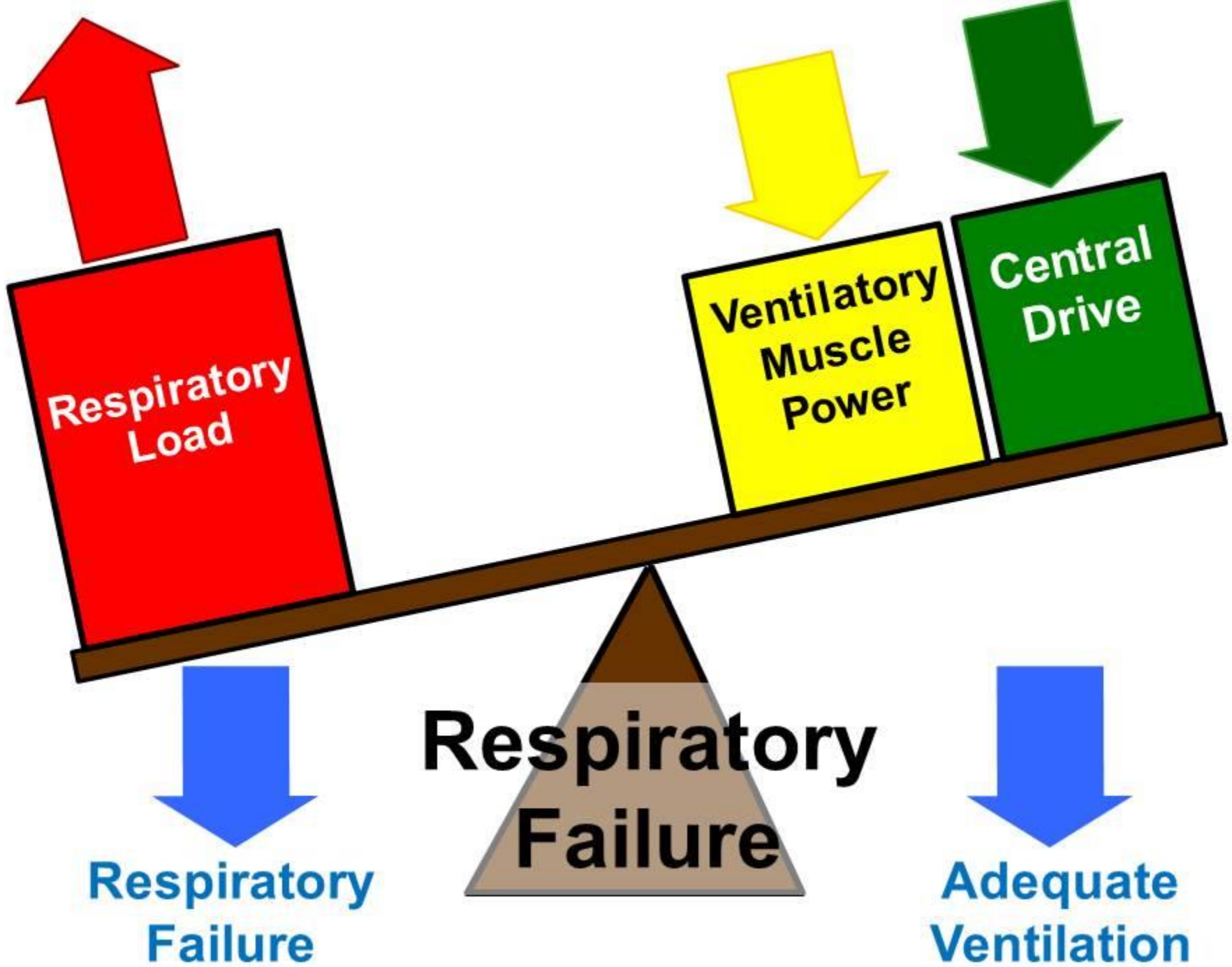
1977: How It Started For Us

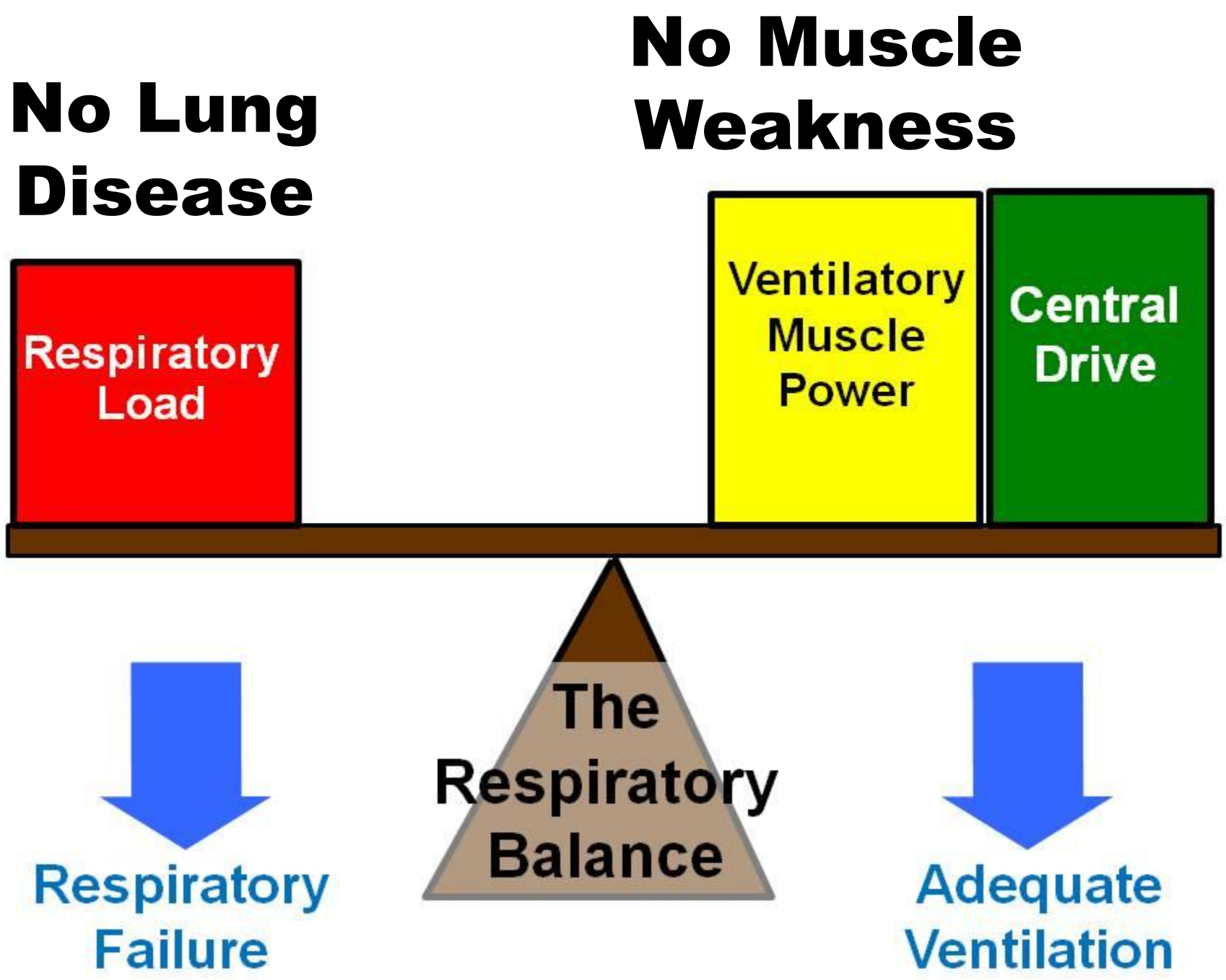


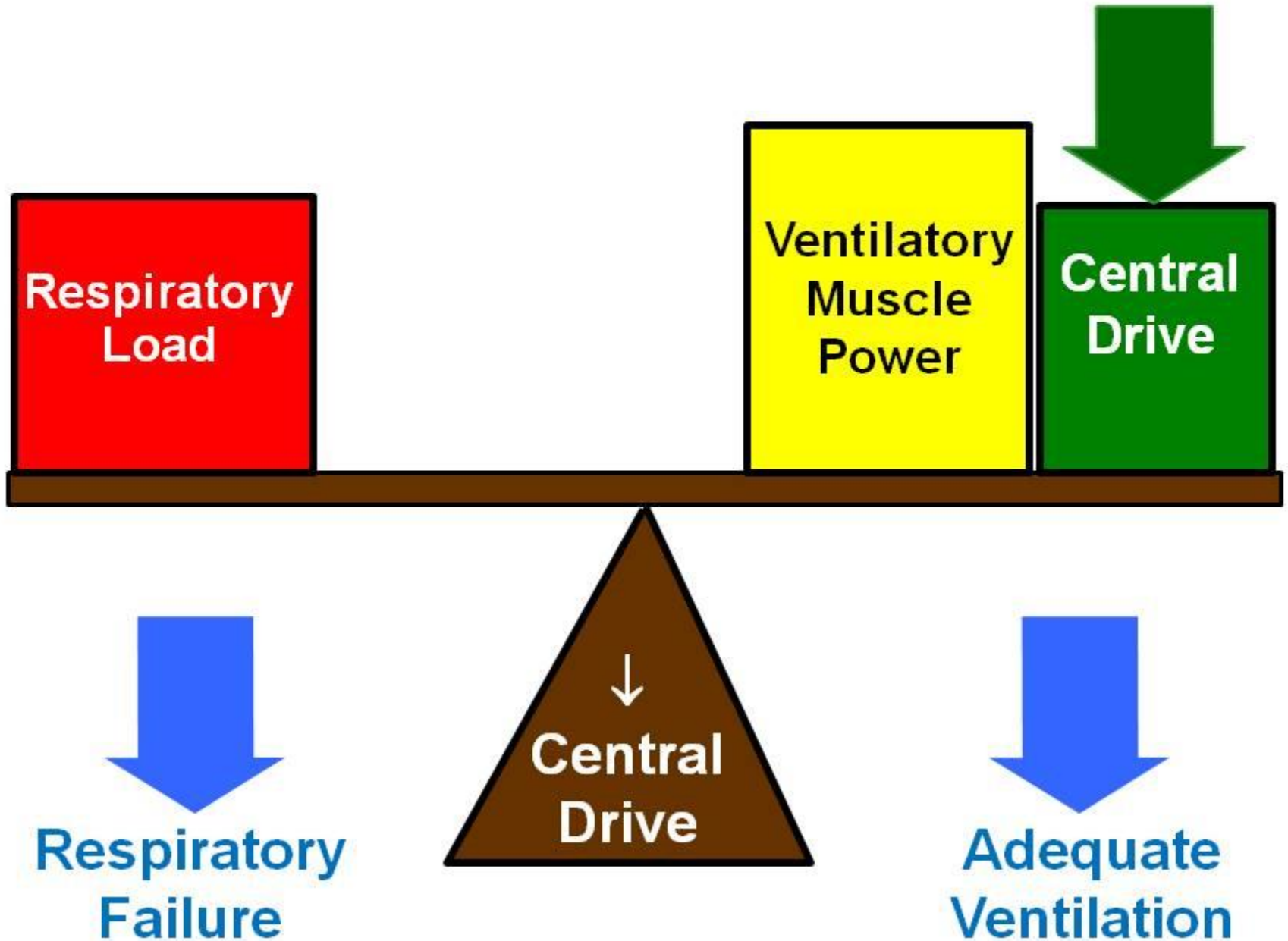
- 1-month old male admitted for pulmonary hypertension.
- Cardiac catheterization showed systemic pulmonary hypertension, but no structural heart disease.
- Recurrent cycle of respiratory arrest; to PICU; ventilation; weaned over a few days; back to the floor again; arrested again; … the cycle goes on and on.

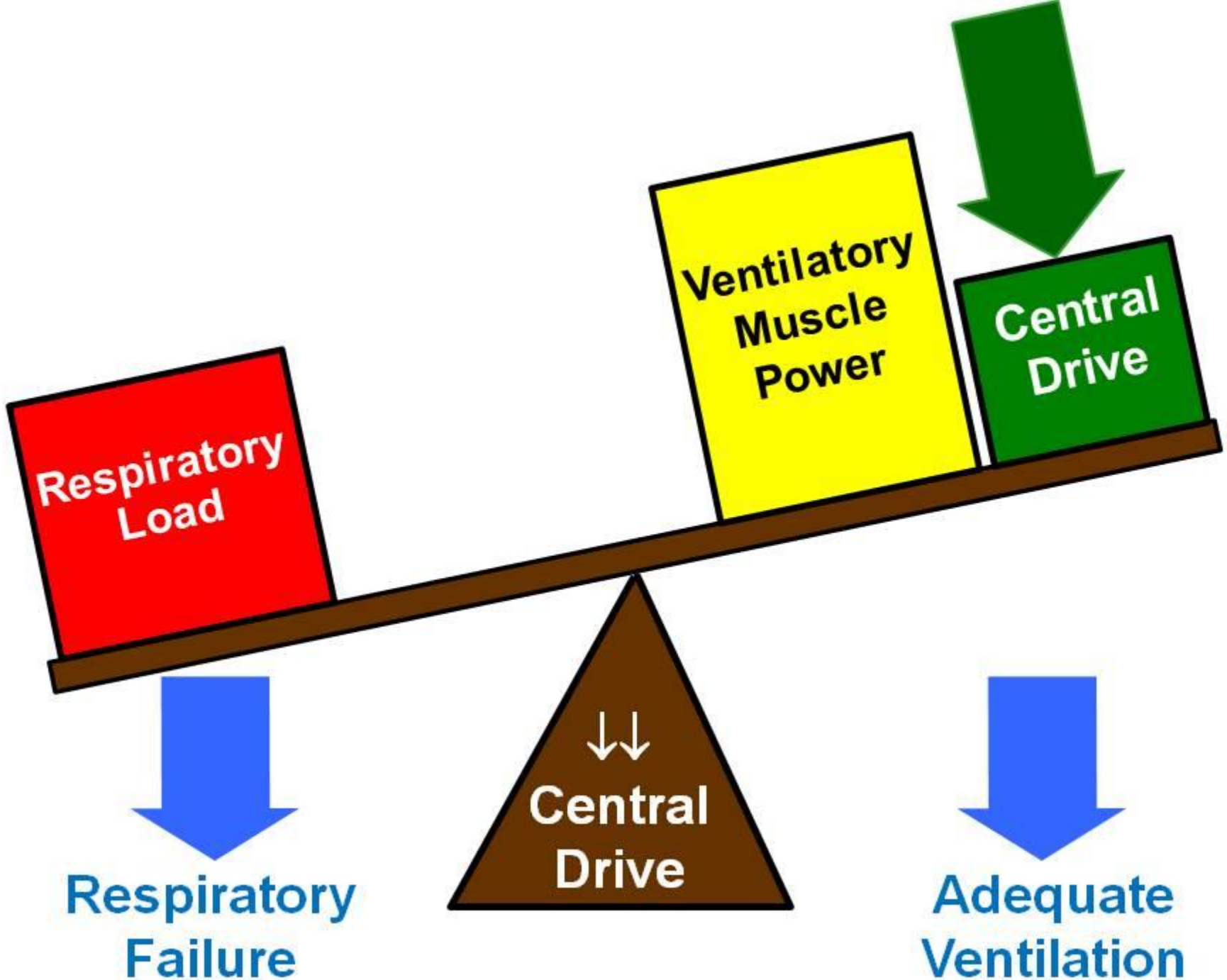

Respiratory Load
Ventilatory Muscle Power
Central Drive
The Respiratory Balance
Respiratory Failure
Adequate Ventilation


Respiratory Load
Ventilatory Muscle Power
Central Drive
Normal Person
Respiratory Failure
Adequate Ventilation


Respiratory Load
Ventilatory Muscle Power
Central Drive
Respiratory Failure
Respiratory Failure
Adequate Ventilation

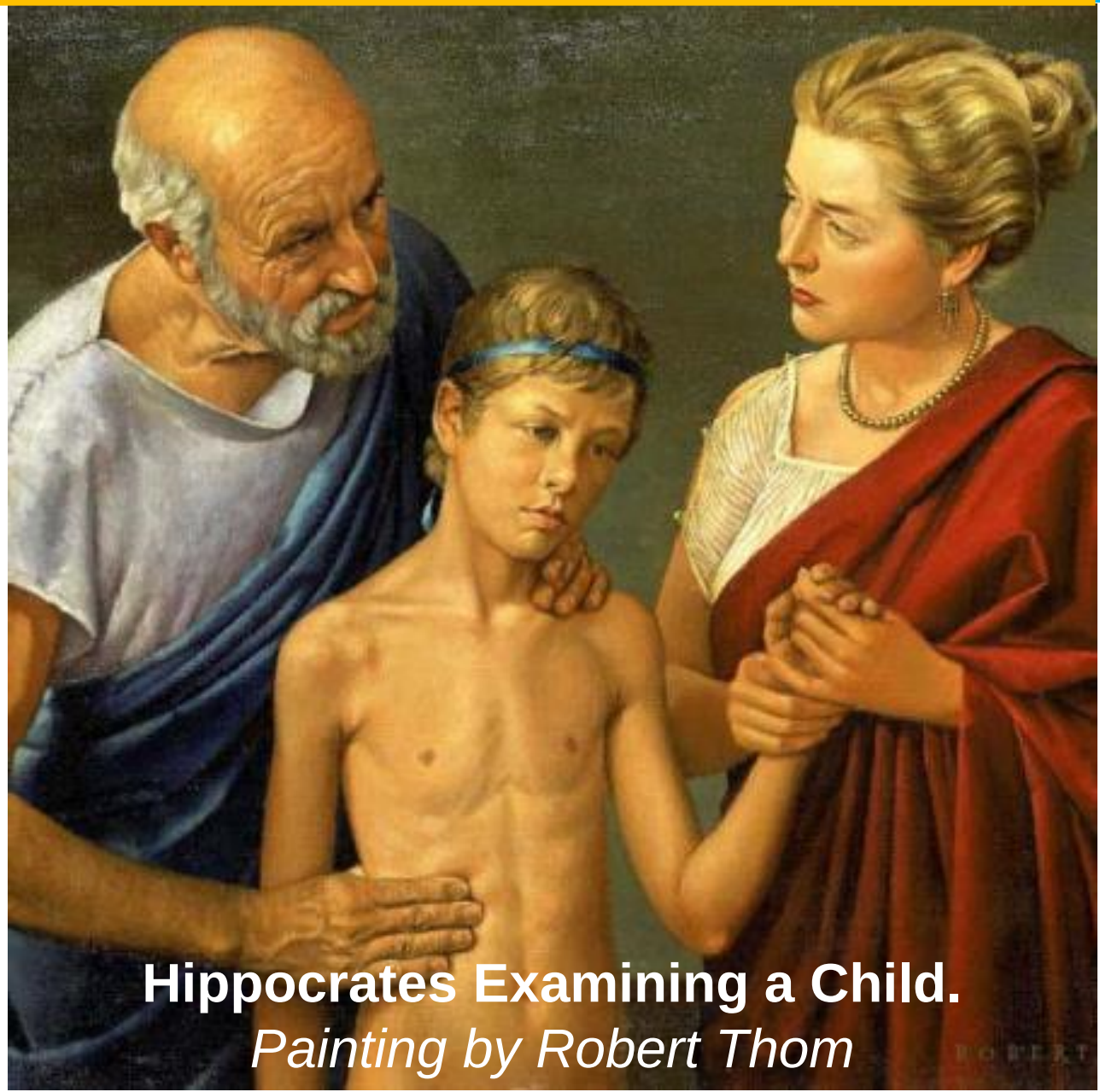

No Lung Disease
No Muscle Weakness
Respiratory Load
Ventilatory Muscle Power
Central Drive
The Respiratory Balance
Respiratory Failure
Adequate Ventilation


Respiratory Load
Ventilatory Muscle Power
Central Drive
↓
Central Drive
Respiratory Failure
Adequate Ventilation


Respiratory Load
Ventilatory Muscle Power
Central Drive
↓↓
Central Drive
Respiratory Failure
Adequate Ventilation

Three Diagnoses You Never Make

- The one you don't **know** about.
- The one you don't **think** about.
- The one you don't **ask** about or **look for**.



Hippocrates Examining a Child.
Painting by Robert Thom

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FAILURE OF AUTOMATIC CONTROL OF VENTILATION (ONDINE'S CURSE)

REPORT OF AN INFANT BORN WITH THIS SYNDROME AND REVIEW OF THE LITERATURE[1]

ROBERT B. MELLINS, M.D.[2] HENRY H. BALFOUR, JR., M.D., GERARD M. TURINO, M.D.[3] AND ROBERT W. WINTERS, M.D.[4]

Ondine: Live Hans. You too will forget.
Hans: Live! It's easy to say. If at least I could work up a little interest in living, but I'm too tired to make the effort. Since you left me, Ondine, all the things my b once did by itself, it does now only by special order . It's an exhausting piece of management I've undertal I have to supervise five senses, two hundred bones, a thousand muscles. A single moment of inattention, a forget to breathe. He died, they will say, because it w a nuisance to breathe . . .
From Act 3, Ondine by Jean Giraudoux (15)

I. INTRODUCTION

Alveolar hypoventilation resulting from disease of the lungs, dysfunction of the bellows action of the chest, or from destructive lesions of the central nervous system is well recognized (9). Alveolar hypoventilation in the absence of these conditions is

The original
Jean Giraud
more applic
there is no
alveolar hyp
normality in
tion by the central nervous system.
In all of the patients previously recognized

Mellins, R.B., et al. *Medicine, 49:* 487-504, 1970.

Primary Alveolar Hypoventilation Syndrome (Ondine's Curse)

Association With Manifestations of Hypothalmic Disease

L. S. FISHMAN, MD; J. H. SAMSON, MD; AND D. R. SPERLING, MD, LOS ANGELES

THIS PAPER REPORTS a case of alveolar hypoventilation associated with presumptive evidence of hypothalamic disease. Primary alveolar hypoventilation syndromes have been reported in adults and children, presumably secondary to brain stem disease [3-16] and to obesity in adults [17-27] and children.[28-32] To our knowledge, alveolar hypoventilation in patients with clinical evidence of hypothalamic disease has not been reported.

Report of a Case

First Admission.—A 3½-year-old white male (Fig 1, *A* and *B*) was in good health until nine months prior to admission, when he developed [illegible] Angeles where treatment with oxygen seemed to relieve the distress.

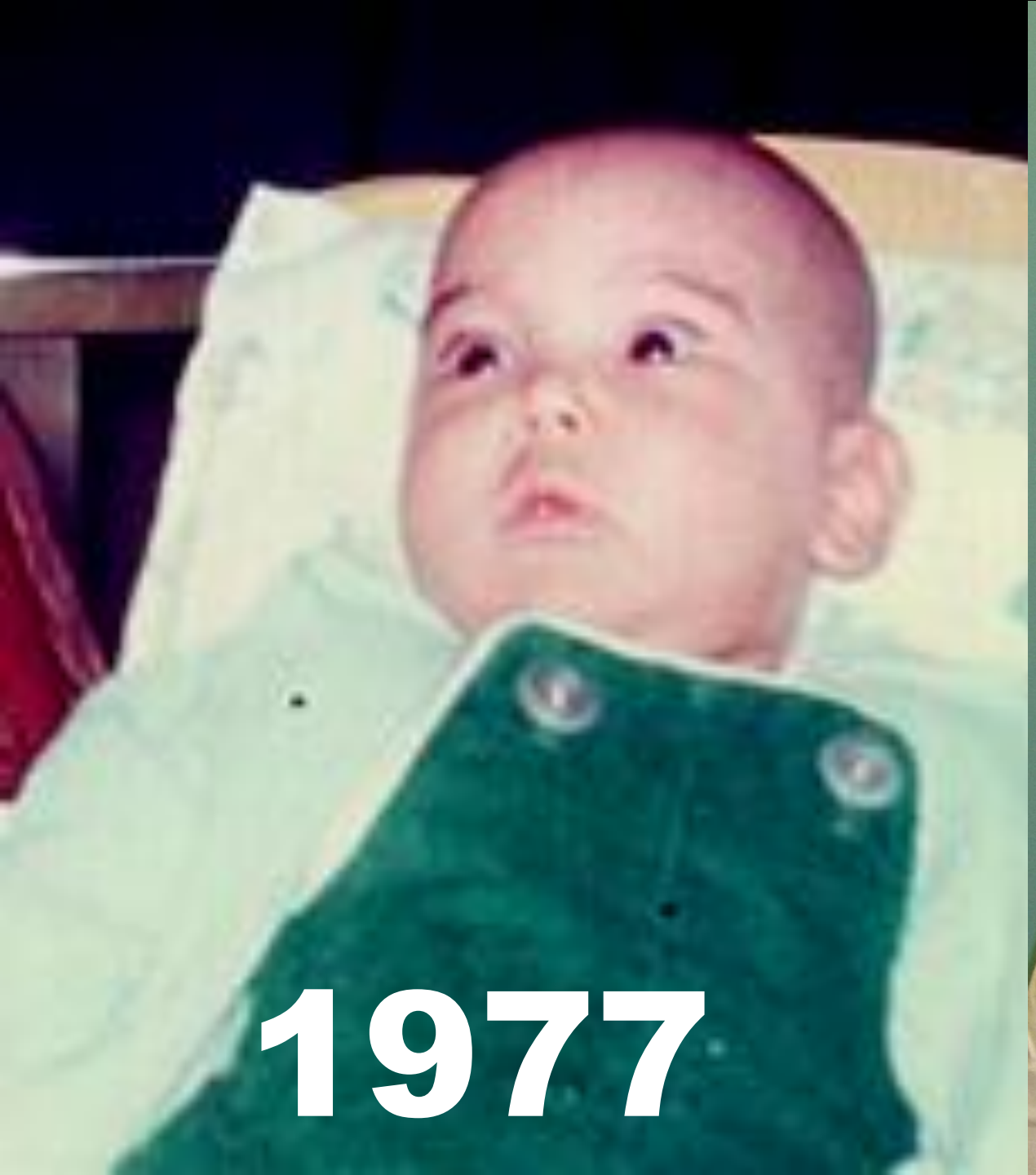
The past history revealed normal linear growth and development. He had been considered more intelligent than the average child of his age. He was noted to have had a right exotropia for 12 months prior to admission.

The patient's older sister had died at 3 years of age, 18 months before the patient's first admission, and nine months prior to his first symptoms of lethargy and increased appetite. The cause of death, confirmed by autopsy, was encephalitis of unknown etiology. The patient had bronchitis lasting three days during his sister's fatal illness. The chest x-ray revealed the heart to be of normal size and no abnormal neurologic findings were noted.

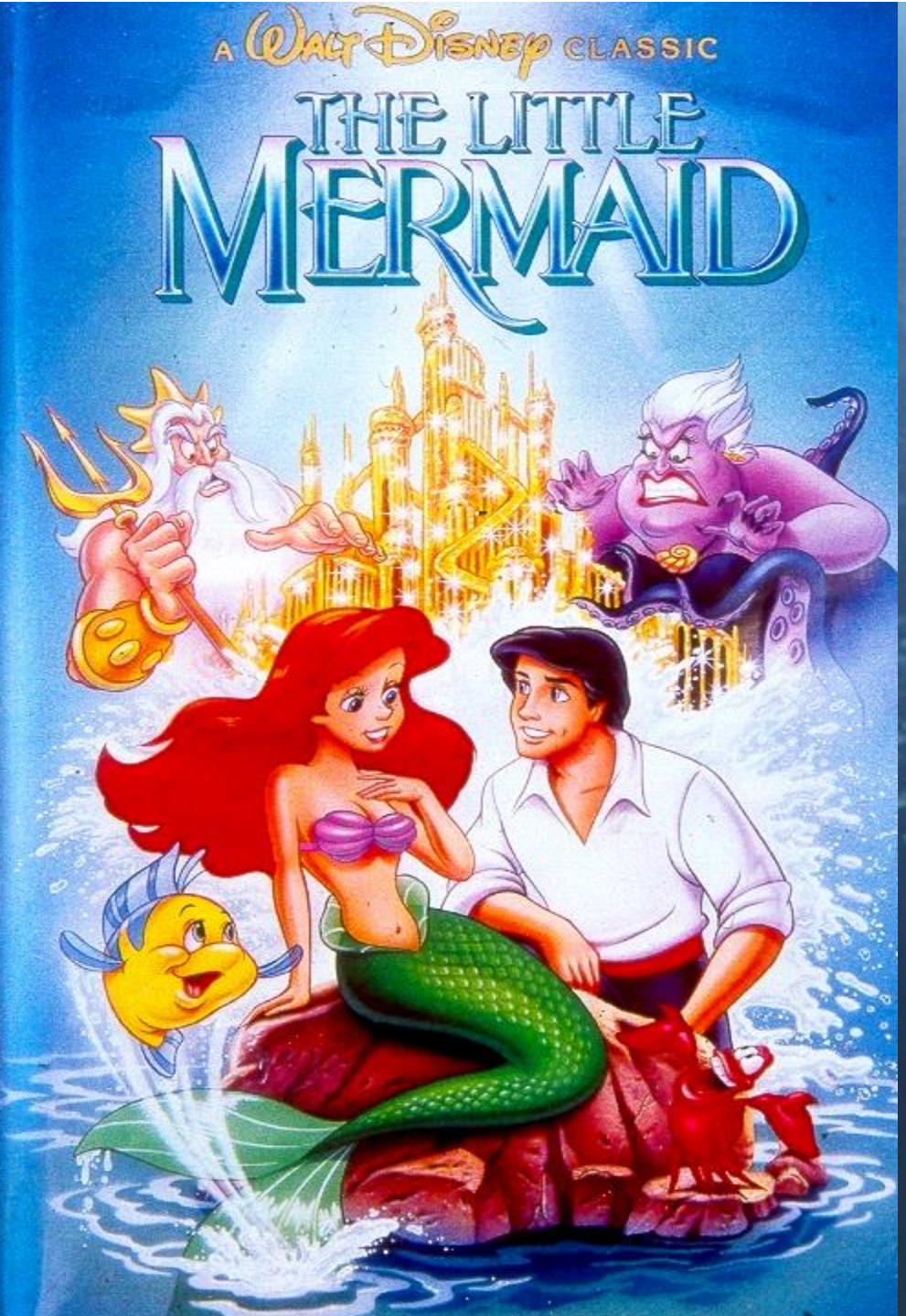
On admission on Dec 10, 1963, physical examination revealed moderate obesity, no cyanosis, and no acute

Fishman, L.S., et al. *Amer. J. Dis. Child., 110:* 155-161, 1965.

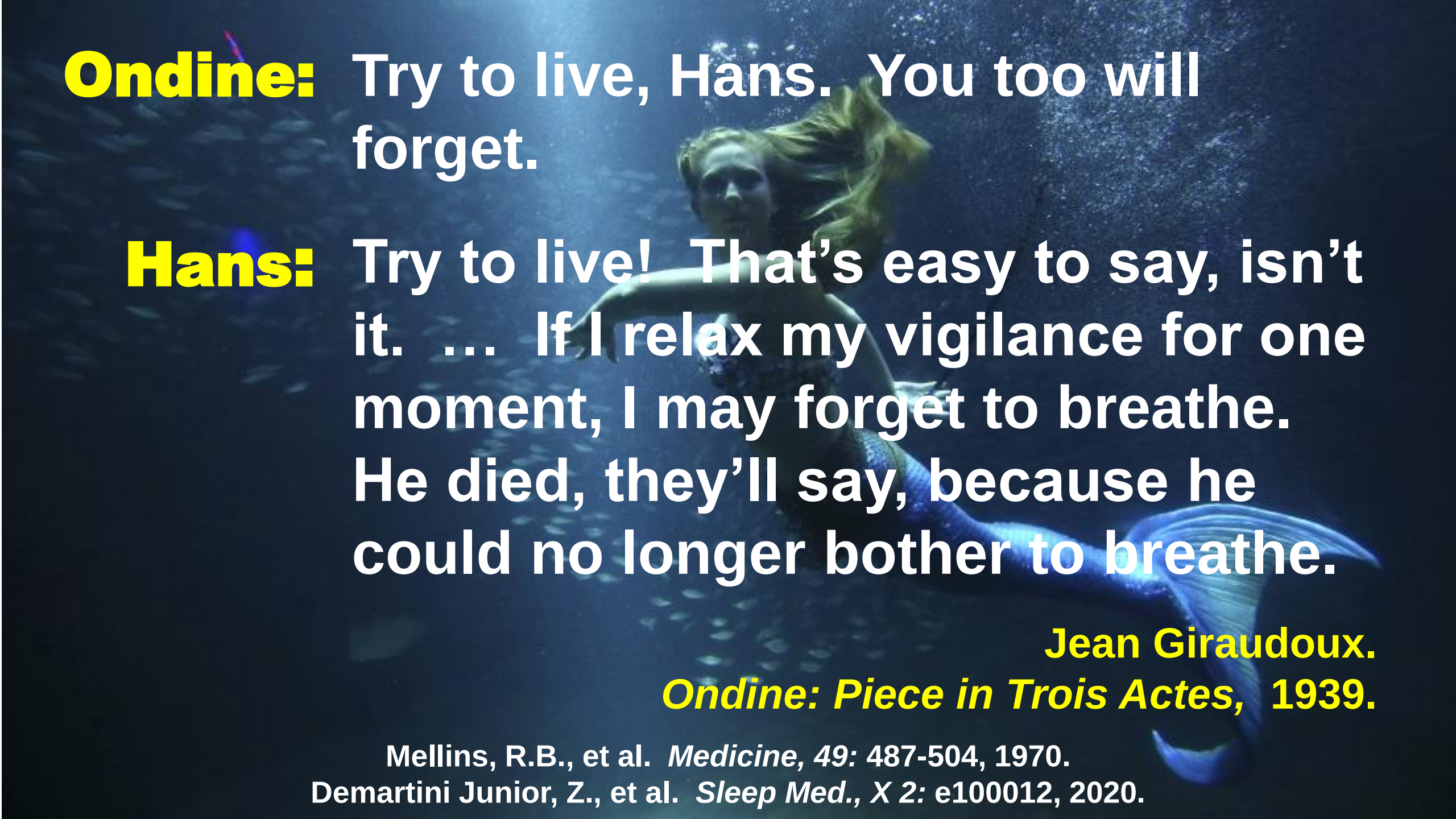

bird
corporation
palm springs
california
u.s.a
MARK 7
respirator
OFF
inspiratory
time
5 FLOWRATE
for pulmonary conformance
pull out
2 AIR-MIX
expiratory
time
3 for APNEA
DECREASE
OFF
PRESSURE
R15
R10
Limit
1
7
5


1977


2021



Mellins, R.B., et al. *Medicine, 49:* 487-504, 1970.
Demartini Junior, Z., et al. *Sleep Med., X 2:* e100012, 2020.



Ondine: Try to live, Hans. You too will forget.

Hans: Try to live! That's easy to say, isn't it. … If I relax my vigilance for one moment, I may forget to breathe. He died, they'll say, because he could no longer bother to breathe.

Jean Giraudoux.
***Ondine: Piece in Trois Actes,* 1939.**

Mellins, R.B., et al. *Medicine, 49:* 487-504, 1970.
Demartini Junior, Z., et al. *Sleep Med., X 2:* e100012, 2020.

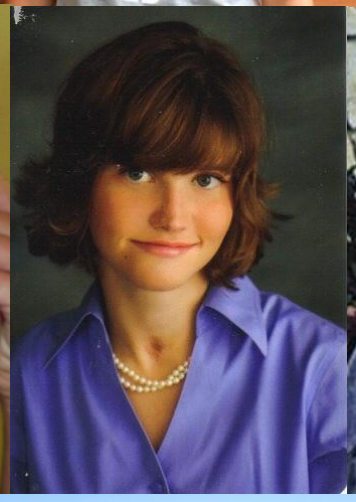



Verizon FiOS
Trojans
Trojans
20 03

NAMA-STAY
IN
BED

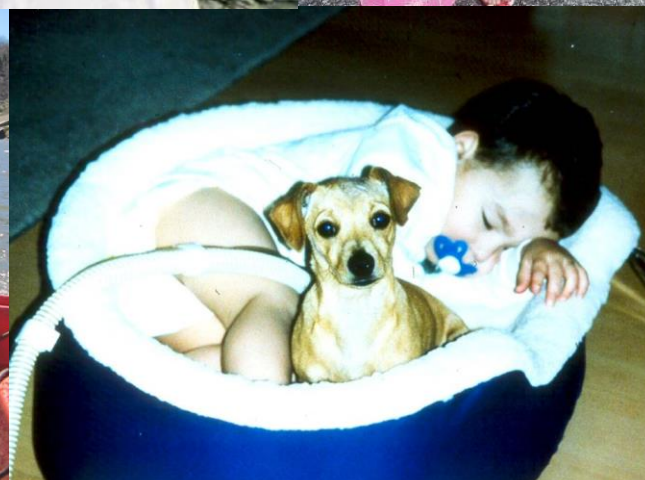


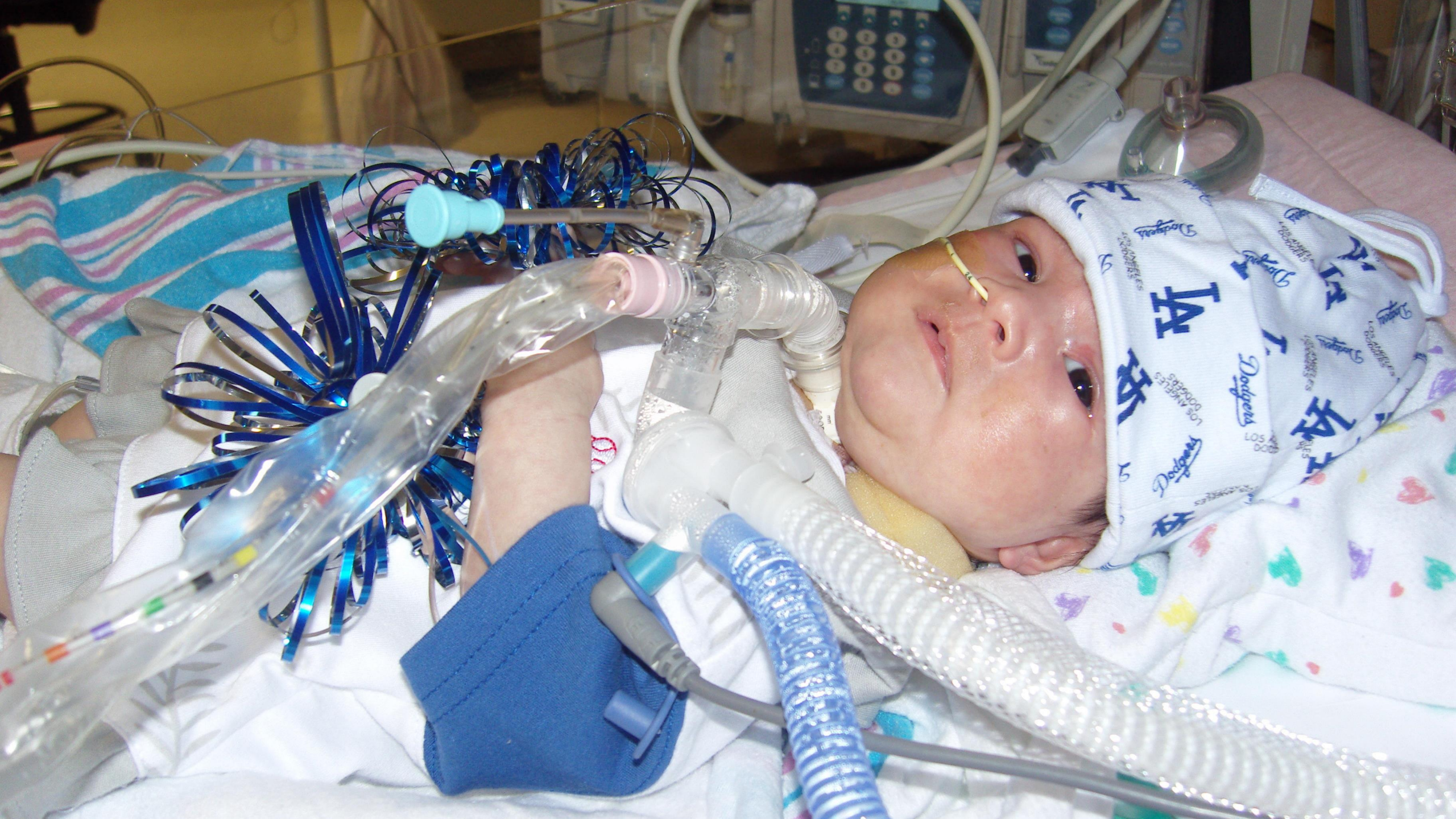


MONIQUE PONCE
RT STUDENT
09/03/2010






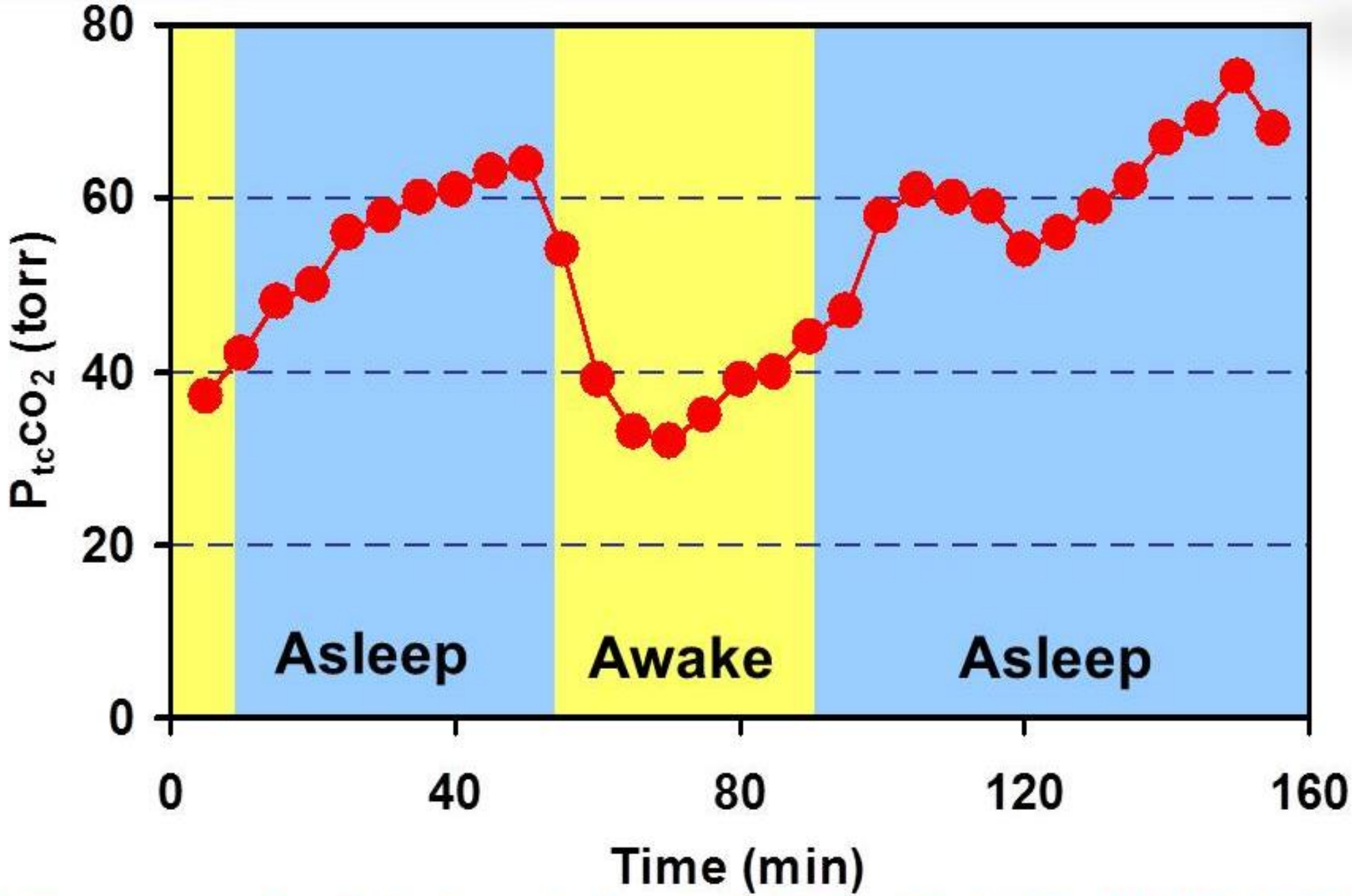



Dodgers
LOS ANGELES

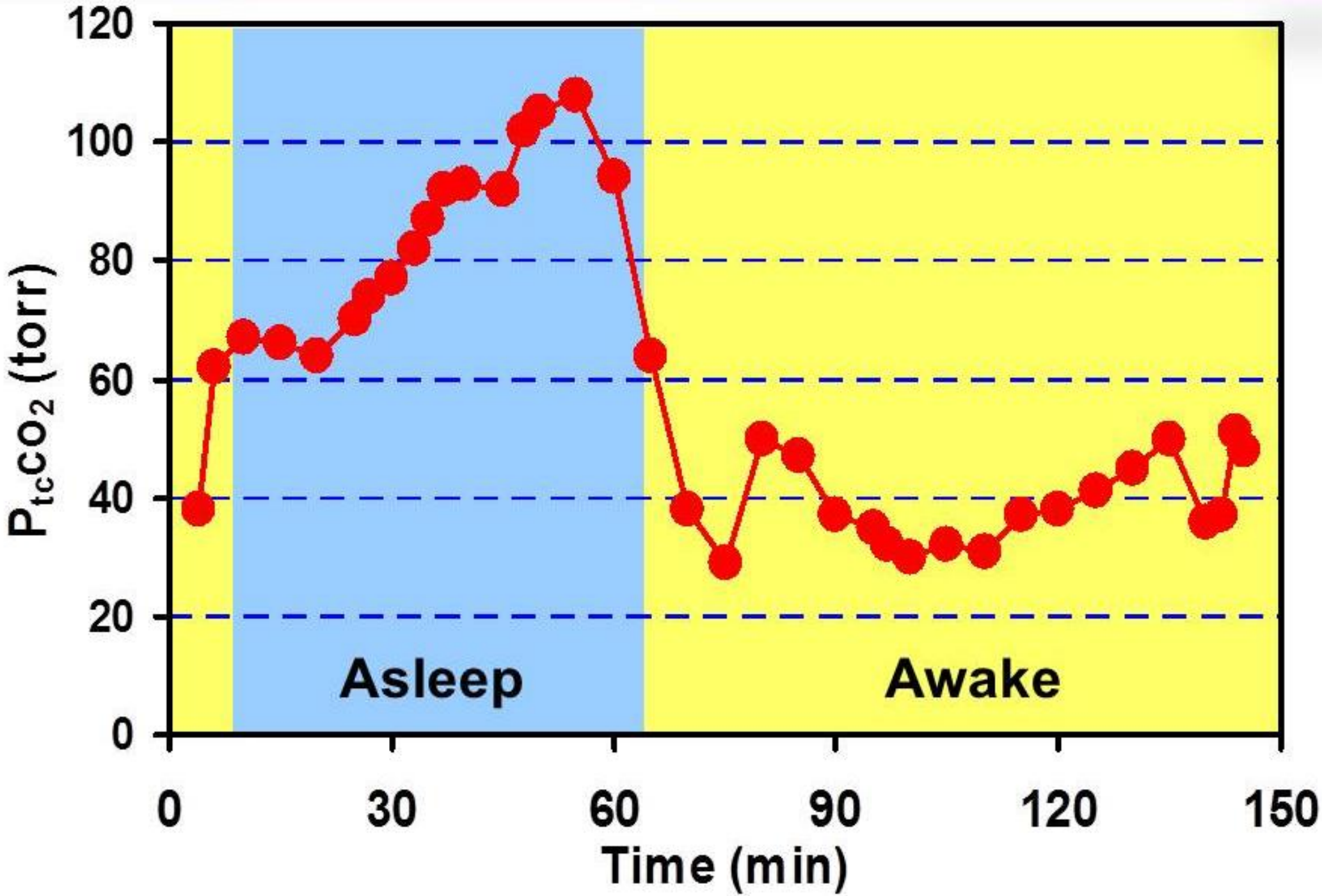
Congenital Central Hypoventilation Syndrome (CCHS)

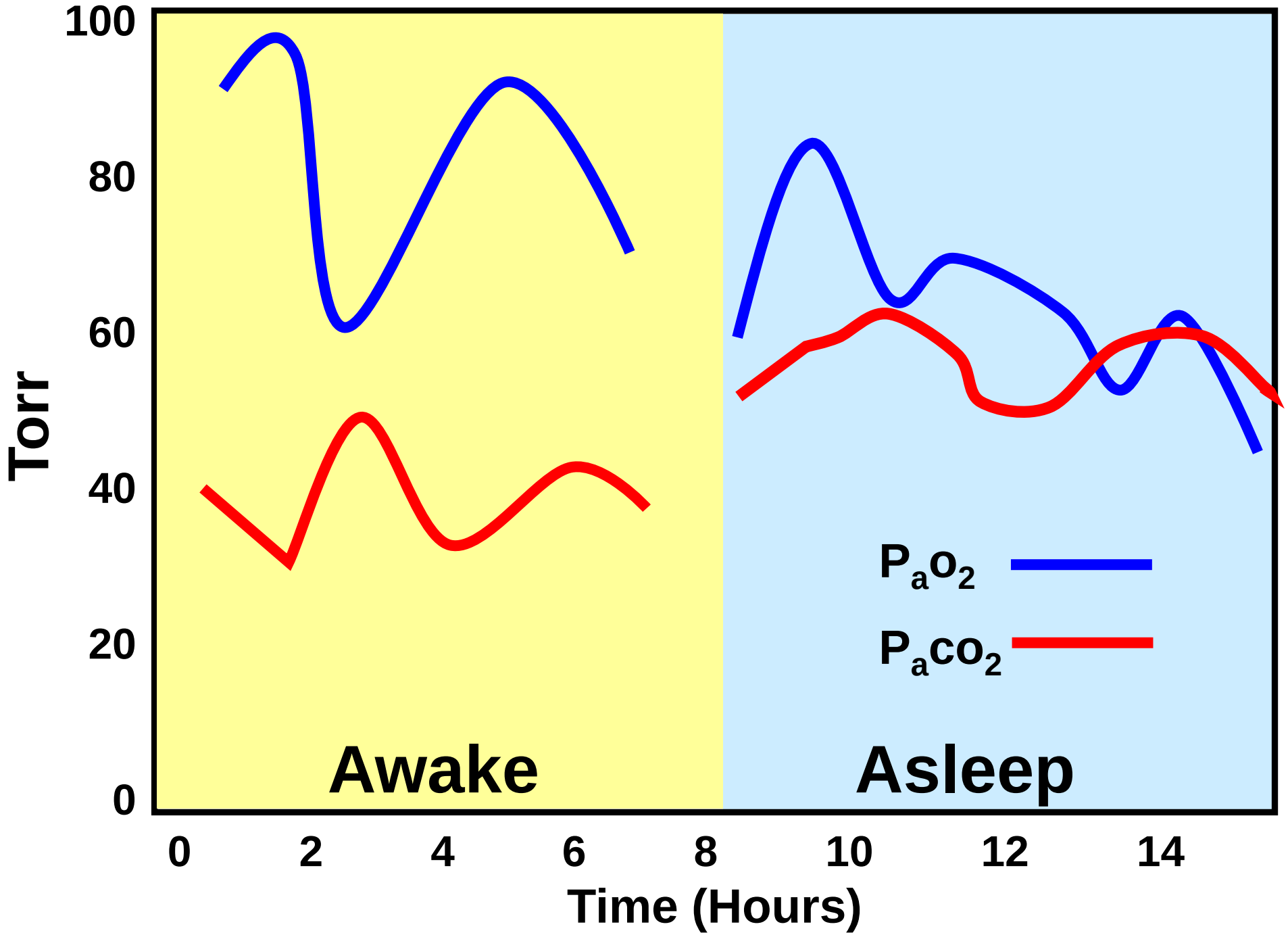
- Failure of automatic control of breathing.
- Hypoventilation and/or hypoxia which is worse during sleep than during wakefulness.
- Absence of primary lung disease, heart disease, ventilatory muscle weakness, neurologic or metabolic disease.

Chen, M.L., and T.G. Keens. *Paediatr. Resp. Rev., 5:* 182-189, 2004.
Weese-Mayer, D.E., et al. *Amer. J. Resp. Crit. Care Med., 181:* 626-644, 2010.
Kasi, A., et al. *Pediatr. Health Med. Therap., 7:* 99-107, 2016.
Maloney, M.A., et al. *Expert Rev. Respir. Med., 12:* 282-292, 2018.

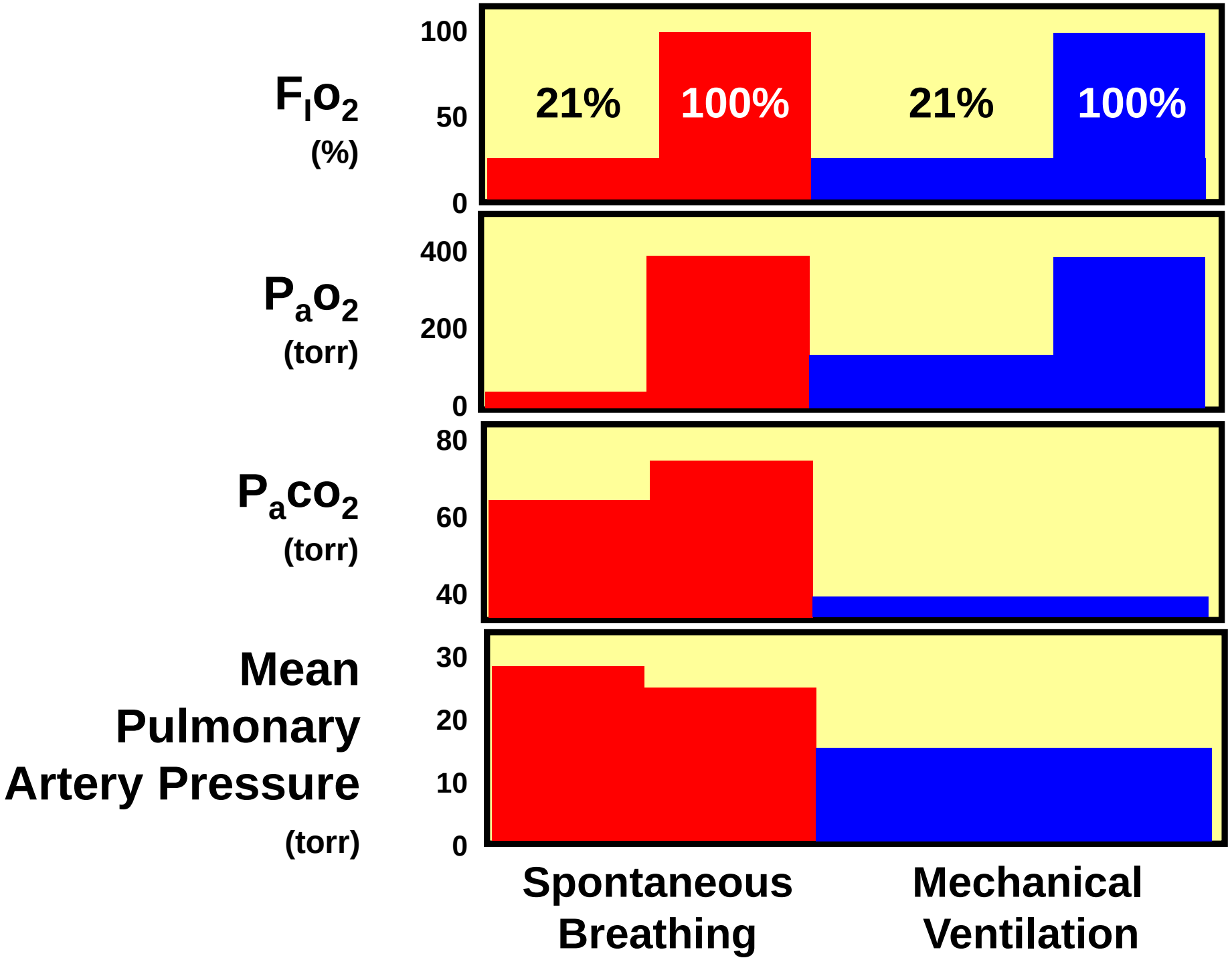


Sritippayawan, S., et al. *Amer. J. Respir. Crit. Care Med., 166:* 367-369, 2002.


120
100
80
60
40
20
0
$P_{tc}CO_2$ (torr)
Asleep
Awake
0
30
60
90
120
150
Time (min)


100
80
60
40
20
0
Torr
0
2
4
6
8
10
12
14
Time (Hours)
Awake
Asleep
P_aO_2
P_aCO_2


Do they need to be ventilated?
Wouldn't supplemental oxygen be good enough?
Trojans
2003


F_IO_2
(%)
100
50
0
21%
100%
21%
100%
P_aO_2
(torr)
400
200
0
P_aCO_2
(torr)
80
60
40
Mean
Pulmonary
Artery Pressure
(torr)
30
20
10
0
Spontaneous
Breathing
Mechanical
Ventilation

Treatment of CCHS

Problem:

- CCHS patients do not breathe.

Treatment:

- Breathe for them!

Chen, M.L., and T.G. Keens. *Paediatr. Resp. Rev., 5:* 182-189, 2004.
Weese-Mayer, D.E., et al. *Amer. J. Resp. Crit. Care Med., 181:* 626-644, 2010.
Kasi, A., et al. *Pediatr. Health Med. Therap., 7:* 99-107, 2016.
Maloney, M.A., et al. *Expert Rev. Respir. Med., 12:* 282-292, 2018.

Treatment of CCHS

- **Ensure optimal ventilation and oxygenation during sleep and wakefulness.**
- **Supplemental oxygen alone will not prevent pulmonary hypertension.**
- **Ventilation is required, not just oxygen.**

Chen, M.L., and T.G. Keens. *Paediatr. Resp. Rev., 5:* 182-189, 2004.
Weese-Mayer, D.E., et al. *Amer. J. Resp. Crit. Care Med., 181:* 626-644, 2010.
Kasi, A., et al. *Pediatr. Health Med. Therap., 7:* 99-107, 2016.
Maloney, M.A., et al. *Expert Rev. Respir. Med., 12:* 282-292, 2018.

Treatment of CCHS

- **Pharmacological respiratory stimulants do not work.**
- **Disorder is life-long.**
- **Weaning from ventilatory support is not realistic.**

Chen, M.L., and T.G. Keens. *Paediatr. Resp. Rev., 5:* 182-189, 2004.
Weese-Mayer, D.E., et al. *Amer. J. Resp. Crit. Care Med., 181:* 626-644, 2010.
Kasi, A., et al. *Pediatr. Health Med. Therap., 7:* 99-107, 2016.
Maloney, M.A., et al. *Expert Rev. Respir. Med., 12:* 282-292, 2018.

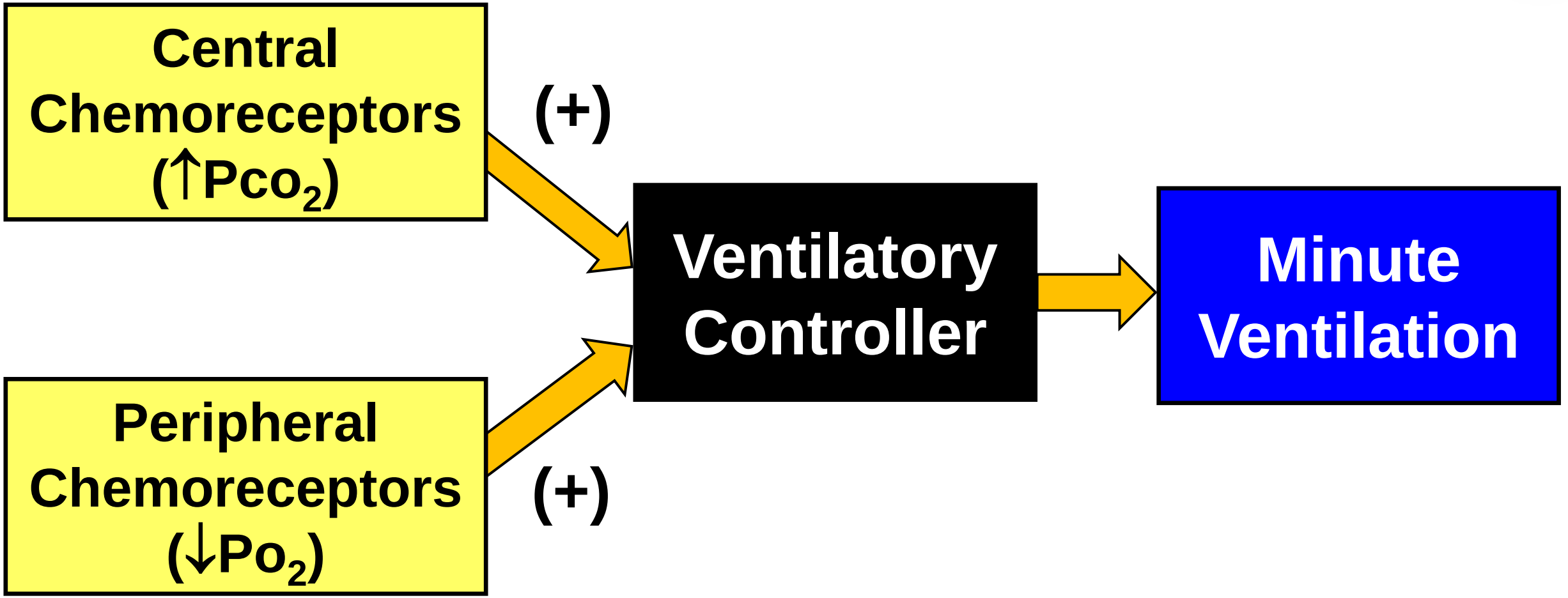
Early Reports of Long-Term Survival at Home

- 12-22 years after Mellins' description, four centers report successful home mechanical ventilation of 55 children with CCHS at home.
- Good quality of life.
- Good survival.

Guilleminault, C., et al. *Pediatrics, 70:* 684-694, 1982.
Oren, J., et al. *Pediatrics, 80:* 375-380, 1987.
Marcus, C.L., et al. *J. Pediatr., 119:* 888-895, 1991.
Weese-Mayer, D.E., et al. *J. Pediatr., 120:* 381-387, 1992.

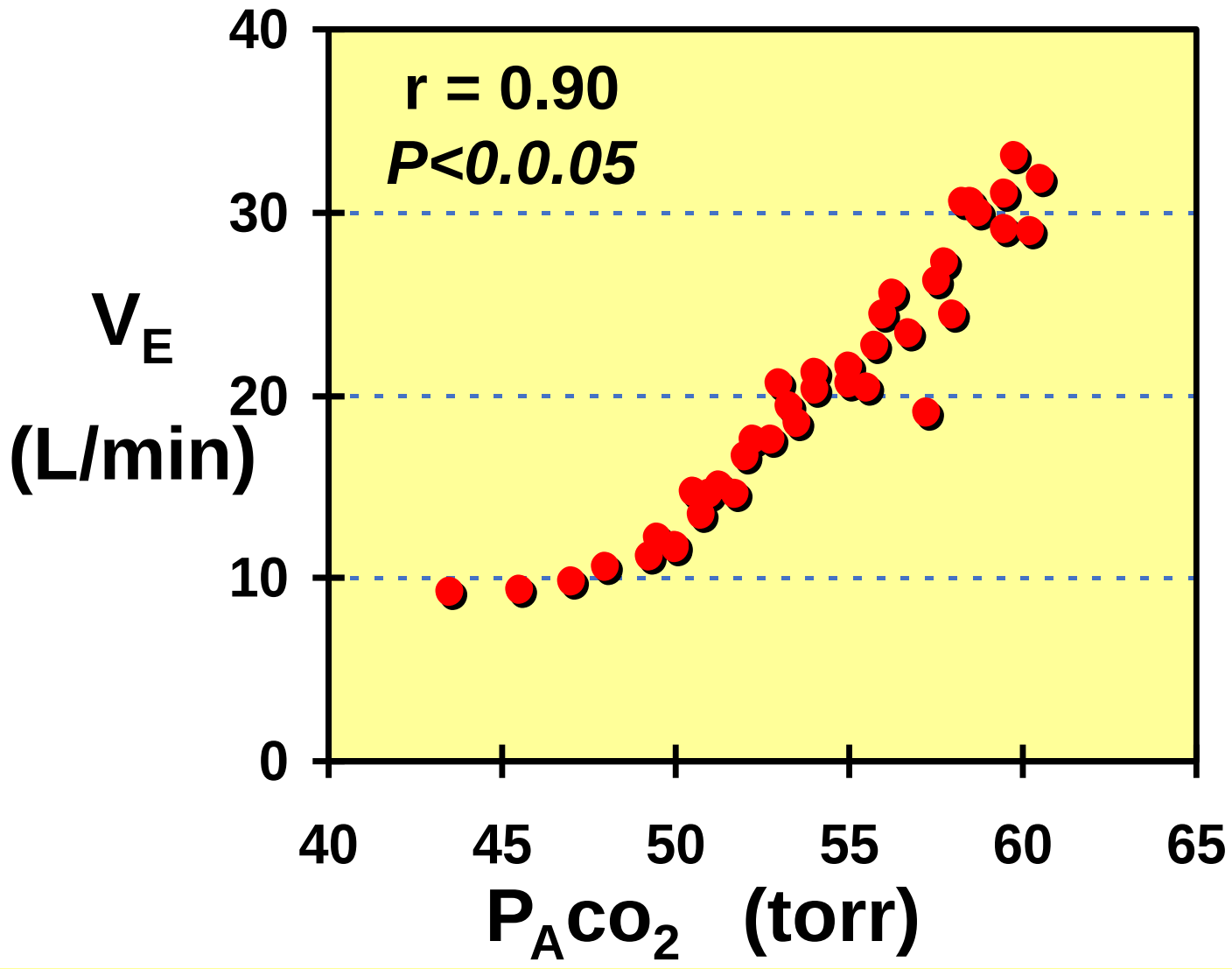

HI!

Control of Breathing



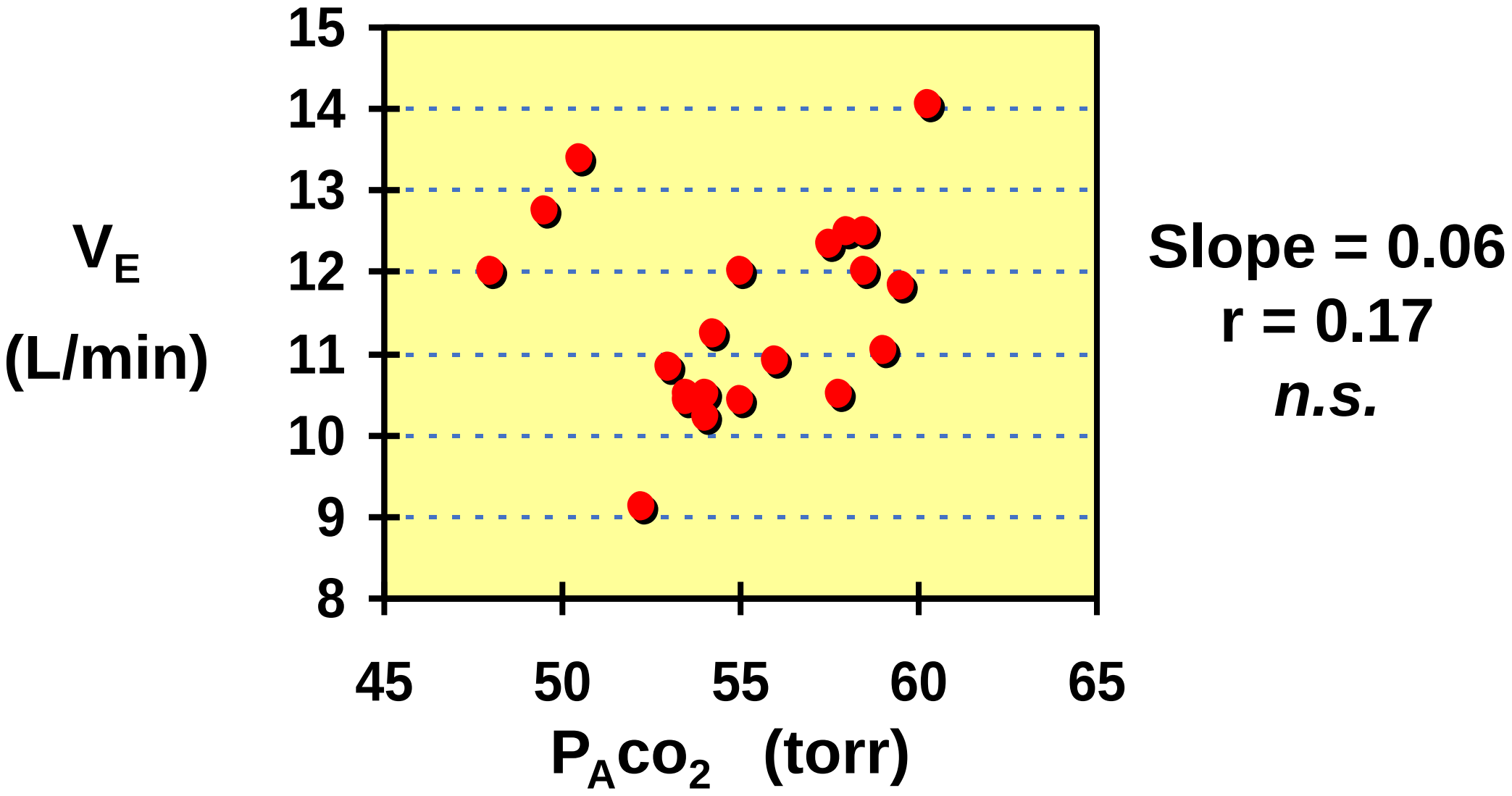
Sensors Integration Motor Response

Normal Hypercapneic Ventilatory Response

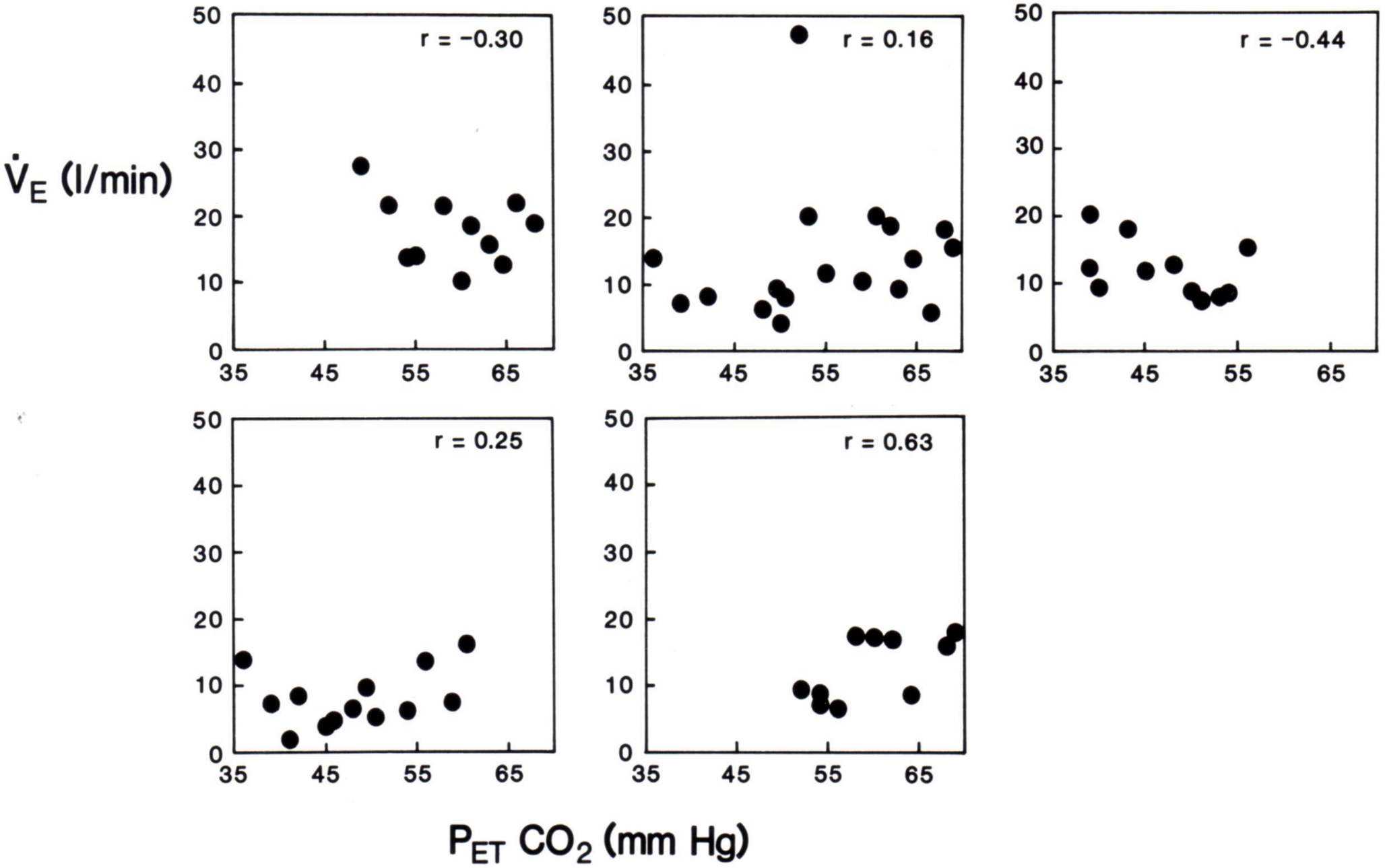


Rebreathing Hypercapnic Ventilatory Response

Congenital Central Hypoventilation Syndrome

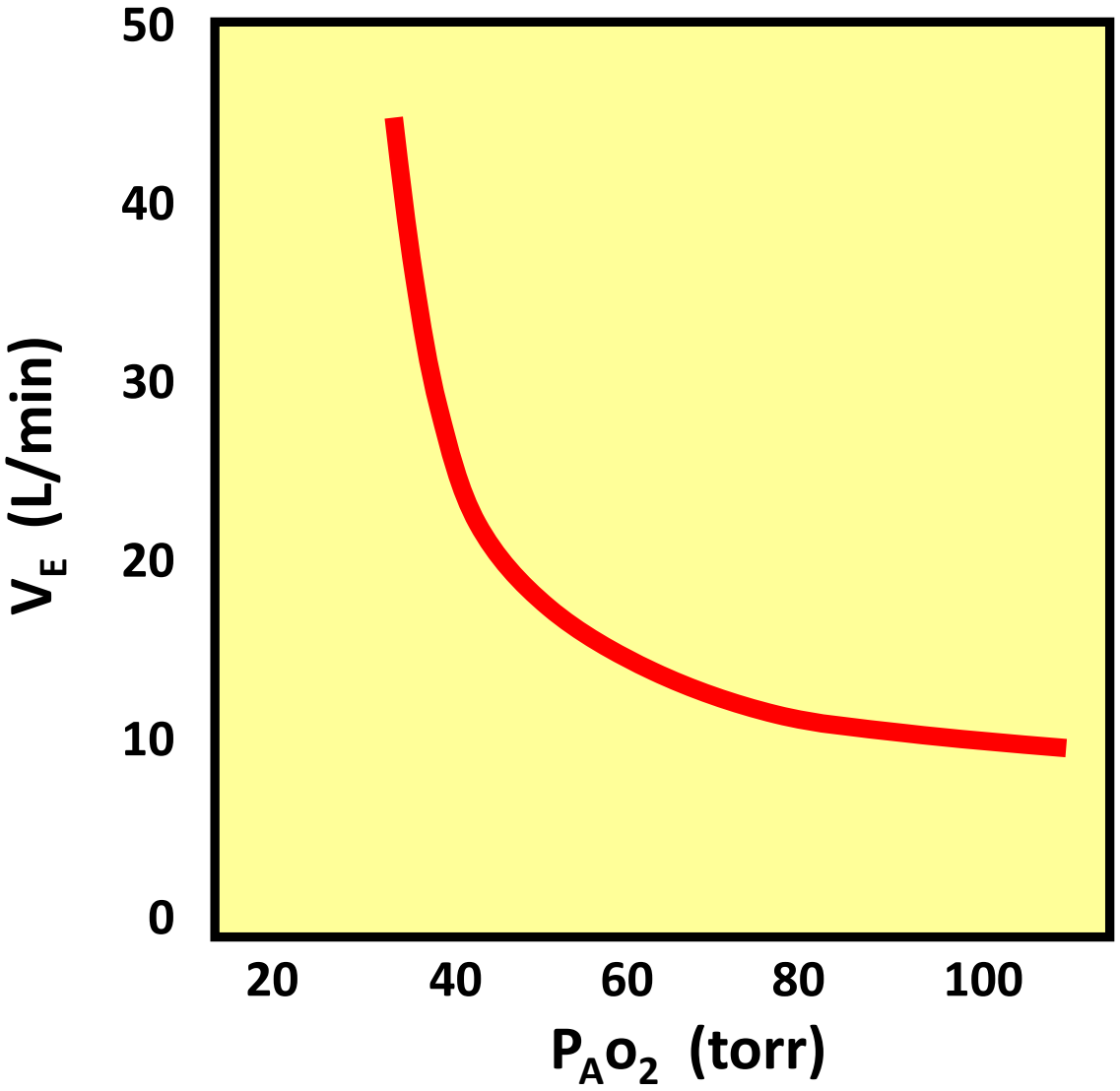


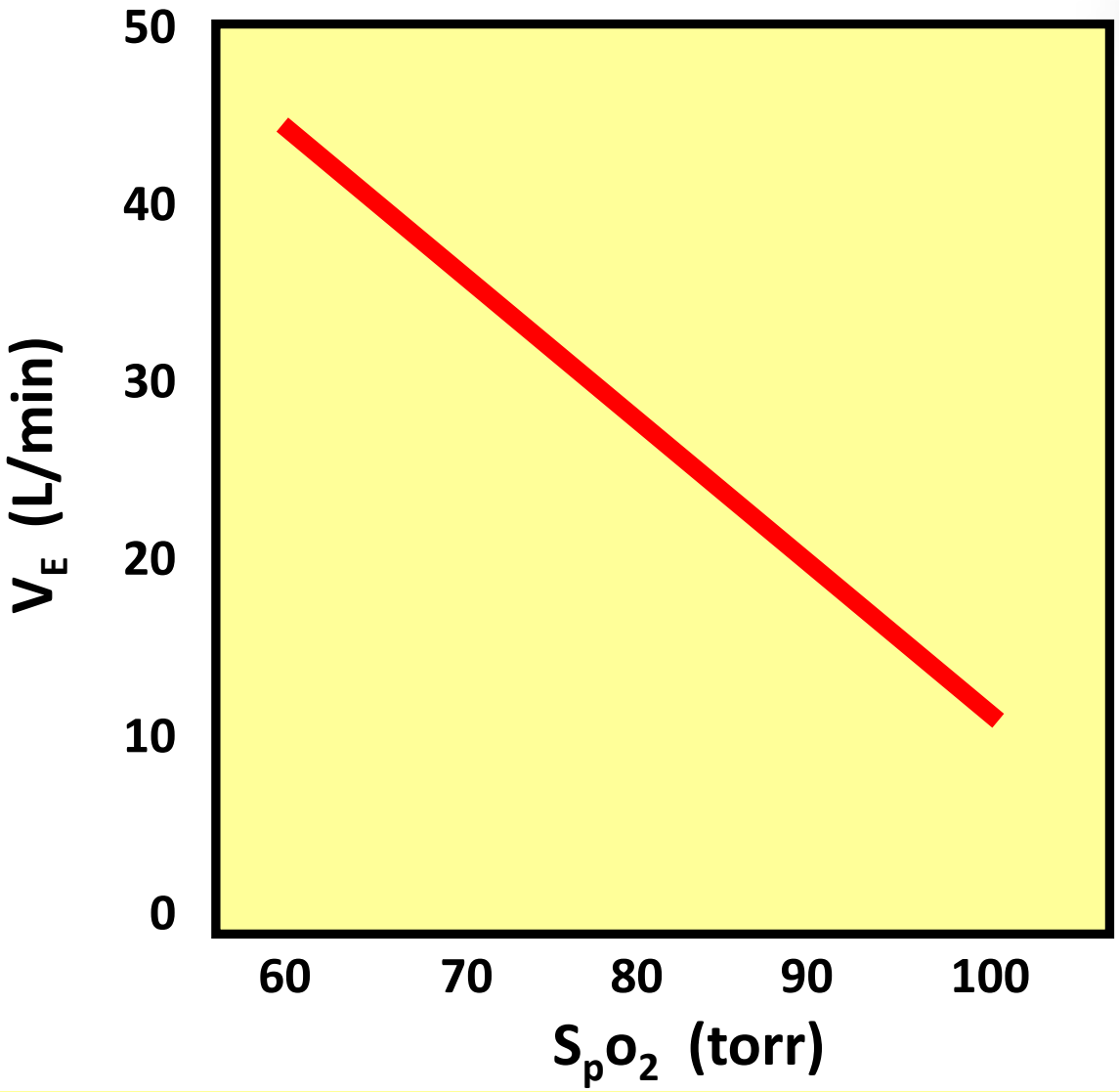
Rebreathing Hypercapnic Ventilatory Response



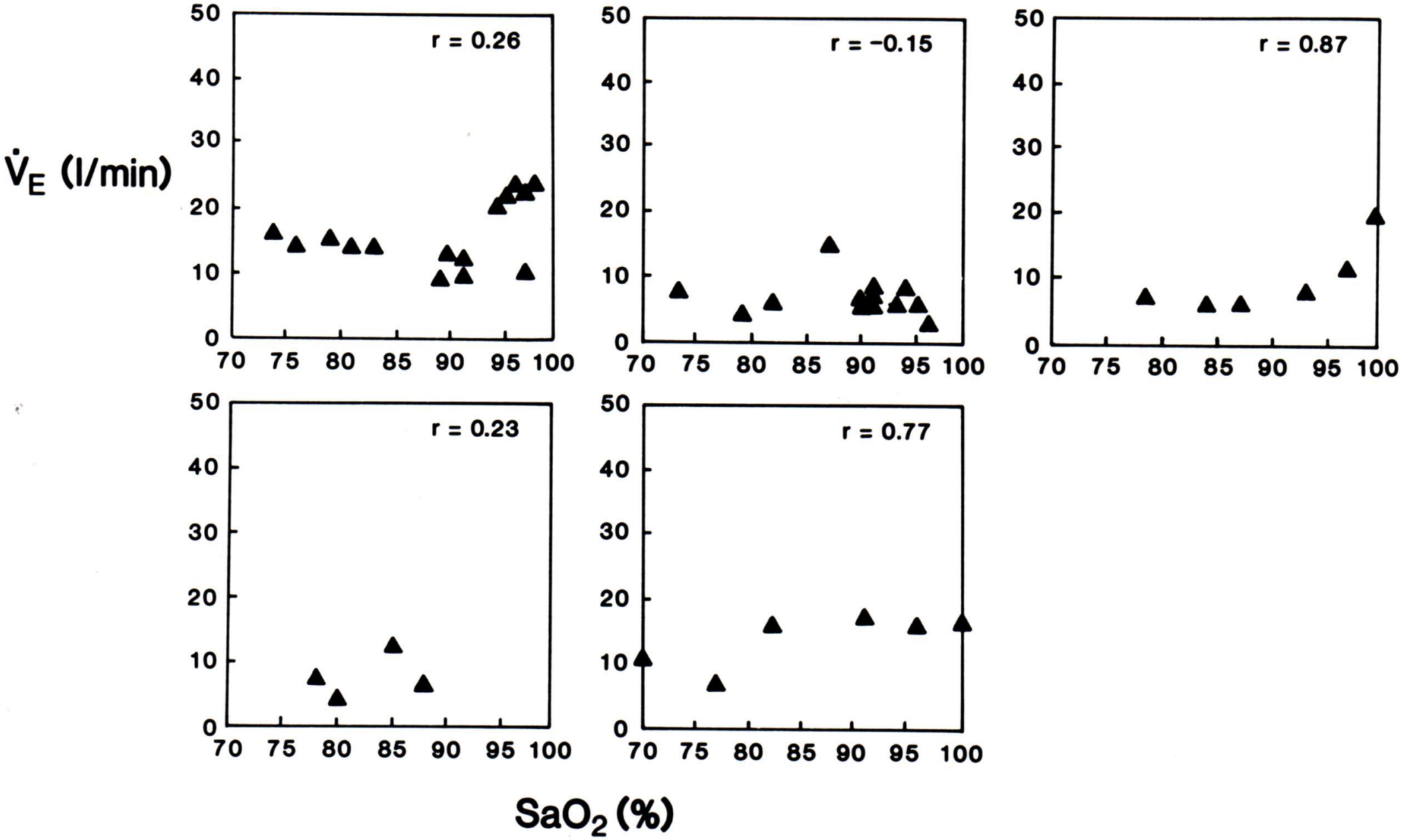
Paton, J.Y., et. al. *Amer. Rev. Respir. Dis., 140:* 368-372, 1989.

Normal Hypoxic Ventilatory Response





Rebreathing Hypoxic Ventilatory Response



Paton, J.Y., et. al. *Amer. Rev. Respir. Dis., 140:* 368-372, 1989.

So What?

- **CCHS patients are *objectively* and *subjectively* insensitive to hypoxia and hypercapnia.**
- **Clinical signs of hypoxia and hypercapnia are absent even awake.**
- **Profound hypoxia and hypercapnia can be missed clinically.**
- **One of the most difficult clinical care problems.**

Treatment of CCHS

Problem:

- CCHS patients do not breathe.

Treatment:

- Breathe for them!

Chen, M.L., and T.G. Keens. *Paediatr. Resp. Rev., 5:* 182-189, 2004.
Weese-Mayer, D.E., et al. *Amer. J. Resp. Crit. Care Med., 181:* 626-644, 2010.
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Maloney, M.A., et al. *Expert Rev. Respir. Med., 12:* 282-292, 2018.

American Thoracic Society
MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Idiopathic Congenital Central Hypoventilation Syndrome

Diagnosis and Management

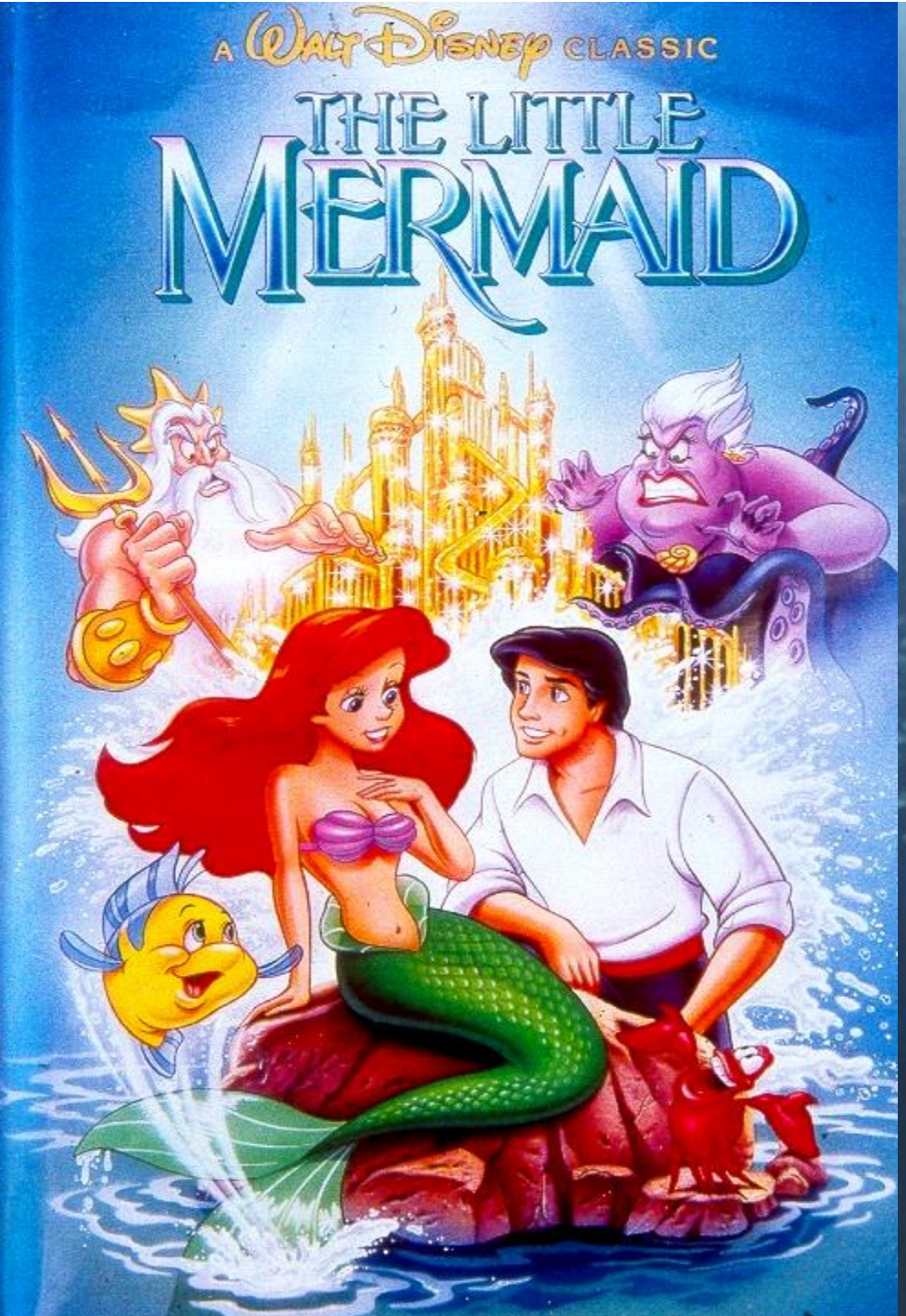
THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, FEBRUARY, 1999

OBJECTIVES

1. To improve general knowledge regarding idiopathic congenital central hypoventilation syndrome (CCHS), with recognition that because of the rarity of CCHS, many practitioners have not seen a case and therefore do not make the diagnosis in a timely manner.
2. To minimize time delays between onset of clinical symptoms and the diagnosis of CCHS, thereby decreasing initial health care costs and minimizing exposure to significant as-

acterized by generally adequate ventilation while the patient is awake but alveolar hypoventilation with typically normal respiratory rates and shallow breathing (diminished tidal volume) during sleep (1). Although not unique to CCHS, these patients will occasionally demonstrate apneic pauses after discontinuation of mechanical ventilation and before initiation of spontaneous breathing. More severely affected children hypoventilate both while awake and asleep. While asleep, children with CCHS experience progressive hypercapnia and hypoxemia (1-18). Their ventilation is better in rapid eye move-

Weese-Mayer, D.E., D.C. Shannon, T.G. Keens, and J.M. Silvestri.
***Amer. J. Respir. Crit. Care Med., 160:* 368-373, 1999.**



Mellins, R.B., et al. *Medicine, 49:* 487-504, 1970.
Demartini Junior, Z., et al. *Sleep Med., X 2:* e100012, 2020.

Is CCHS Only a Ventilatory Control Disorder?

- Hirschsprung's disease is present in ~25%-35% of children with CCHS.
- Weese-Mayer hypothesized that CCHS may be a generalized autonomic nervous system disorder.
- She surveyed 2353 relatives of CCHS and controls; ANSD much more likely in CCHS relatives.
- Woo found decreased heart rate variability and preferential sympathetic control during sleep.

Haddad, G.G., et al. *Medicine, 57:* 517-526, 1978.
Weese-Mayer, D.E., et al. *Amer. J. Med. Genet., 100:* 237-245, 2001.
Woo, M.S., et al. *Pediatr. Res., 31:* 291-296, 1992.

Is CCHS Only a Ventilatory Control Disorder?

We now know that Children with CCHS can have:

- Potentially life threatening cardiac arrhythmias.
- Hirschsprung's disease and other disorders of gastrointestinal motility.
- Neural crest tumors.
- Neuro-ophthalmologic abnormalities.
- Neurocognitive dysfunction.
- Poor heat tolerance.

Weese-Mayer, D.E., et al. *Amer. J. Resp. Crit. Care Med., 181:* 626-644, 2010.

Is CCHS Inherited?

- CCHS reported in siblings.
- CCHS reported in monozygotic twins.
- Familial pattern of autonomic nervous system dysfunction in CCHS families.

Haddad, G.G., et al. *Medicine, 57:* 517-526, 1978.
Khalifa, M.M., et al. *J. Pediatr., 113:* 853-855, 1988.
Hamilton, J., and J.N. Bodurtha. *J. Med. Genet., 26:* 272-274, 1989.
Kerbl, R., et al. *Eur. J. Pediatr., 155:* 977-980, 1996.
Marazita, M.L., et al. *Amer. J. Med. Genet., 100:* 229-236, 2001.
Weese-Mayer. D.E., et al. *Amer. J. Med. Genet., 100:* 237-245, 2001.
Sritippayawan, S., et al. *Amer. J. Respir. Crit. Care Med., 166:* 367-369, 2002
Silvestri, J.M., et al. *Amer. J. Med. Genet., 112:* 46-50, 2002.

Is CCHS Inherited?

Sritippayawan, S., et al. *Amer. J. Respir. Crit. Care Med., 166:* 367-369, 2002

Silvestri, J.M., et al. *Amer. J. Med. Genet., 112:* 46-50, 2002.

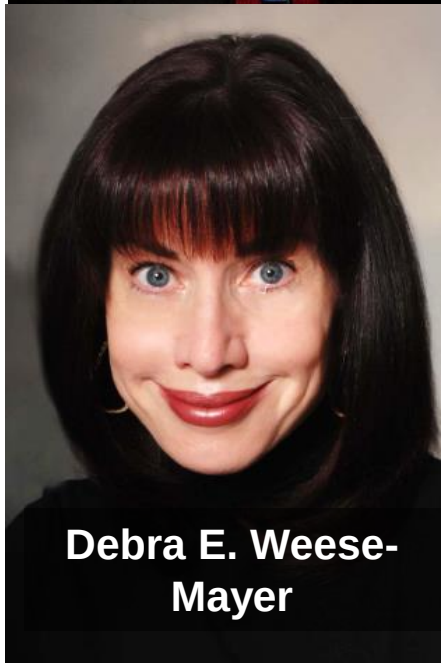
Is CCHS Inherited?

- Two reports of 5 total CCHS parents who had children with CCHS or with ANSD.
- Suggest autosomal dominant inheritance.

Sritippayawan, S., et al. *Amer. J. Respir. Crit. Care Med., 166:* 367-369, 2002
Silvestri, J.M., et al. *Amer. J. Med. Genet., 112:* 46-50, 2002.

PHOX2B Abnormalities in CCHS


Jeanne Amiel


Debra E. Weese-Mayer

- PHOX2B is a transcription factor controlling development of the ANS.
- PHOX2B gene mutation (chromosome 4p12) in humans is diagnostic of CCHS.
- Autosomal dominant inheritance, though most CCHS patients are probably due to spontaneous mutations.

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Sasaki, A, et al. *Human Genet., 114:* 22-26, 2003.
Weese-Mayer, D.E., et al. *Am. J. Med. Genet., 123A:* 267-278, 2003.
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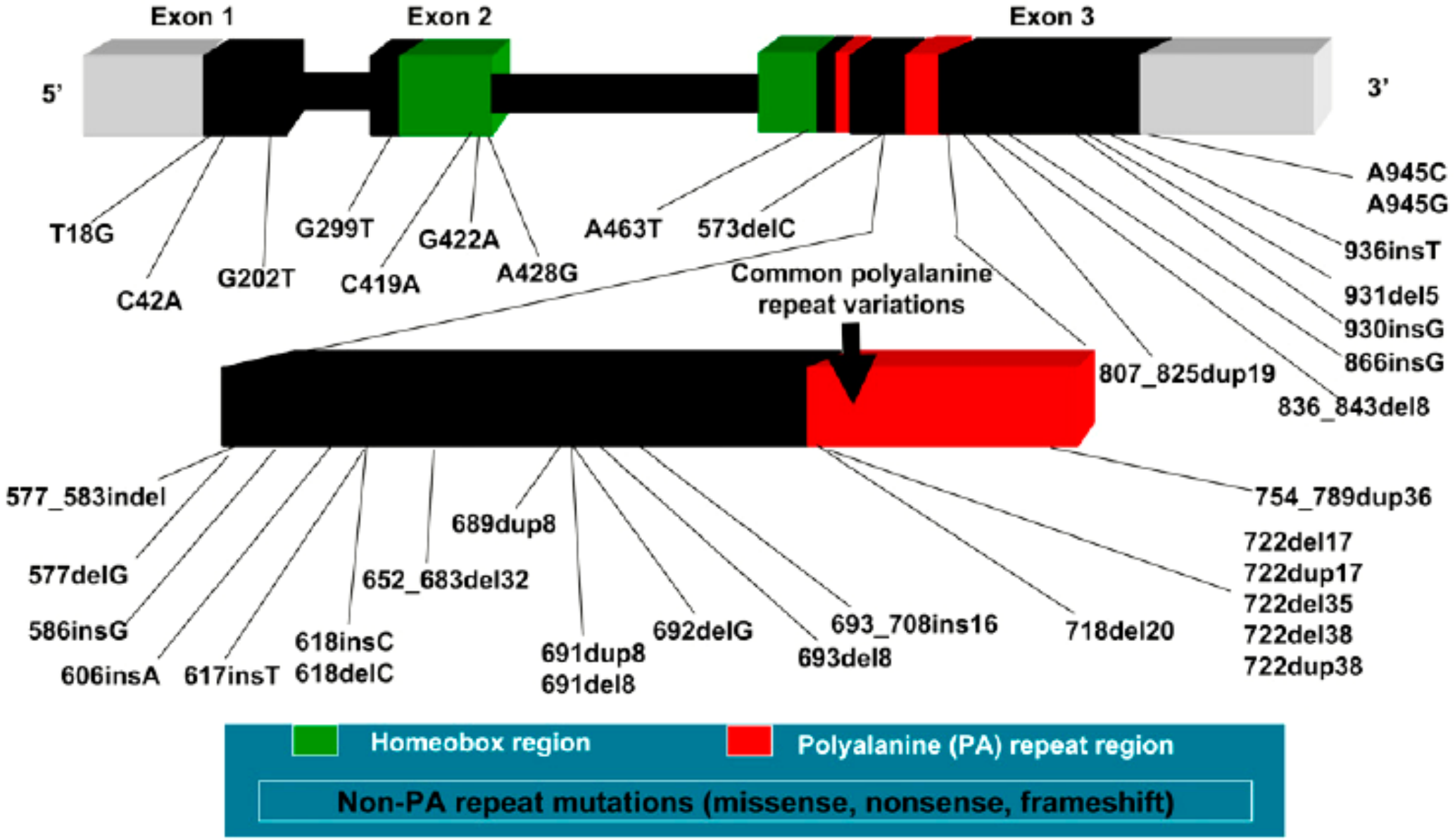
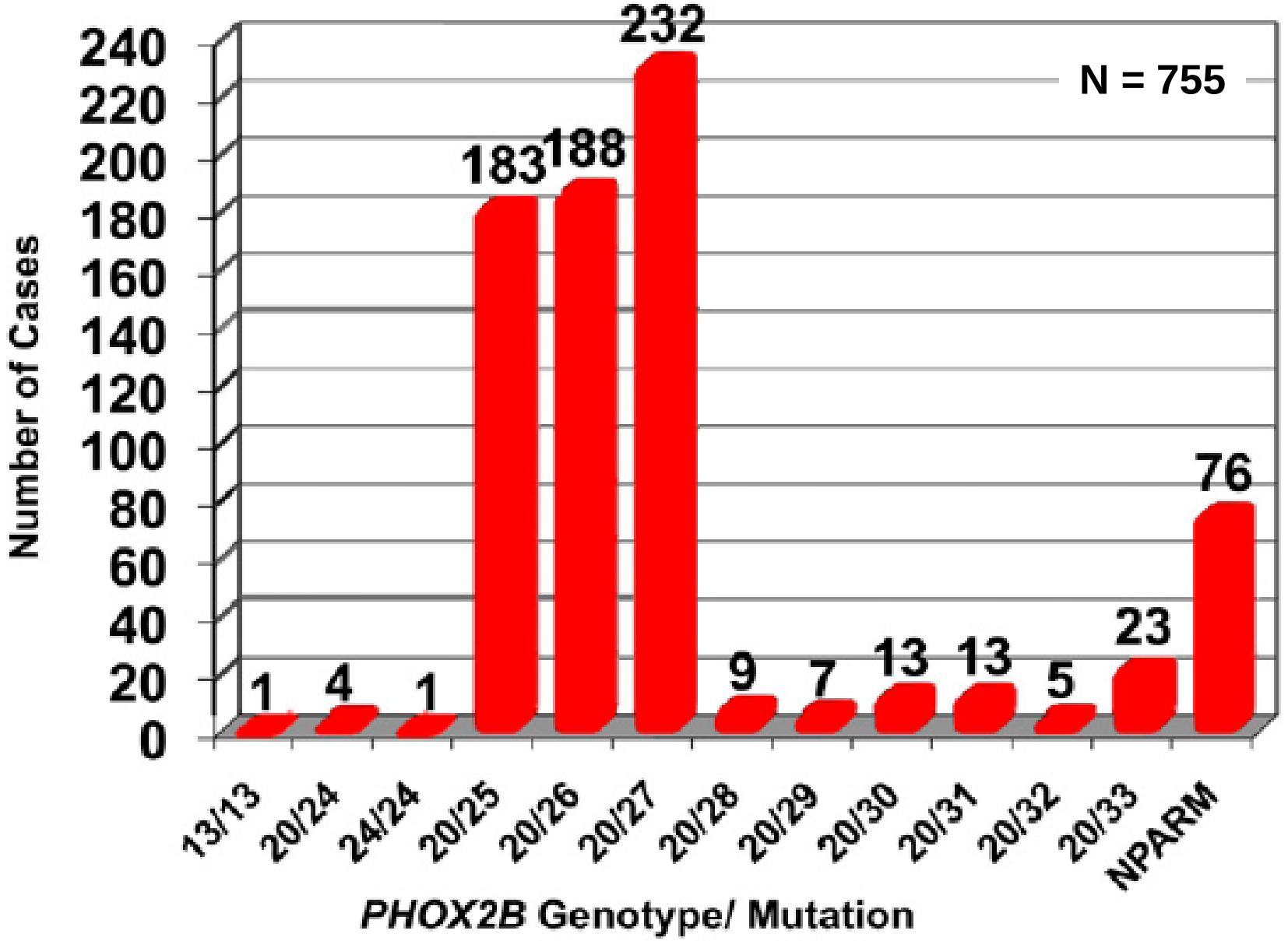


Weese-Mayer, D.E., et al. *Pediatr. Pulmonol., 44:* 521-535, 2009.

Weese-Mayer, D.E., et al. *Amer. J. Respir. Crit. Care Med., 181:* 626-644, 2010.



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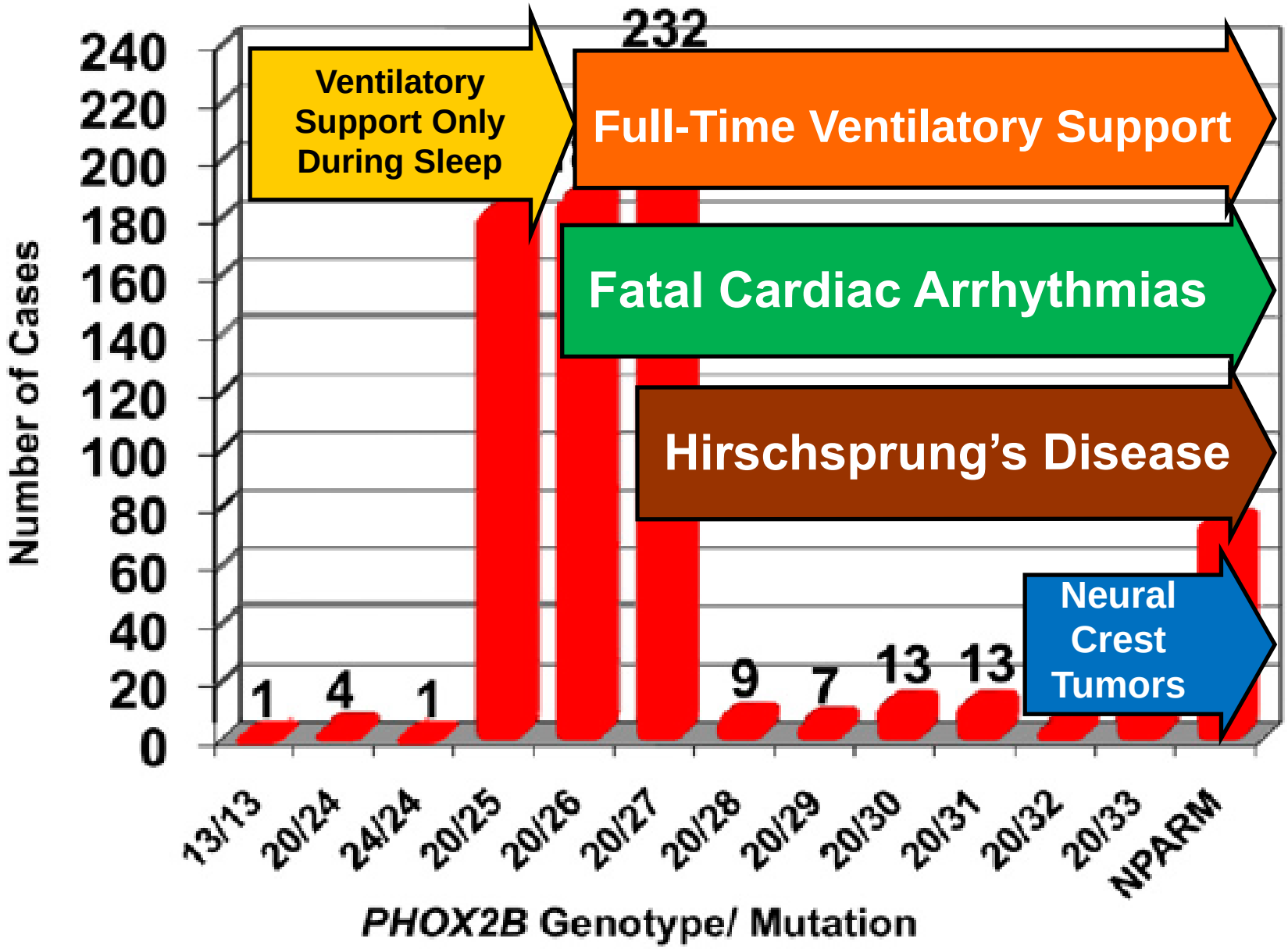


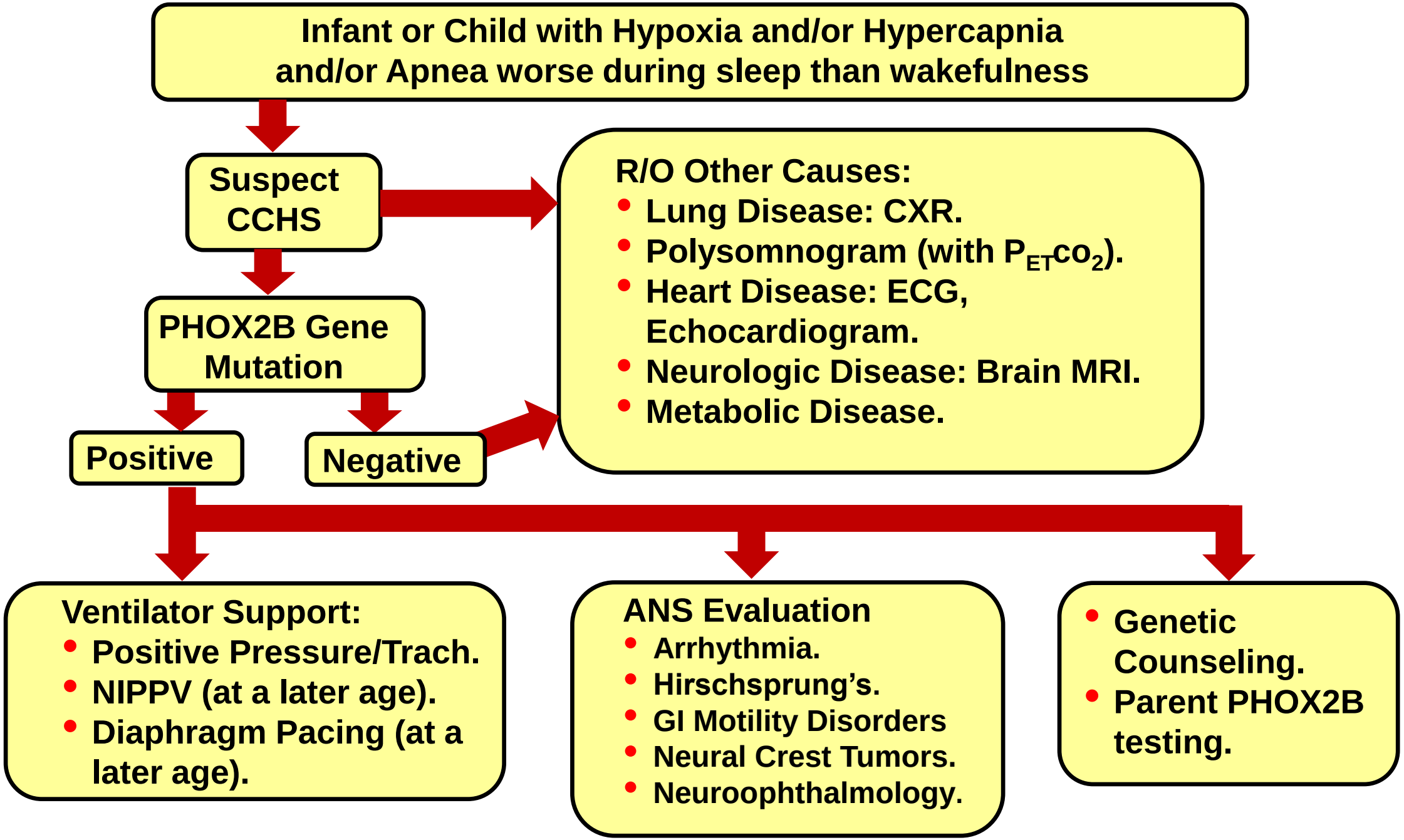
Weese-Mayer, D.E., et al. *Pediatr. Pulmonol., 44:* 521-535, 2009.
Weese-Mayer, D.E., et al. *Amer. J. Respir. Crit. Care Med., 181:* 626-644, 2010.

Children of CCHS Patients

- **PHOX2B mutation has autosomal dominant inheritance.**
- **50% chance of transmitting CCHS to children.**
- **Genetic counseling should be done for adolescents, and especially before marriage.**

Sritippayawan, S., et al. *Amer. J. Respir. Crit. Care Med., 166:* 367-369, 2002.

Silvestri, J.M., et al. *Amer. J. Med. Genet., 112:* 46-50, 2002.


Infant or Child with Hypoxia and/or Hypercapnia and/or Apnea worse during sleep than wakefulness
Suspect CCHS
PHOX2B Gene Mutation
Positive
Negative
R/O Other Causes:
Lung Disease: CXR.
Polysomnogram (with $P_{ET}co_2$).
Heart Disease: ECG, Echocardiogram.
Neurologic Disease: Brain MRI.
Metabolic Disease.
Ventilator Support:
Positive Pressure/Trach.
NIPPV (at a later age).
Diaphragm Pacing (at a later age).
ANS Evaluation
Arrhythmia.
Hirschsprung's.
GI Motility Disorders
Neural Crest Tumors.
Neuroophthalmology.
Genetic Counseling.
Parent PHOX2B testing.

American Thoracic Society Documents

An Official ATS Clinical Policy Statement: Congenital Central Hypoventilation Syndrome

Genetic Basis, Diagnosis, and Management

Debra E. Weese-Mayer, Elizabeth M. Berry-Kravis, Isabella Ceccherini, Thomas G. Keens, Darius A. Loghmanee, and Ha Trang, on behalf of the ATS Congenital Central Hypoventilation Syndrome Subcommittee

THIS OFFICIAL CLINICAL POLICY STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS SEPTEMBER 2009.

Background: Congenital central hypoventilation syndrome (CCHS) is characterized by alveolar hypoventilation and autonomic dysregulation.

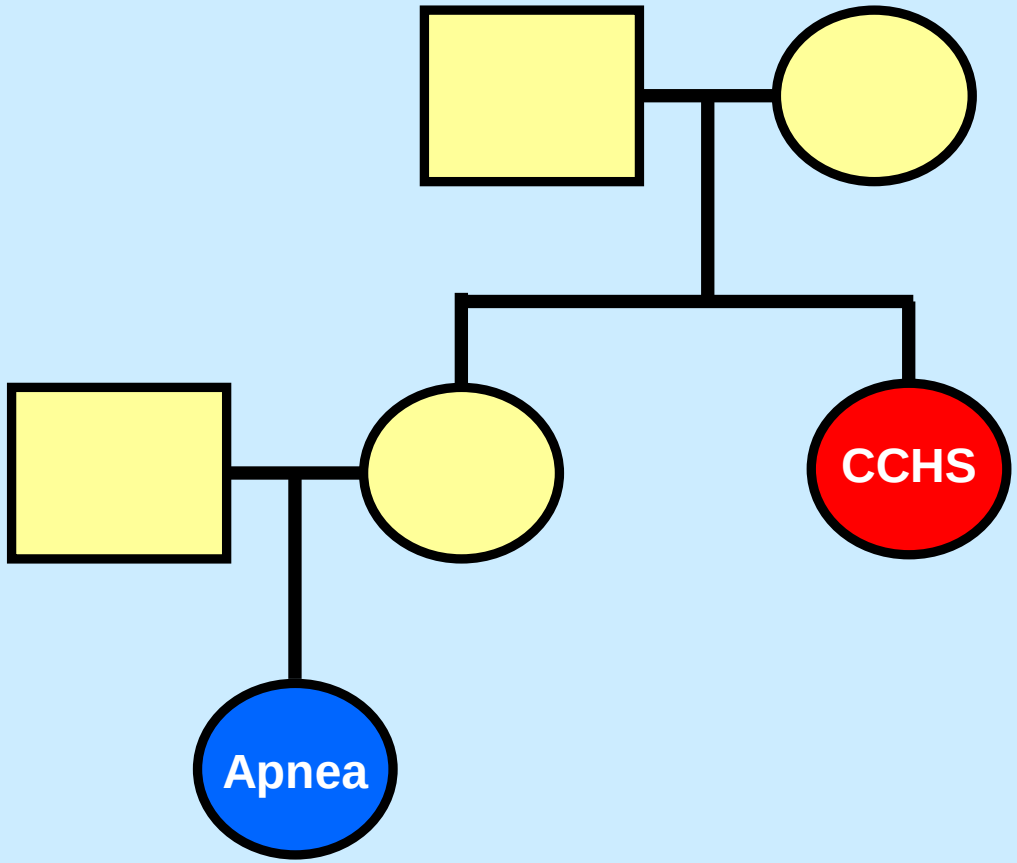
Purpose: (*1*) To demonstrate the importance of *PHOX2B* testing in diagnosing and treating patients with CCHS, (*2*) to summarize recent advances in understanding how mutations in the *PHOX2B* gene lead to the CCHS phenotype, and (*3*) to provide an update on recommendations for diagnosis and treatment of patients with CCHS.

Methods: Committee members were invited on the basis of their expertise in CCHS and asked to review the current state of the science by independently completing literature searches. Consensus on

Weese-Mayer, D.E., et al. *Amer. J. Respir. Crit. Care Med., 181:* 626-644, 2010.

Genetics Is Not Always That Easy

CCHS Phenotype

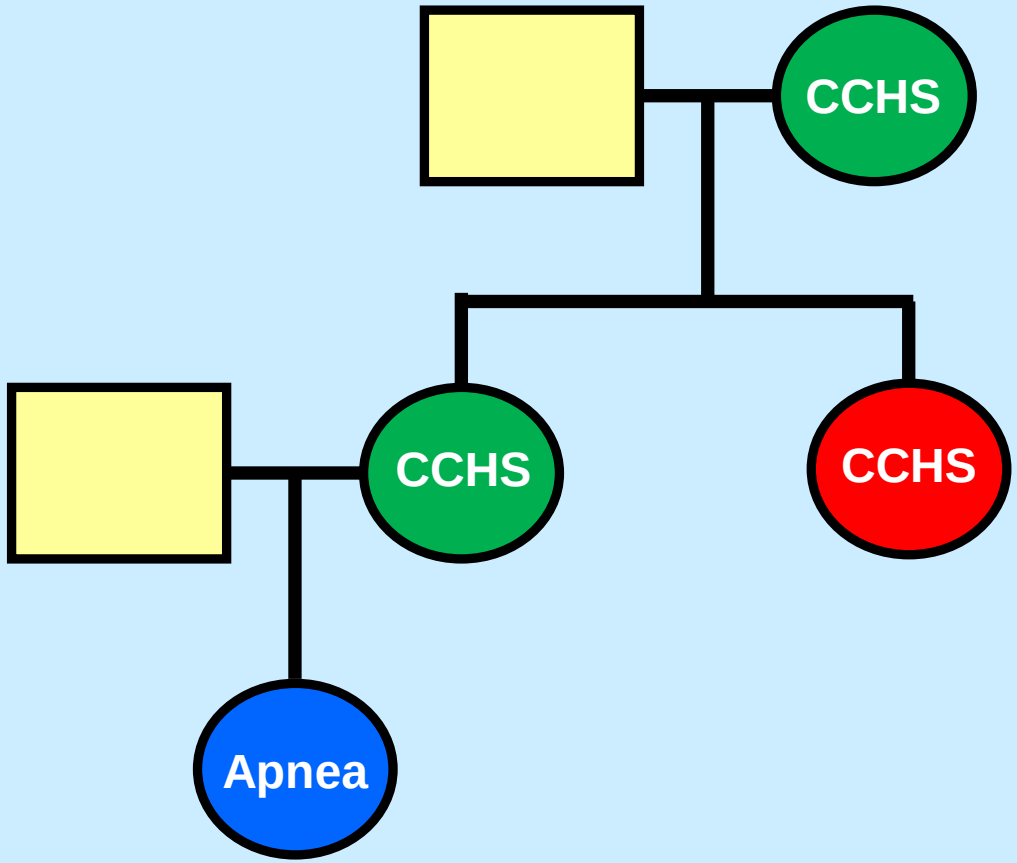


- Newborn infant with severe apnea.
- Maternal aunt has CCHS.
- Could this infant have CCHS?

Kasi, A., et al. *Journal of Clinical Sleep Medicine, 13:* 925-927, 2017

Genetics Is Not Always That Easy

CCHS Phenotype

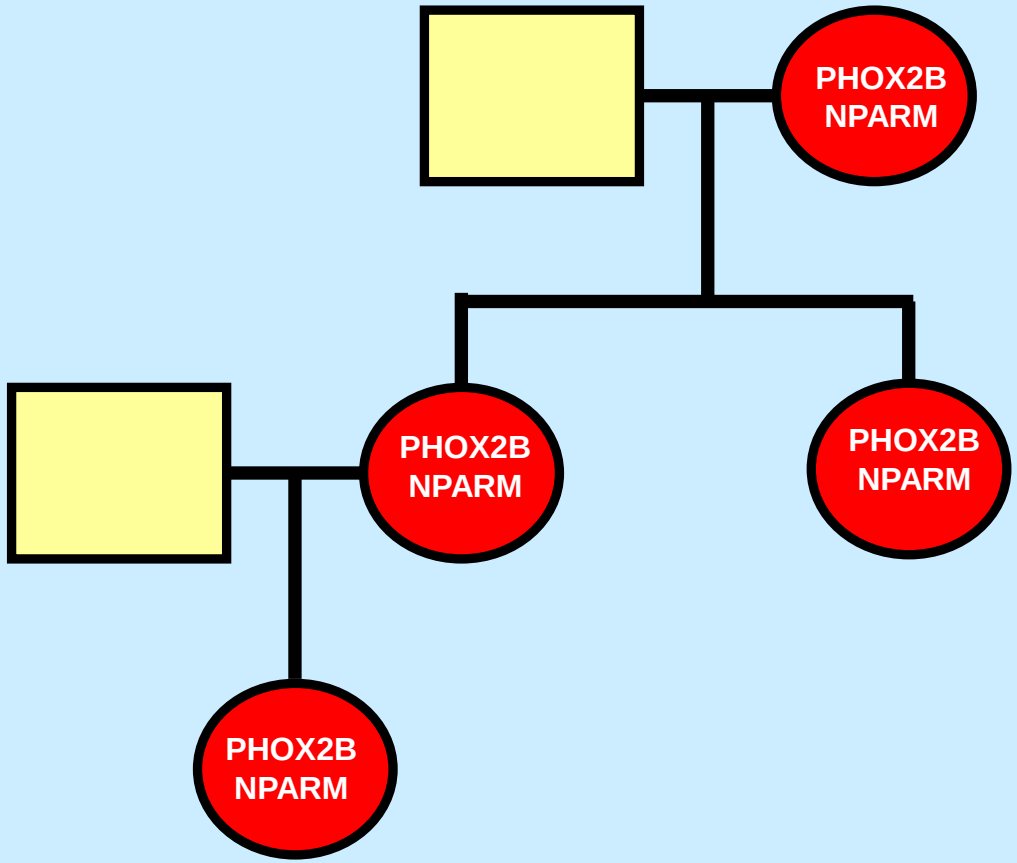


- **Since CCHS inherited as autosomal dominant.**
- **Mother and grandmother (or grandfather) would also have to have CCHS.**

Kasi, A., et al. *Journal of Clinical Sleep Medicine, 13:* 925-927, 2017

Genetics Is Not Always That Easy

CCHS Genotype

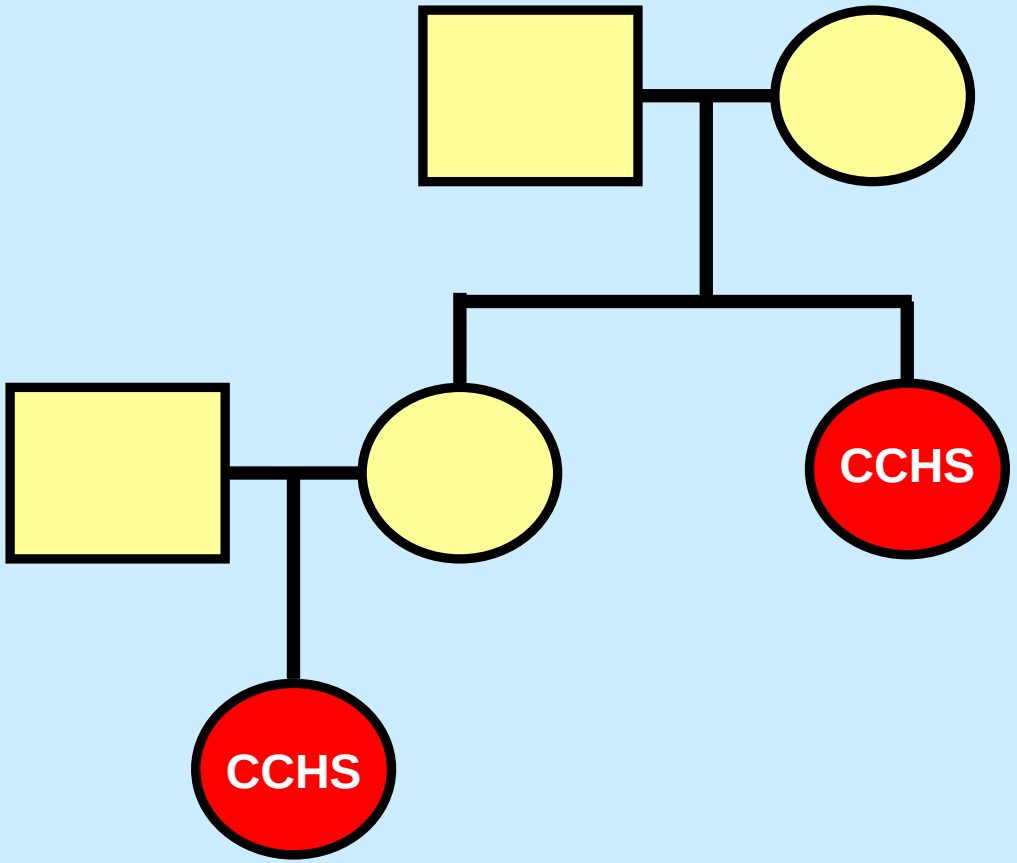


- On PHOX2B testing, the infant with apnea, mother, and grandmother all have the same NPARM mutation as the affected aunt.
- But the mother and grandmother do not have the CCHS phenotype.

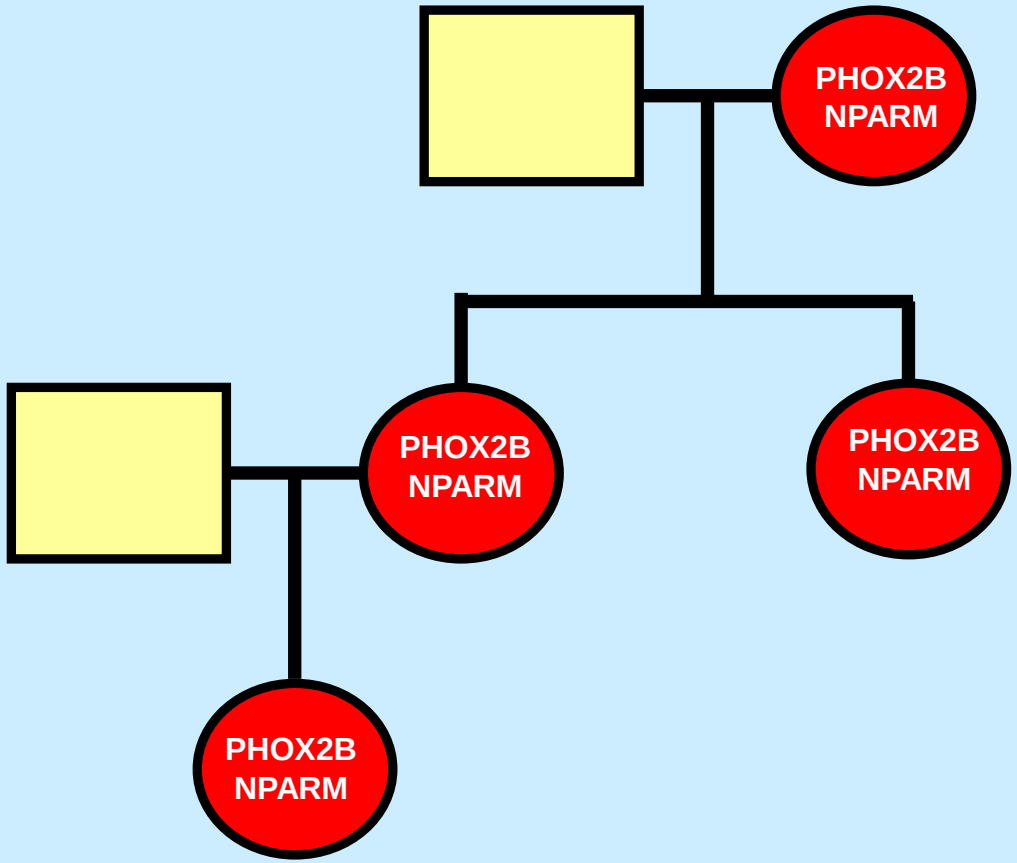
Kasi, A., et al. *Journal of Clinical Sleep Medicine, 13:* 925-927, 2017

Genetics Is Not Always That Easy

CCHS Phenotype

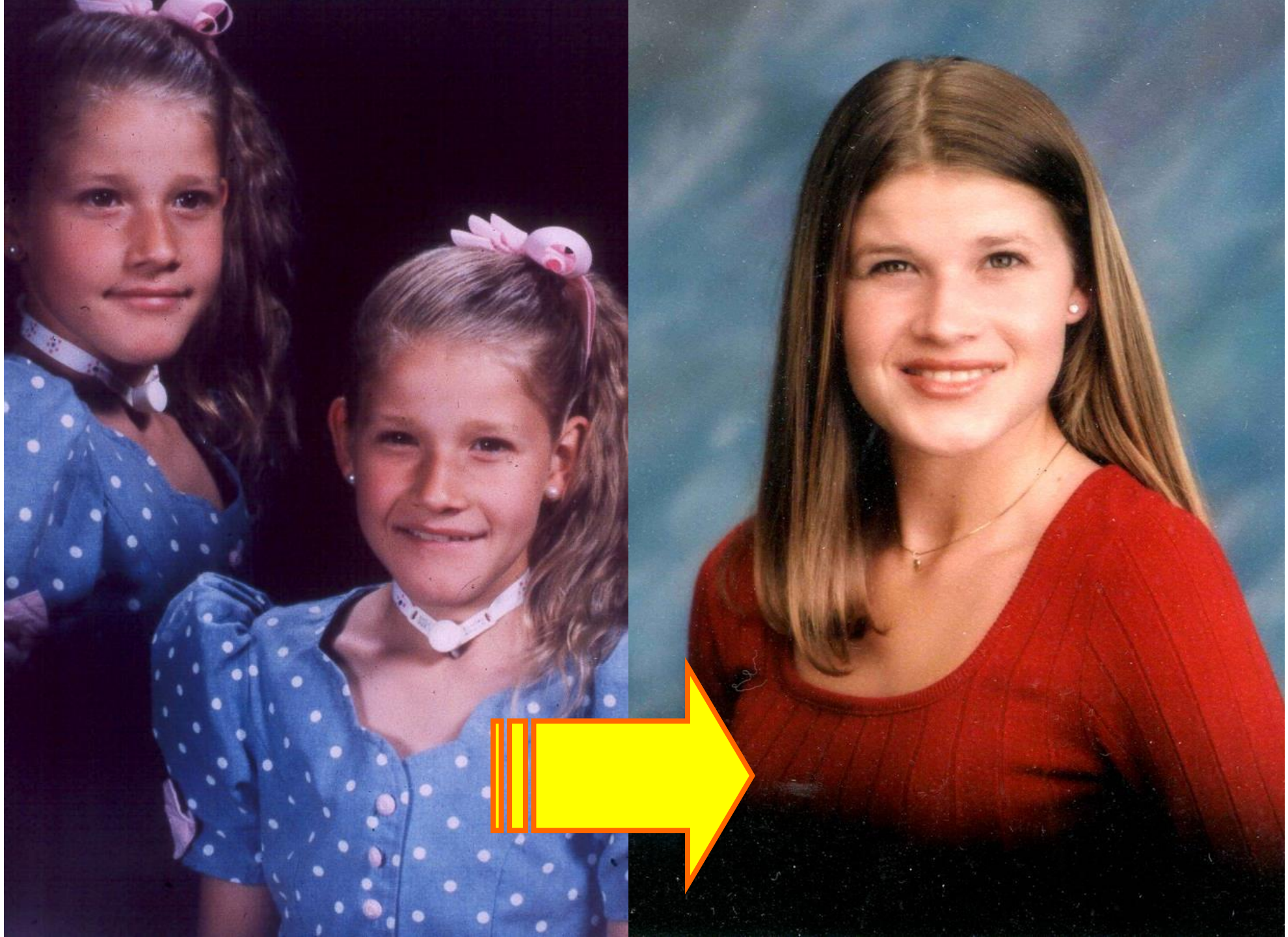


CCHS Genotype



Kasi, A., et al. *Journal of Clinical Sleep Medicine, 13:* 925-927, 2017

Can you tell that this young lady has CCHS?

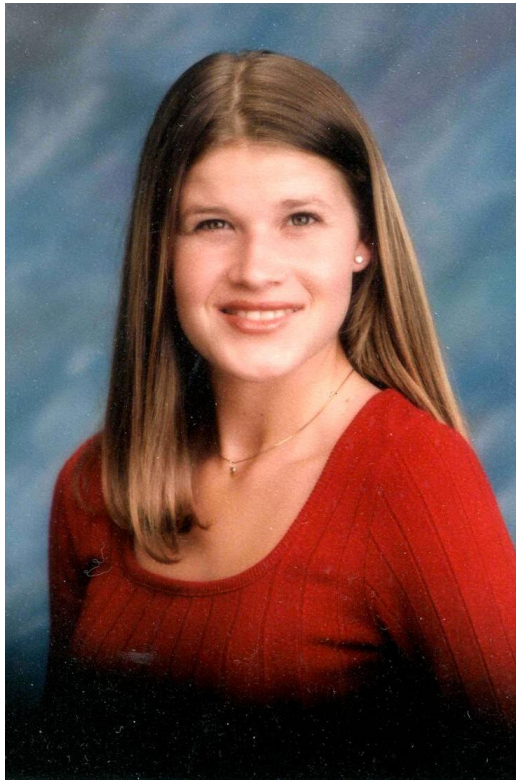


CCHS Home Ventilation

- In the 1970's and 1980's, it was a challenge just to keep CCHS patients alive.
- As outcome improved, the goal became quality of life.

Noninvasive Ventilation.

Remove the Tracheostomy



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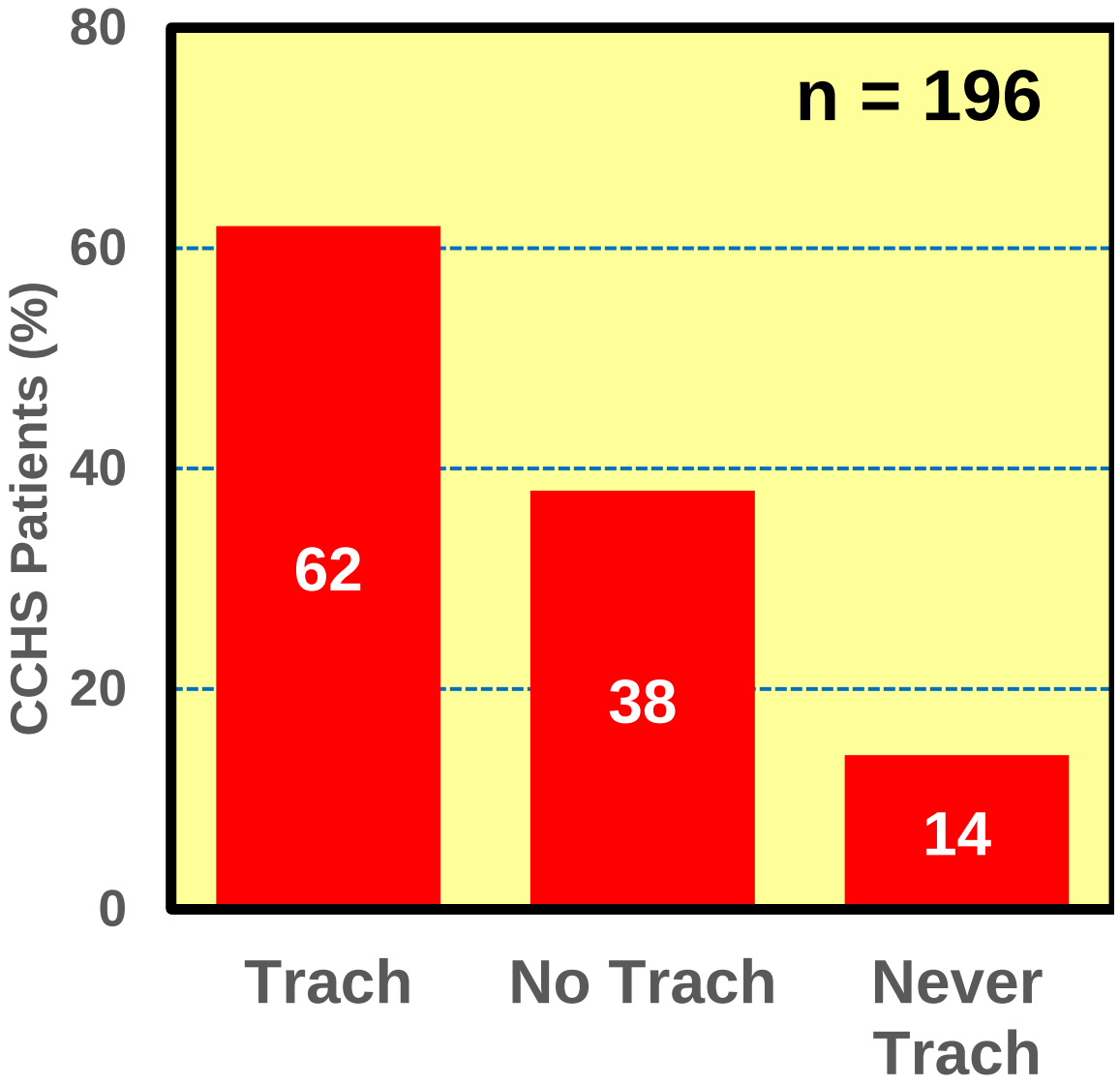
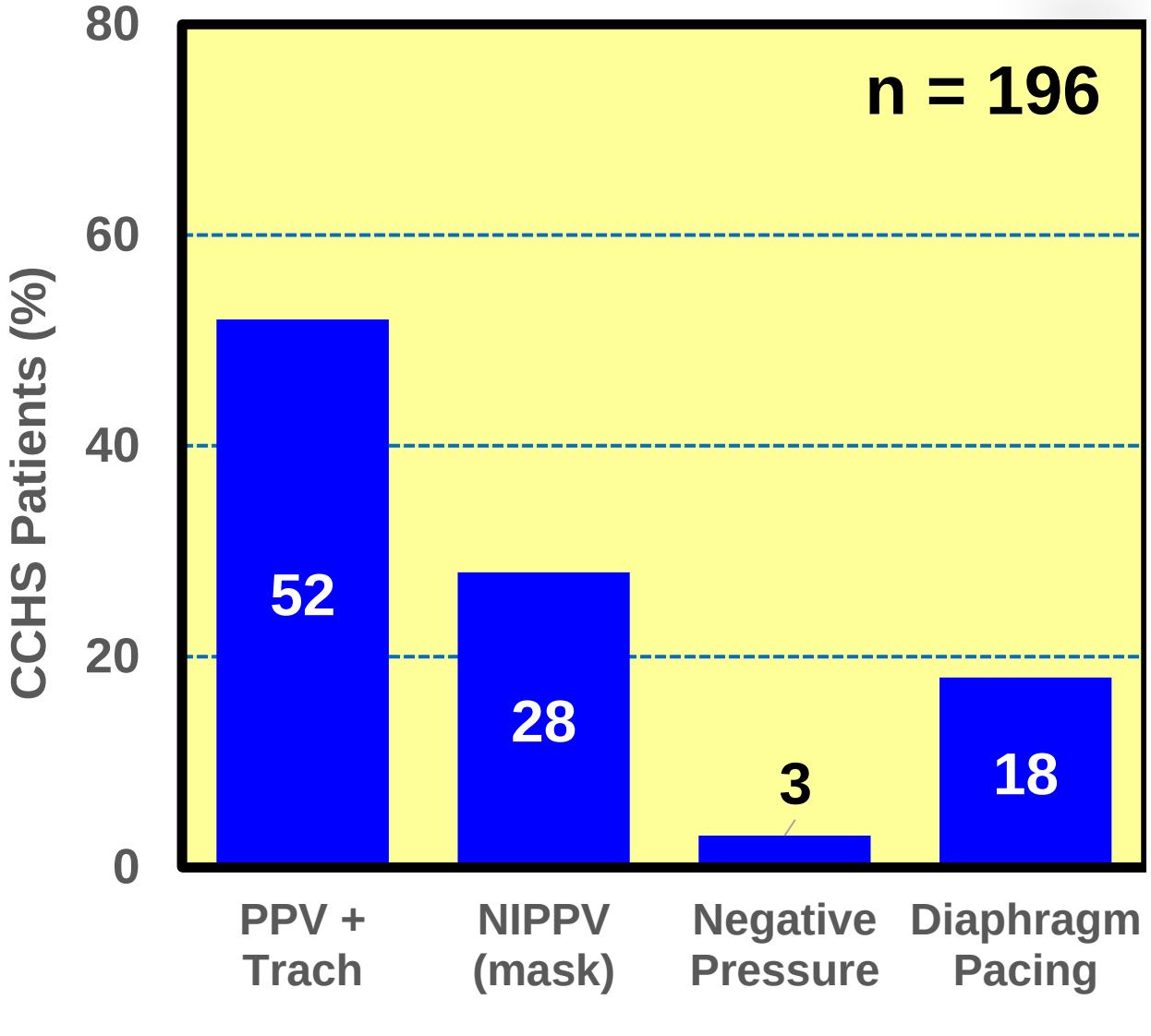
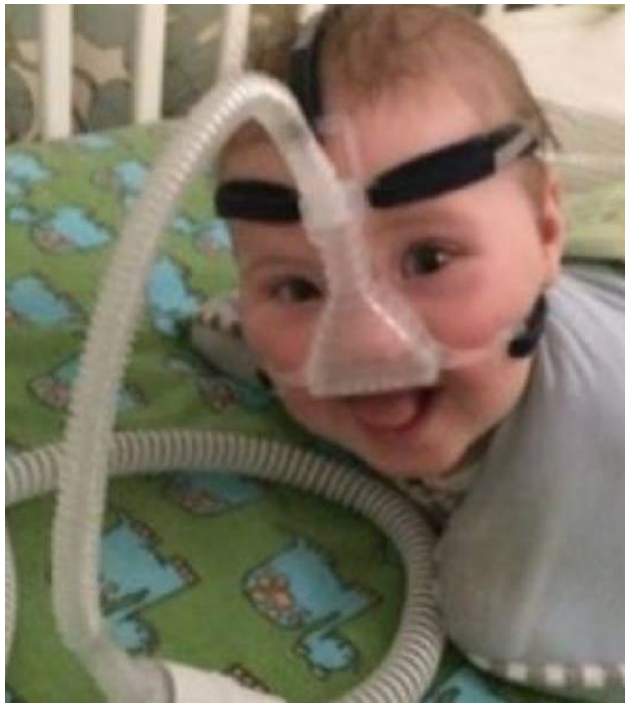
CCHS Home Ventilation





Vanderlaan, M., et al. *Pediatr. Pulmonol., 37:* 217-229, 2004.



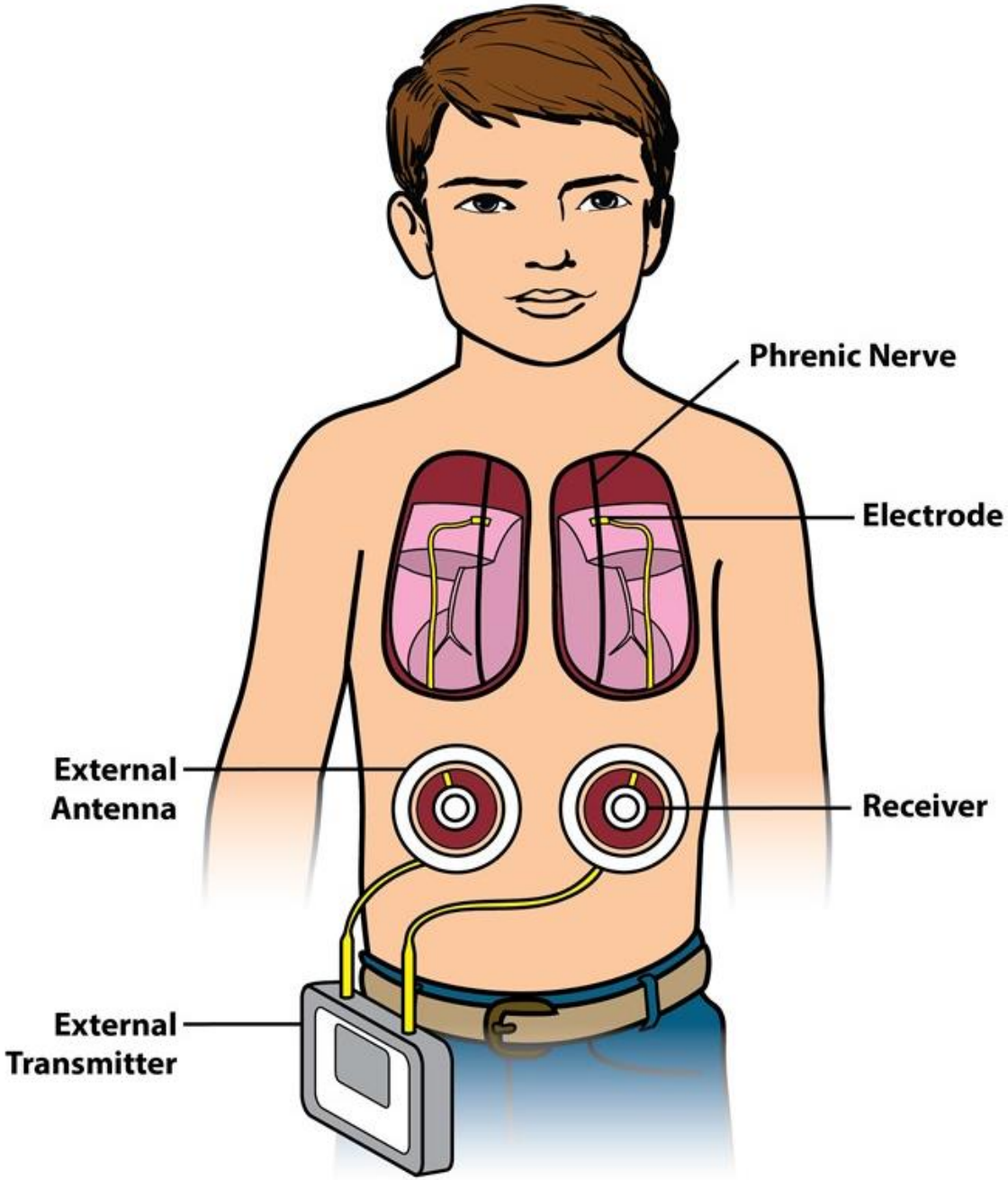


Figure by Bill Franz

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REVIEW ARTICLE

Transitional care and clinical management of adolescents, young adults, and suspected new adult patients with congenital central hypoventilation syndrome

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Abstract

Purpose With contemporaneous advances in congenital central hypoventilation syndrome (CCHS), recognition, confirmatory diagnostics with *PHOX2B* genetic testing, and conservative management to reduce the risk of early morbidity and mortality,

Slattery, S.M., et al. *Clinical Autonomic Research, 33:* 231-249, 2023.

Successes

- Advances in home ventilation result in long-term survival with high quality of life.
- People with CCHS survive, graduate from high school and college, marry, have families, and have productive careers.
- Many live independently.

Successes

- Research improves our understanding of CCHS pathophysiology and results in better treatment.
- Better awareness of non-ventilation symptoms and improved treatment.
- Recruitment of basic scientists to better understand pathology and seek treatments.

Challenges

- CCHS adults need expert internal medicine care.
- What do we do with people who have PHOX2B mutations but do not hypoventilate?
- What is the role, if any for medications: progesterone, CNS stimulants, etc.
- Can basic research give us a cure?

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