Heliox as an Adjunctive Therapy to Treat Rhinovirus/Enterovirus-Related Respiratory Failure in Infants and Children

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Conflict of Interest

- I have no real or perceived conflict of interest that relates to this presentation.
- Any use of brand names is not in any way meant to be an endorsement of a specific product, but to merely illustrate a point of emphasis.

- Respiratory syndromes caused by viral infections has been of major global concern for the health care industry for centuries.
- Significantly effect morbidity and mortality with regard to children with and without premorbid conditions when associated with viral bronchoconstriction related respiratory failure (RF).
- Huge impact on global health care resources and finances
- The etiology of respiratory infections, likely community acquired;
  - easily spread & highly pathogenic
  - replicate into different strains and/or structures
- Possible root cause;
  - epidemics
  - pandemics

30 Years of Clinical Practice Observations and Investigation - Lessons Learned

- **Classification of Airflow Obstructions**
  - Airflow obstruction 1 - Asthma
  - Airflow obstruction 2 – Viral Bronchiolitis
- **Clinical Identification of Respiratory Syndromes**
  - Clinical breathing-asthma scoring assessment (CBASA)
  - Chest radiography
  - Respiratory viral panel (RVP)
- **Respiratory Care Interventions for Airflow (AFO) Obstruction;**
  - Volumetric aerosolized continuous Beta-agonist
  - High Flow Nasal Cannula (HFNC)
  - Mechanical Ventilation
  - Helium- oxygen (Heliox) 80/20

Prevention and Vaccines

- Global influenza vaccine prevention.
  - Most are developed for H-N influenza
  - Vaccines are not available for viruses outside of H-N influenza structure
- Less effective against premorbid conditions and more acute in situations such as;
  - Exacerbation caused by cold and flu=respiratory distress
    - Asthma - COPD
    - Immune compromised
    - Small infants and children
    - Malnourished
    - Pregnancy
    - Past 6W Chicago has experienced an increase of animal and UCM 25% increase of human flu ADMISSIONS.

Viral Respiratory Distress

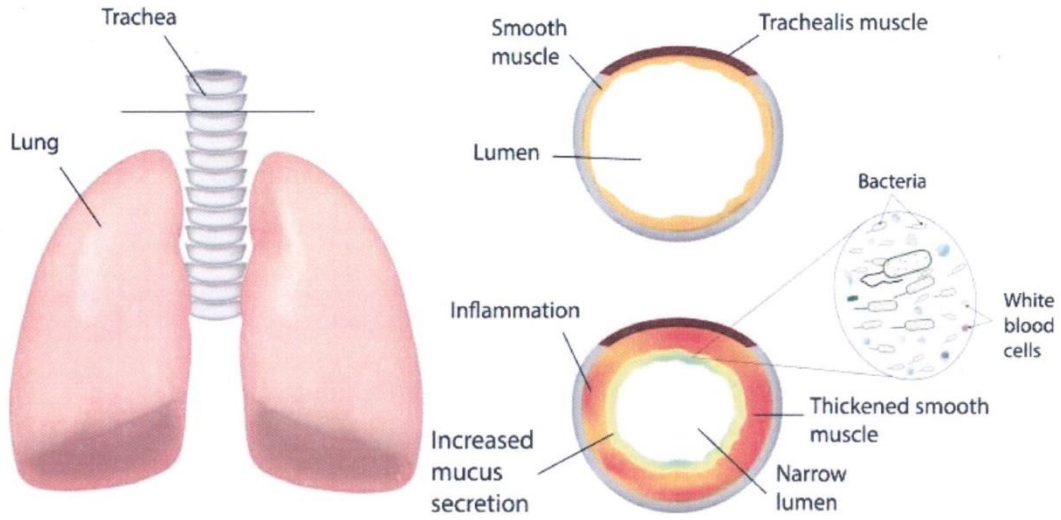
- Same illness whether you are young or old
  - common cold
  - severe acute respiratory distress (SARS) - like symptoms
- Increasingly, respiratory syndromes such as Rhinovirus and Enterovirus (RE) are recognized as precipitants of acute respiratory distress and RF.
- These illnesses mandate hospitalization.
- Respiratory syndromes (RS) are **grossly overlooked and underestimated** as the **root cause** of RF.

- It is important to accurately understand and identify the source of respiratory distress, masquerades as asthma-like
- Viral wheezing or bronchospasm – not simple asthma like bronchospasm, actually related to fluid rhonchi / rales related bronchoconstriction .
  - Because initial differential diagnosis include asthma
    - Leads to treatment confusion
    - Too much focus on asthma component of AFO
    - American Academy for Pediatrics' advise against use of bronchodilator is controversial
- First line beta-agonist medications are usually not effective for relief of respiratory distress.

Influenza-Like Respiratory Syndromes

- Etiology of Viral related air gas flow obstruction;
  - Airway wall (AWW) swelling-constriction - thickening
  - AWW changes are not clearly defined. Hypothesis, million of virus cells attack AWW and cause structure change that is define as peri-bronchial wall thickening
  - AWW structure changes temporary or permanent?
- Infections are now documented to be caused by multiple viral agents, starting to see patients with co-infections.
- One pediatric patient back in PICU three times for viral related RF (HCoV-229E & 2RE). Peri-bronchial airway thickening on x-ray. Mechanical ventilation with heliox each time.

Respiratory Tract Infection



Bronchospasm is a symptom of a respiratory tract infection.
Image 2 of 5

Classification of Viruses, Known to be the Source of Respiratory Syndromes that Effect Animals and Humans

- Viruses linked to pulmonary exacerbations of; bronchitis, bronchiolitis, and/or pneumonia in variable combinations, maybe transmitted back and forth between humans and animals.
  Caution: Do not underestimate these viruses, they can be deadly

- Mainly classified as Influenza A and B (bird or swine) = H-N
  - H1N1 -2009, California, Hong Kong, H2N2, H3N2, H5N1, H9N2
  - Respiratory syncytial virus - **(RSV)**
  - Coronavirus (HCoV), **229E**, HRU, NL63, **OC43**
  - Human Metapneumovirus
  - Rhinovirus (HRV), HRV-A, HRV-B, **HRV-C**, HRV-D
  - Enterovirus (EV). **EV68**, EV70, EV94
  - Adenovirus
  - Parainfluenza (**1-4**)

Clinical Bronchiolitis / Asthma Scoring Assessment (CBASA)

- It is age specific assessments that includes;
  - respiratory rate,
  - SpO_2
  - dyspnea
  - chest retractions
  - Auscultations
- Results gives a severity rating and alert staff of when to escalate care;
  - Mild (5-7)
  - Moderate (8-11)
  - Severe (12-15)

Chest Radiography – Interpretations of AFO

- Bronchiolitis
- Peri-bronchial airway wall thickening
- Retro-cardiac atelectasis, due to mucus plugging
- Reactive airways
- Pneumonia

Dynamics of Air-flow Obstruction related to Complex Respiratory Failure

- Type 1; AFO - Asthma
  - Smooth muscle bronchospasm (lower airway)
  - V/Q mismatch = Air-trapping in the lungs = hyperinflation > hyper-oxygenation with impaired ventilation, may impede MAP & venous return.

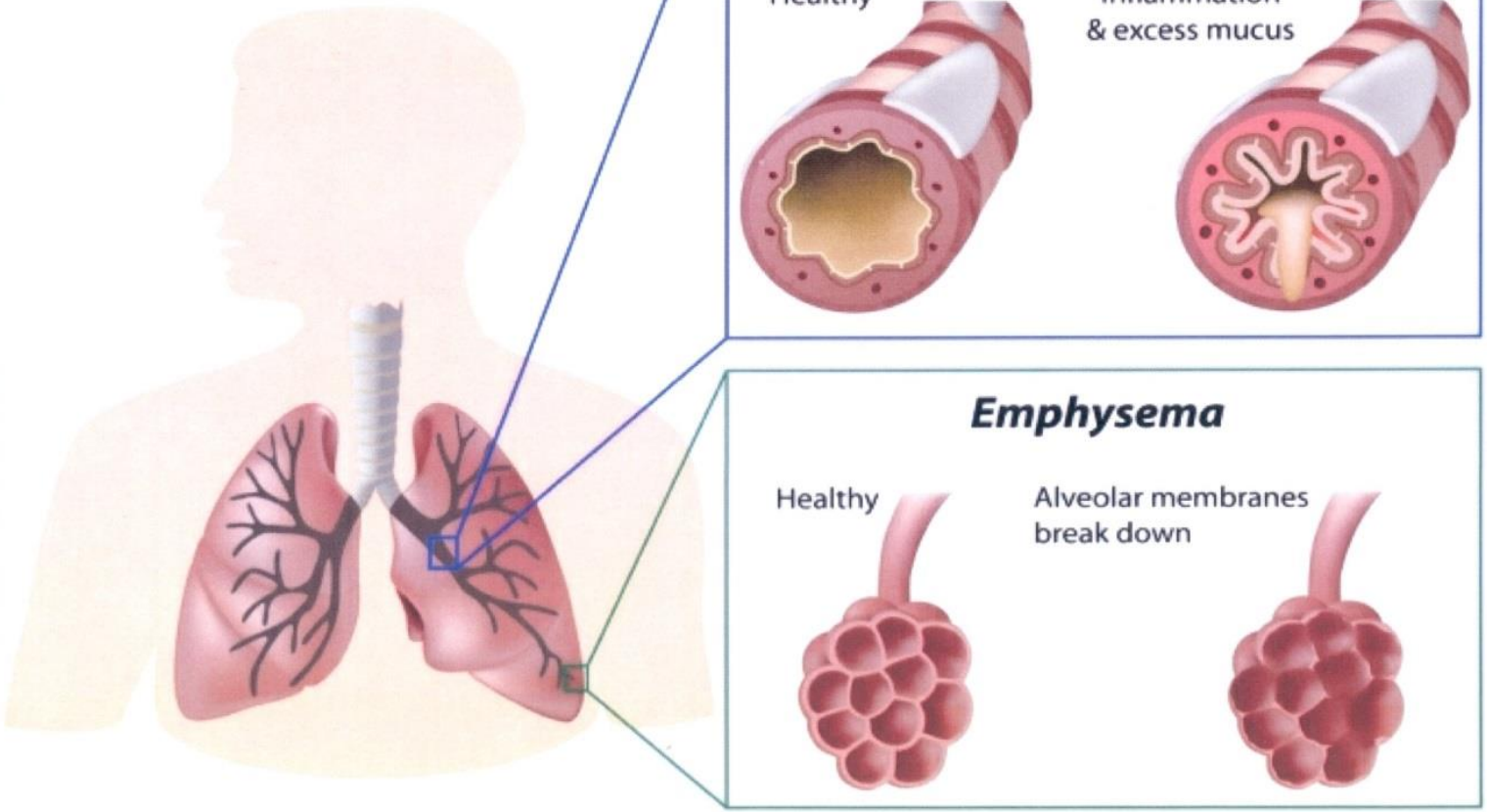
- Type 2; AFO – Bronchiolitis - Bronchoconstriction
  - Etiology - viral, impedes alveolar gas exchange at bronchial interstitium = hypercarbic hypoxia = pulmonary arterial hypertension.
  - If not recognized > ventilation + nitric oxide + proning + Isoflurane = ECMO > tracheostomy

- Early detection and recognition of severity is critical for survival if detected before co-morbidities set in such as; ARDS, kidney failure and organ failure.
- Move the patient earlier rather than later for rescue therapies to be effective.
- ECMO mortality rate is 38% = more complications
- Heliox use as an adjunctive treatment is not well studied for hypercarbic RF of unknown origin, should be used early.
- Bell curve – assessment
- Once there are infiltrates on x-ray = ARDS.
- Kidney failure – prognosis is poor
- The ship is in port and ready to sail

Heliox

- Helium – oxygen (heliox), has been used for more than a century to treat obstructive pulmonary disease.
- Specialty gas 80% helium-20% oxygen.
- The **lower density** and **higher viscosity** of heliox gas mixtures relative to **nitrogen-oxygen** can significantly reduce airway resistance (R_{AW})

Chronic Obstructive Pulmonary Disease (COPD)



Clinical Indications for Heliox

- Clinically, heliox can decrease R_{AW} when associated with;
  - Asthma
  - COPD
  - upper airway obstructions
    - Croup
    - Post extubation stridor
    - Subglottic edema
- Heliox may enhance the bronchodilating effect of *B*-agonist
- Products now being produced world wide to interface with today's respiratory care bedside equipment. (mechanical ventilator - Hamilton G5 & Servo-1; heliox blenders, by Precision Medical® and VapoTherm®).

- I present the case review of three patients who presented with influenza-like respiratory syndrome RF who were treated with adjunctive heliox. Who experienced resolution of their respiratory failure through the use of heliox.
  - Rhinovirus/Enterovirus.
  - One had co-infection HCoV-43

Case Review

- A 10 month-old Hispanic male with a history of seizures was intubated in the field during a seizure episode.
- He was transported to Comer Children's Hospital at The University of Chicago Medicine (UCM)
- He was admitted to PICU for ventilator management and started on anti-seizure medications
- Morgan et al *Respir Care* 2014

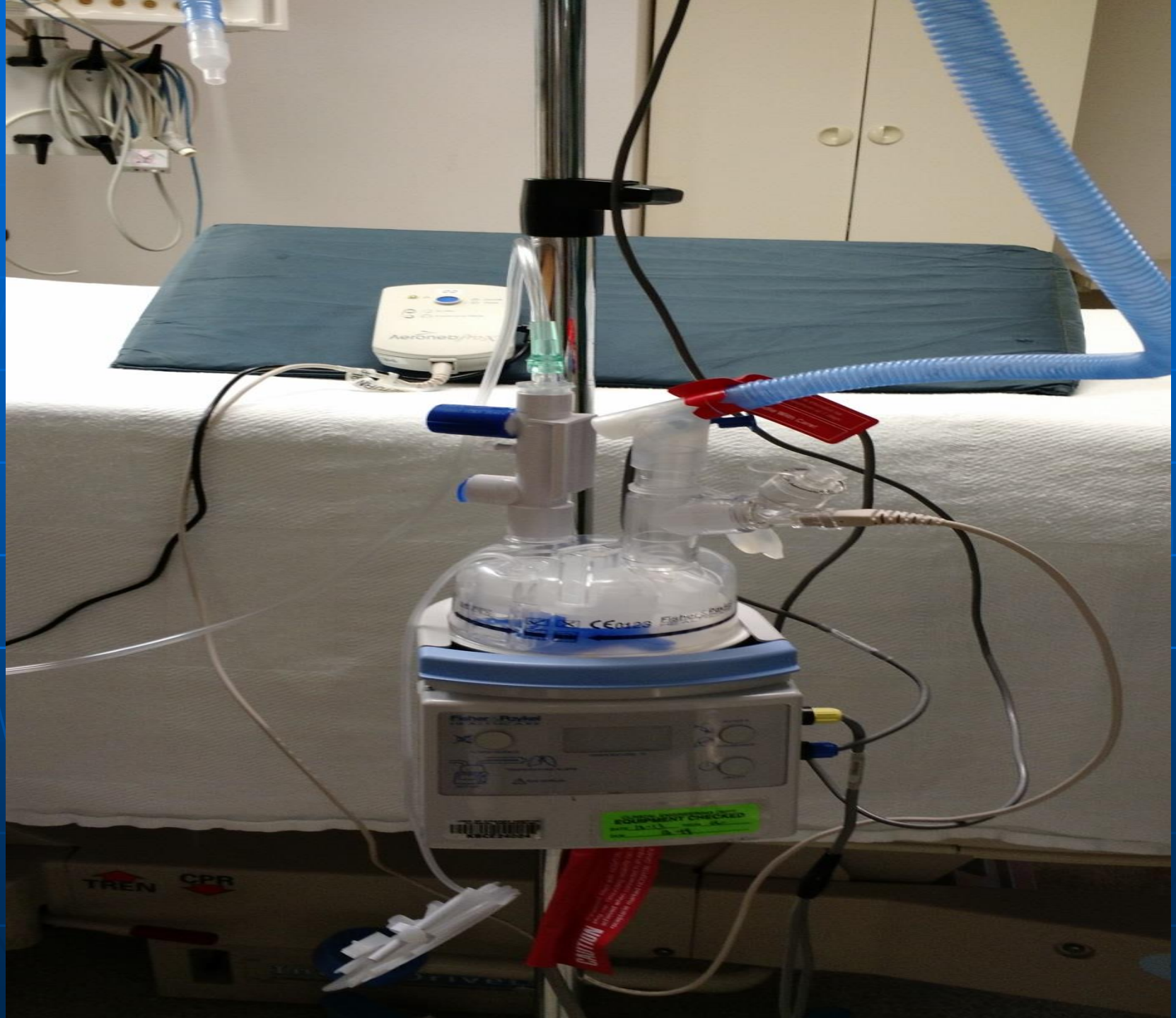
- Chest radiograph =
  - left lower lobe opacity; atelectasis or pneumonia

- The RVP was positive: Polymerase chain reaction (PMR).
  - Rhinovirus / Enterovirus.
  - HCoV- 43
  - Air borne droplet and contact pre-cautions

- Over the next 2d seizures were controlled
- He was extubated and placed on High Flow Nasal Cannula (HFNC) (Fisher & Paykel RT329), FIO_2-1.0 at 5 L/min, breathing at >50 breaths/min.
- Q2 h beta agonist nebulizer treatment and chest physiotherapy

- He had no wheezing or stridor,
  - coarse diminished breath sounds.
  - intermittent fevers,
  - suprasternal chest retraction graded as +5 using the pediatric advanced life support scale

- Agitated and fighting face mask treatments changed to Aerogen Solo® nebulizer via HFNC, all aerosolized medication given with this method there after.


TREN
CPR

- Despite the intense respiratory care treatment regime, reminded in acute respiratory distress.
  - Respiratory rates - **60 to 70** breaths/min,
  - continued prominent chest wall retractions
  - 24 hours post-extubation

- In addition, he experienced periods of arterial desaturation down to 80% that was measured by pulse oximetry (SpO_2).
  - ? Chemoreceptor response

  - Continue Inhaled beta-agonist
  - Administered intravenous corticosteroids

- The pediatric ICU team became concerned that he was depleting his respiratory muscle reserve due to increased work of breathing (WOB)
- AFO was thought to be post extubation related distress originally.
  - desaturation despite HFNC targeting an FIO_2 of 1.0.

- More aggressive respiratory options were considered;
  - Bi-level
  - Infant nasal CPAP
  - re-intubation.

- patients with air-flow obstruction can be very complex to manage on positive pressure ventilation. Therefore, a trial of heliox via HFNC was attempted to reduce R_{AW} and possibly prevent re-intubation,,

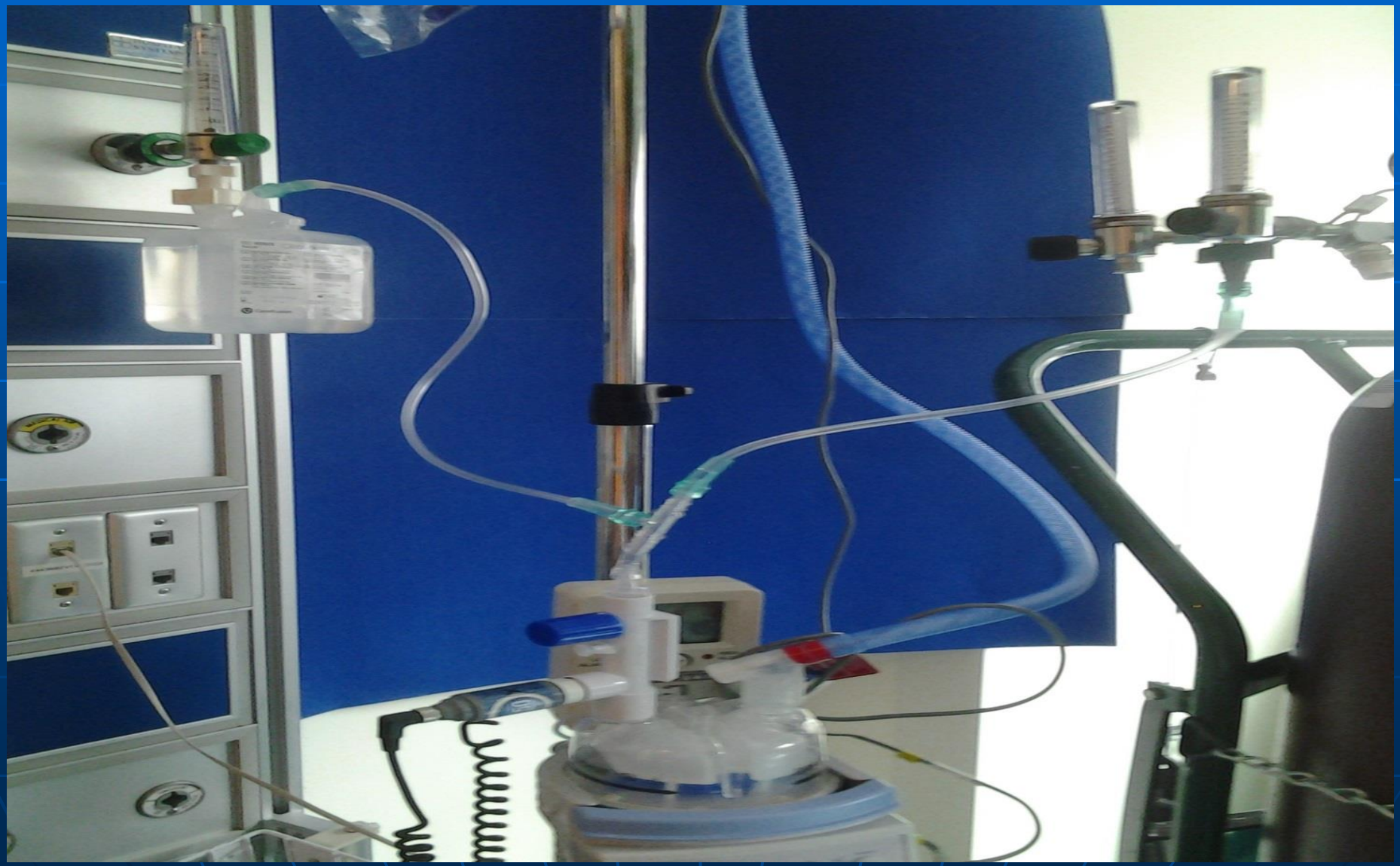
- The American Academy for Pediatrics (AAP) definition of severe acute respiratory distress in infant and children is

- Respiratory rates; **60 to 70** breaths/min

- **Pre heliox treatment;** respiratory rate assessment –

- 60 to 70 breaths/min
  - prominent chest retractions,
  - nasal flaring
  - suprasternal chest retractions

Heliox and HFNC Set-up



Heliox Blender

- HFNC @ 5 L/min, SpO_2 was 94%
- SpO_2 would intermittently drop down to as low as 84% before heliox.
- HFNC /Heliox flow calculations, heliox flow started at 8 L/min with oxygen flow at 1 L/min = total flow of 9 L/min
- He was started 70% helium and 30% oxygen, then changed to 60/40

- One minute after heliox initiation;
- Resp. rate fell to 31 to 36 breaths/min.
- chest retractions & nasal flaring improved
- Appeared to be in less distress, not working as hard to breath.

- during the first 24h of heliox
  - respiratory rate increased to 50 to 60 breaths/min,
  - retraction returned
  - SpO_2 fell to 89%

- Upon investigation, heliox gas line had become disconnected from the HFNC.
- heliox gas line was reconnected,
  - respiratory rate decreased to 27 breaths/min
  - SpO_2 improved to 96%.
- After heliox initiation, the patient's condition improved from critical to serious/stable.

- Bronchiolitis, aerosolized Pulmicort (0.25 mg)
  - every 12h with heliox augmented HFNC
  - Racemic epinephrine tx via heliox-HFNC
- There was no respiratory deterioration.
- With improvement in his respiratory status,
  - albuterol treatment decreased to every 4h as needed.
  - Nutritional support
  - CPT continued

- heliox was discontinued on day 3
- HFNC oxygen flow was 7 L/min and Pulmicort remained at every 12h.
- discharged from PICU to a floor on day 10.
- 7 d later, discharged home with clinic follow-up

Ventilator & Heliox Management Strategies:

- Set tidal Volume at 4-5 cc/kg
- Control mode and age specific set breaths/min (deep sedation & paralytics)
- Ventilate using plateau pressure (Pplateau) as lung pressure measurement
  - Pplateau < 30 cm H_2O, look for auto-PEEP
- Set helium to oxygen concentrations to an FIO_2 to achieve or maintain SpO_2 > 88%
- Permissive hypercapnia to avoid ventilator associated lung injury (VALI)

pH / PCO_2 – Historical Control

Patient	pH-t=1	pH-t=2	$PaCO_2$- t=1	$PaCO_2$-t=2
1)	7.30	7.36	36	29
2)	7.27	7.28	46	46
3)	7.33	7.36	36	30
4)	7.28	7.54	64	31
5)	7.13	7.13	64	70
6)	7.30	7.30	46	39
7)	7.03	7.05	60	85
8)	6.98	7.05	125	102
9)	7.09	7.29	82	54
10)	7.07	7.10	65	62
11)	7.14	7.14	74	70
		P=.04		P=0.17
Mean	7.16	7.24	63	56
SD	0.12	0.16	25	24

- Shaffer et al *Critical Care Med 1999*

Alveolar-arterial Oxygenation Gradient - Control

Patient	A-a t=1	A-a t=2	FIO_2 t=1	FIO_2 t=2
1)	177	104	1.0	.50
2)	185	216	.60	.60
3)	221	124	1.0	.60
4)	273	213	.60	.60
5)	227	224	.60	.60
6)	183	208	---	---
7)	207	270	.60	.60
8)	345	226	.60	1.0
9)	395	171	1.0	.06
10)	153	120	.60	.40
11)	126	117	1.0	.60
		P=0.09		P=0.07
Mean	226	181	.80	.62
SD	82	56	21	15

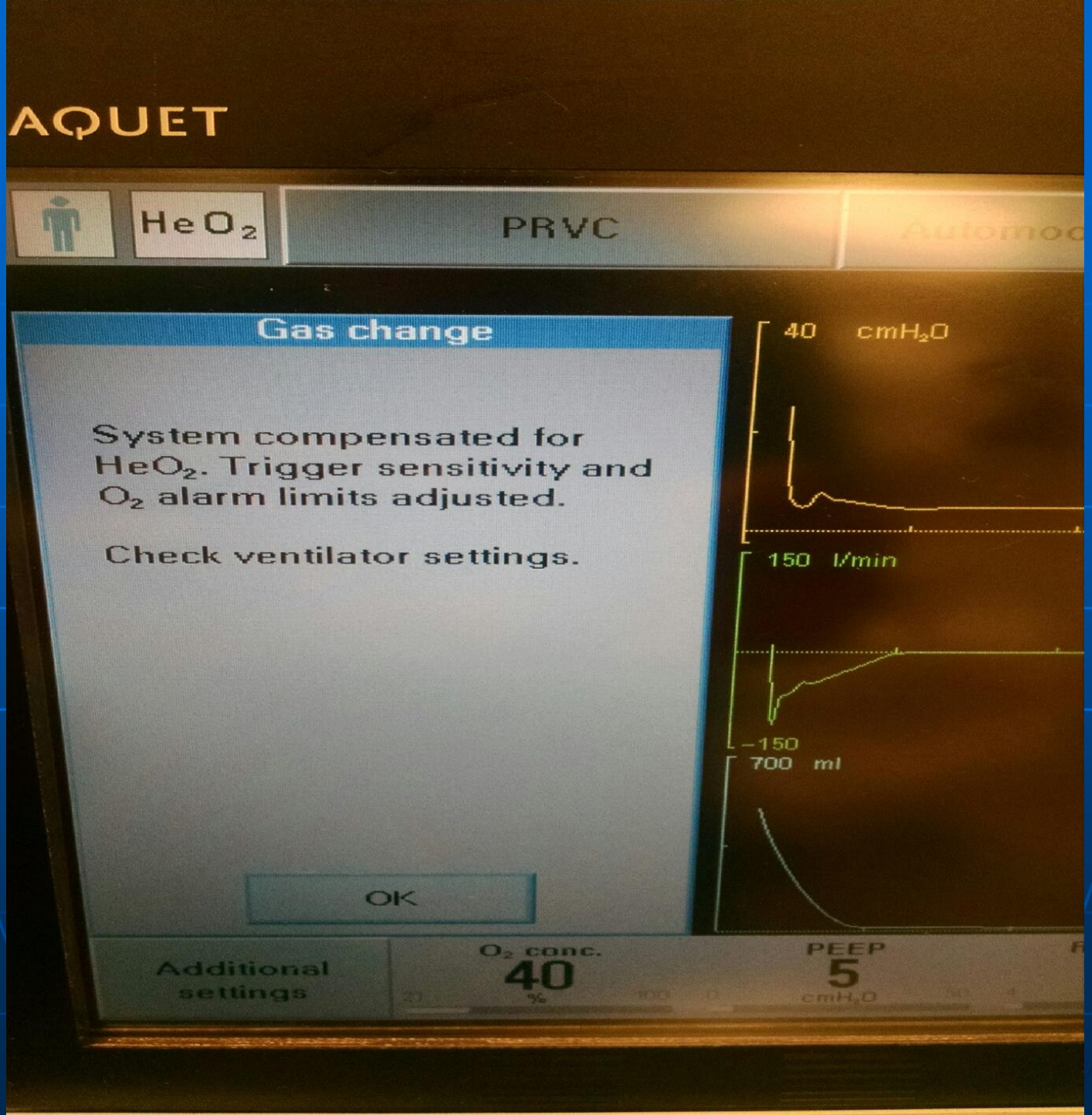
pH / PCO_2 - Heliox

Patient	pH-t=1	pH-t=2	$PaCO_2$- t=1	$PaCO_2$-t=2
1)	7.12	7.17	83	71
2)	7.17	7.15	63	61
3)	7.33	7.31	42	49
4)	7.28	7.28	69	71
5)	7.07	7.05	85	61
6)	6.79	7.07	197	102
7)	7.12	7.08	66	86
8)	7.33	7.33	46	46
9)	6.87	7.00	137	91
10)	7.00	7.16	128	89
11)	7.22	7.31	66	56
		P=.09		P=.06
Mean	7.12	7.17	89	70
SD	0.18	0.12	47	21

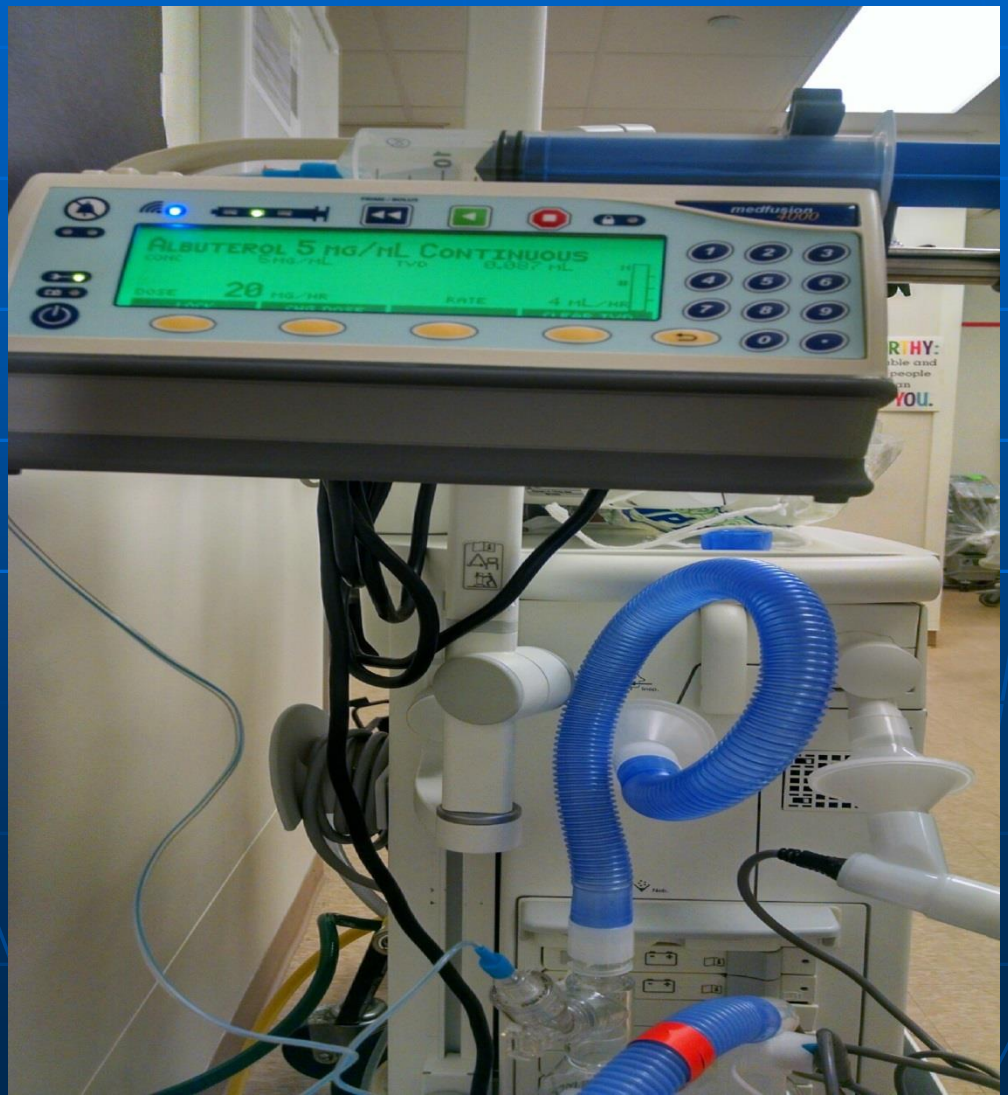
Alveolar-arterial Oxygenation Gradient - Heliox

Patient	A-a t=1	A-a t=2	FIO_2 t=1	FIO_2 t=2
1)	332	70	.70	.30
2)	147	54	1.0	.30
3)	181	85	1.0	.25
4)	405	55	.80	.30
5)	217	181	1.0	.50
6)	255	144	1.0	.50
7)	231	78	1.0	.30
8)	146	226	.60	1.0
9)	216	84	1.0	.60
10)	179	104	.40	.40
11)	68	36	.40	.40
		P=0.001		P=0.002
Mean	216	85	.81	.37
SD	92	44	.25	.12

MAQUET® Servo-I Heliox


AQUET
HeO2
PRVC
Gas change
System compensated for HeO2. Trigger sensitivity and O2 alarm limits adjusted.
Check ventilator settings.
OK
40 cmH2O
150 l/min
-150
700 ml
Additional settings
O2 conc.
40
%
PEEP
5
cmH2O

Volumetric Medication Delivery



Case study #2

- 4 year old white female 16.5 kg was transferred to Comer's Children's Hospital at UCM due to hypercarbic RF ($PaCO_2$-118 mmHg)
- no previous documentation for a history of asthma

- Intubated at OSH
- Difficult to ventilate with ventilator and transport team had to hand ventilate for transport

- Chest Radiography –
  - moderate peri-bronchial thickening

- RVP indicated:
  - Rhinovirus-Enterovirus (RE).

Medication list for 24h before heliox

Continuous albuterol nebulizer	15 mg/hr
Aminophylline	1 mg/kg/hr
Cisatracurum	0.1 mg/kg/hr
Fentanyl	1.5 mcg/kg/hr
Ketamine	20 mcg/kg/hr
Midazolam	0.07 mg/kg/hr
Terbutaline	2.5 mcg/kg/hr
MethylPREDISolone	1 mg/kg – Q6
Atrovent	500 mcg – Q2
Budnesonide	0.5 – Q12

ABG Before Heliox = T1 - T2=3h Later

	T1	T2	Day 2
PH	6.99	7.11	7.37
$PaCO_2$	107	77	60
PO_2	73	97	77
FIO_2/helium	.60	60/40	50/50

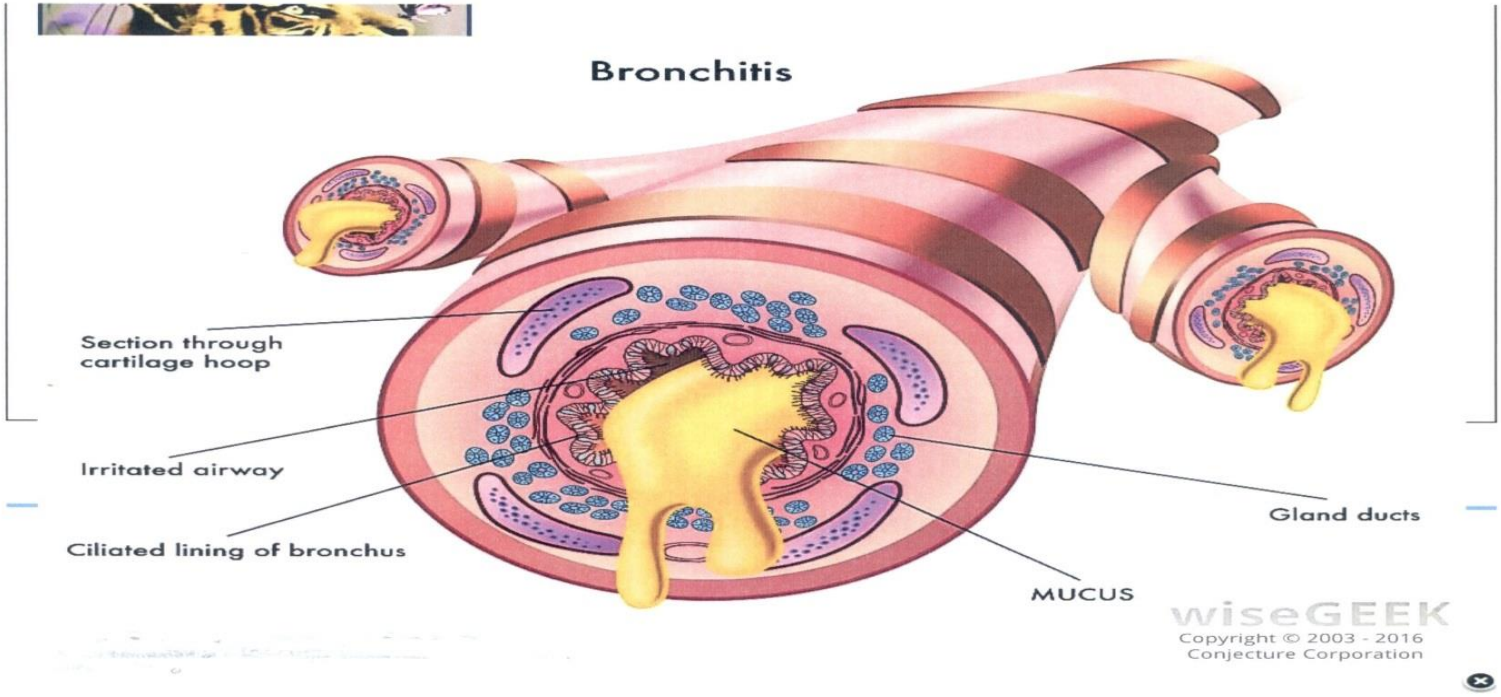
- Vent setting; V_T 140, PRVC -18, FIO_2/heliox - 60/40, +5 PEEP.
- P_{AW} – 36 cm H_2O, plateau pressure-22cm H_2O, Set PEEP +5 cm H_2O, total PEEP +9 cm H_2O, air-trapping not observed.
- Heliox D/C after two days, stayed on the ventilator for 8 days.
- Her course was complicated by severe post sedation delirium.

Case study #3

- 36 year old male African American with a history of asthma.
- Transferred to UCM for management of hypercarbic RF.
- Air transported to UCM for evaluation for possible ECMO for asthma:
- Initial management:
  - intravenous corticosteroids – MethylPREDNISLONE - 40 mg,
  - continuous beta agonist – 15 mg/hr x 72 hr
  - non-invasive mask ventilation

- Respiratory acidosis ($PaCO_2$-115 mmHg) progressed
  - required mechanical ventilation (MV),
  - deep sedation -(Propofol 1% and Fentanyl 1000mcg
  - Paralytic – (Cisatracurium = 1 - 5mcg/kg/min
- Isoflurane was administered:
  - relieve bronchospasm
  - improve alveolar ventilation.
- Upon arrival at UCM MICU $PaCO_2$ – 111 mmHg

- He was placed on a heliox compatible ventilator in the assist control mode.
- Chest radiography was notable;
  - **retro-cardiac atelectasis, likely due to mucus plugging.**
- RVP, abnormal positive for Rhinovirus / Enterovirus.


Bronchitis
Section through cartilage hoop
Irritated airway
Ciliated lining of bronchus
Gland ducts
MUCUS
wiseGEEK
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ABG Before Heliox = T1 - T2=3h Later

	11:45a	15:30p	Day 2
pH	7.19	7.38	7.52
$PaCO_2$	111	71	54
PaO_2	48	54	60
P_{AW}	55	54	60
Pplat	39	22	21

- Vent setting; V_T - 450, assist control -10 - 12, HO/FIO_2 ratio – 70/30, set PEEP +5.
- He was given a spontaneous breathing trial and extubated three days after transfer. Follow-up chest radiography demonstrated peri-bronchial wall structure thickening
- His course was complicated by significant weakness, likely due to prolonged neuromuscular blockage

Discussion

- Respiratory syndromes are frequent trigger for status asthmaticus like exacerbations, that are difficult to manage even with today modern day medicine.
- Viral related bronchoconstriction appears to be the etiology of influenza like RF .
- Heliox has been used for over a century to treat pulmonary exacerbations,
- though little data evidence exist regarding the efficacy of heliox for the treatment of viral related pulmonary exacerbations.

- The use of heliox was first reported in 1935 by Alvin Barach.
- He observed that breathing heliox appeared to relieve dyspnea in children and adults with asthma and upper airway obstruction.
- In 1950, Barach, Peabody and Levine, called it generalized obstruction or partial obstruction of the airway, general appearance of asphyxiation accompanied with rapid shallow breathing. “Total obstruction not compatible with the living”.

- Although the earlier reports were non-controlled, the improvement observed in these patients strongly suggest an positive effect of breathing heliox on R_{AW}.

- In addition, as witnessed in our case,
- Relapse occurred when heliox was discontinued even briefly.

- Regardless of the possible contributions, our patient's appeared to respond to inhaled helium oxygen mixtures.

- The morbidity and mortality is significant with regard to infants

- Viral respiratory AFO is like flying an airplane, with turbulent air flow.
- You have to trust clinical instruments and clinical information.
- Chest radiography, CBASA, and RVP
- Application of heliox is not widely recognized and considered an adjunct

- Between 2012 and 2014, over 1,200 kids were admitted for one or another respiratory syndromes, some patients had co-morbiditites
- In the summer of 2014 > 600 kids were admitted to Comer Children's Hospital, 12 cases were near fatal, 2 went on ECMO, one fatal.
- Many kids treated with heliox combinations Bilevel, HFNC and MV.
- The majority of the kids were diagnosed with the Rhinovirus / Enterovirus

- Few prospective studies have examined the use of heliox for respiratory syndromes.
- Martinon-Torres et al, investigated 38 non-intubated infants with RSV
- Using a modified version of the Wood's CASA.

- They found significant improvement in scores with heliox after 1h of treatment compared with the control group.
- The total average decrease in scoring was;
  - 4.2 in the heliox group versus
  - 2.5 in the control group

- Kim et al, performed a randomized control trial with 69 spontaneously breathing infants diagnosed with RSV related viral bronchiolitis

- Found a mean change from baseline of;
  - 1.84 CASA for the 70/30 heliox group
  - 0.31 for the oxygen group.

- The only prospective study for the use of heliox for acute viral bronchiolitis in spontaneous breathing children was performed by Hollman et al, 1996.

- The beneficial effects of breathing heliox is derived
  - from reduction in air-flow resistance
  - restoration of laminar gas flow to airways
  - that are obstructed from per-bronchial thickening or mucus plugging
- In normal human airways, the resistive pressure decrease between the glottis and tenth-generation airways varies directly with inspired gas density

- The resistive pressure decrease over the tenth to twentieth generation is density-independent because air-flow in these regions is laminar.

- Because 80% of the inspiratory resistive pressure decrease occur in the more proximal density-dependent segments,

- Breathing a less dense gas can reduce R_{AW} to 28 - 49% of that measured with air in normal patients.
- R_{AW};
  - Normally < 3 cm H_2O/L/s,
  - 40% pressure reduction is clinically unimportant.
- However, in asthma and other causes of influenza-like viral airflow obstruction

- R_{AW} can increase to > 50 cm H_2O/L/s with much of this related to air-flow obstruction from turbulent gas flow associated with airway constriction from;
  - peri-bronchial airway wall structure thickening
  - atelectasis related mucus plugging
- Studies indicate that bronchiolitis is a heterogeneous disease and involves smaller airway and lung interstitium

- Often overlooked, It appears as if bronchoconstriction may be the etiology behind influenza-like respiratory failure.
- Maybe the main source of obstruct air flow and medication entry the lung for gas exchange to occur.

- Because heliox reduces non-laminar air flow, diverse causes of airway disease leading to air-flow obstruction are likely to respond to heliox administration.

- The use of heliox in this situation does not treat the underlying disease or influence the anatomy of the airway.

- Rather, heliox is used as a bridge treatment
  - to reduce airflow resistance,
  - until definitive therapies and
  - time act to reduce R_{AW}
  - reduce the need for heliox,
  - usually within 24 to 48 h.

Conclusion

- More than a century has passed,
  - there are inadequate studies to definitively determine the role of heliox, and its appropriate place in the armamentarium against respiratory syndromes exacerbations.
  - Which has now shown the ability to effect large populations of animals and humans

- To our knowledge, few reports exist with regard to the use of heliox being administered as an adjunctive treatment for viral influenza-like respiratory failure with resolve.

- The hypothesis was that the combination of treatments may have had a cumulative therapeutic effect for the attenuation of acute air-flow obstruction

- Clinically, these patient's breathing improved with heliox treatment

- All three patient's general condition continued to improve after 48 h of
  - heliox
  - aerosolized corticosteroids
  - nutritional support

- The benefit of heliox itself appeared to serve as a bridge to support these patients while time and pharmacologic measures took effect and an underlying infection abated.

- Because patient response may vary, a trial of heliox should be considered when caregivers are confronted with patients with acute air-flow obstruction who still have respiratory reserve and refractory to current treatment methods.
- The patient should be monitored closely for acute changes.

- More prospective study are needed to understand, recognize and treat viral related airflow obstruction and the role of heliox for the treatment of viral pulmonary exacerbation

- which is now documented to be caused by an increased number of viral agents.

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