Feeling Blue?

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FEELING BLUE

Sometimes it's more than just a feeling

Case I

Identification & chief complaint

- 8 year-old patient with hypoxemia on overnight oximetry
- Found to have Pulmonary arterial hypertension associated with congenital heart disease

Eisenmenger Syndrome

Pulmonary Hypertension

Table 3 **Haemodynamic definitions of pulmonary hypertension**[a]

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

[a]All values measured at rest; see also section 8.0.

[b]According to *Table 4*.

[c]Wood Units are preferred to dynes.s.cm^{-5}.

1) Galiè, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal Aug 2015.

Pulmonary Htn Classification

Table 4 Comprehensive clinical classification of pulmonary hypertension (updated from Simonneau *et al.*[5])

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

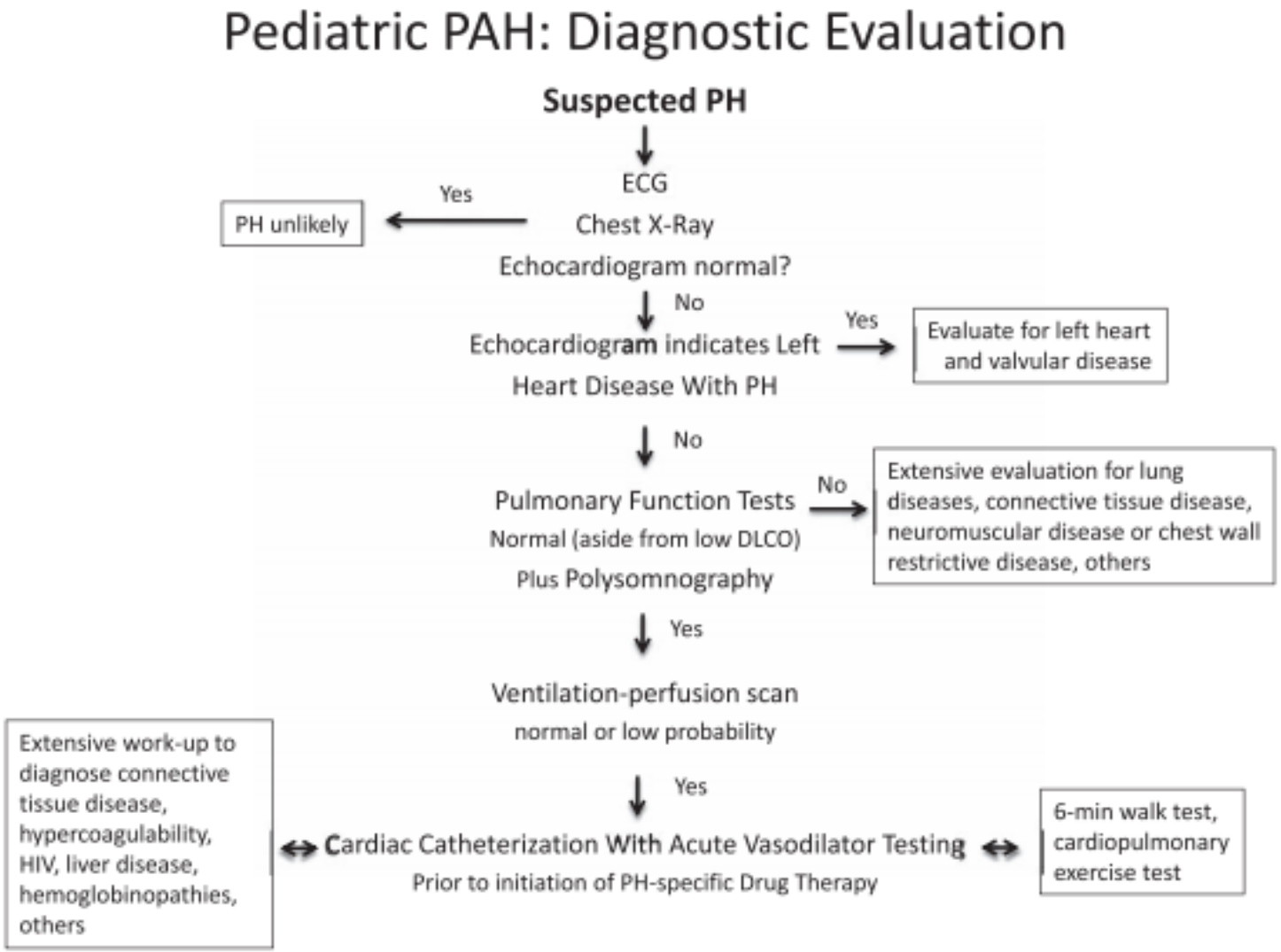
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

1) Adapted from: Galiè, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal Aug 2015.

Diagnosis



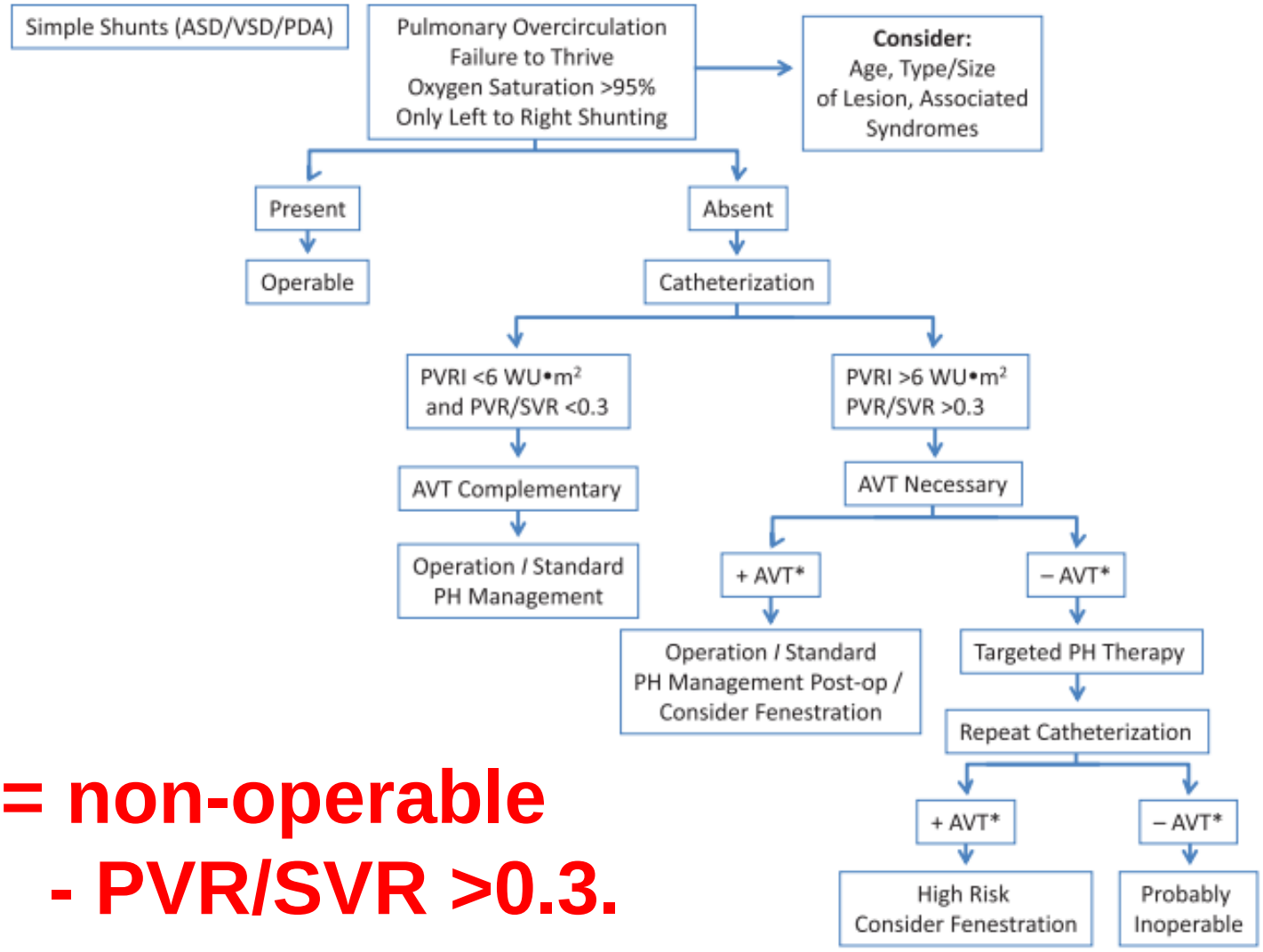
2) Abman, et al. Pediatric Pulmonary Hypertension. Circulation. Nov 2015.

Eisenmenger Teaching

- Eisenmenger's syndrome (ES):
  - Large intra- & extra-cardiac defects
    - VSD, PDA, ASD (adults)
  - Begin as systemic-to-pulmonary shunts
  - Progress to severe elevation of PVR and to reversal or bidirectional shunting
  - Cyanosis, erythrocytosis, and multiple organ involvement are usually present.

1) Galiè, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal Aug 2015.

Operability of Shunt Lesions



ES = non-operable

- PVR/SVR >0.3.

2) Abman, et al. Pediatric Pulmonary Hypertension. Circulation. Nov 2015.

Eisenmenger – Presentation

- Most common:
  - Dyspnea, fatigue, syncope
  - Exercise introlerance*
- At risk of:
  - Hemoptysis, stroke, PE, brain abscess, coagulopathy, sudden death

Eisenmenger – Diagnosis

- Suggestion: ECHO
- Confirmation: Catheterization
- ECHO may miss PDA
  - 2 / 8 patients with diagnosis of iPAH found to have PDA on repeat ECHO

6) Sohn, et al. The Value of Contrast Echocardiography in the Diagnosis of Patent Ductus Arteriosus with Eisenmenger's Syndrome. Journal of the American Society of Echocardiography. Vol 14:1. Jan 2001.

Eisenmenger Treatement

Table 25 Recommendations for pulmonary arterial hypertension associated with congenital heart disease

Recommendations	Class[a]	Level[b]	Ref.[c]
Bosentan is recommended in WHO-FC III patients with Eisenmenger syndrome	I	B	200,322
Other ERAs, PDE-5is and prostanoids should be considered in patients with Eisenmenger syndrome	IIa	C	223,314, 323,324
In the absence of significant haemoptysis, oral anticoagulant treatment may be considered in patients with PA thrombosis or signs of heart failure	IIb	C	
The use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial O_2 saturation and reduces symptoms	IIa	C	179
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered, usually when the haematocrit is >65%	IIa	C	183
The use of supplemental iron treatment may be considered in patients with low ferritin plasma levels	IIb	C	184
Combination drug therapy may be considered in patients with Eisenmenger syndrome	IIb	C	207,314
The use of CCBs is not recommended in patients with Eisenmenger syndrome	III	C	189

-Bosentan therapy reduced PVR and mPAP and increased 6MWD by 53.1 m without worsening gas exchange.[2]

1) Galiè, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal Aug 2015

2) Abman, et al. Pediatric Pulmonary Hypertension. Circulation. Nov 2015.

Case II

Identification

- 8 year-old of South Asian origins
  - Known for mild Asthma.
  - Presenting with fever and non-bilious emesis
  - Found to have oxygen requirement

Differential Diagnosis

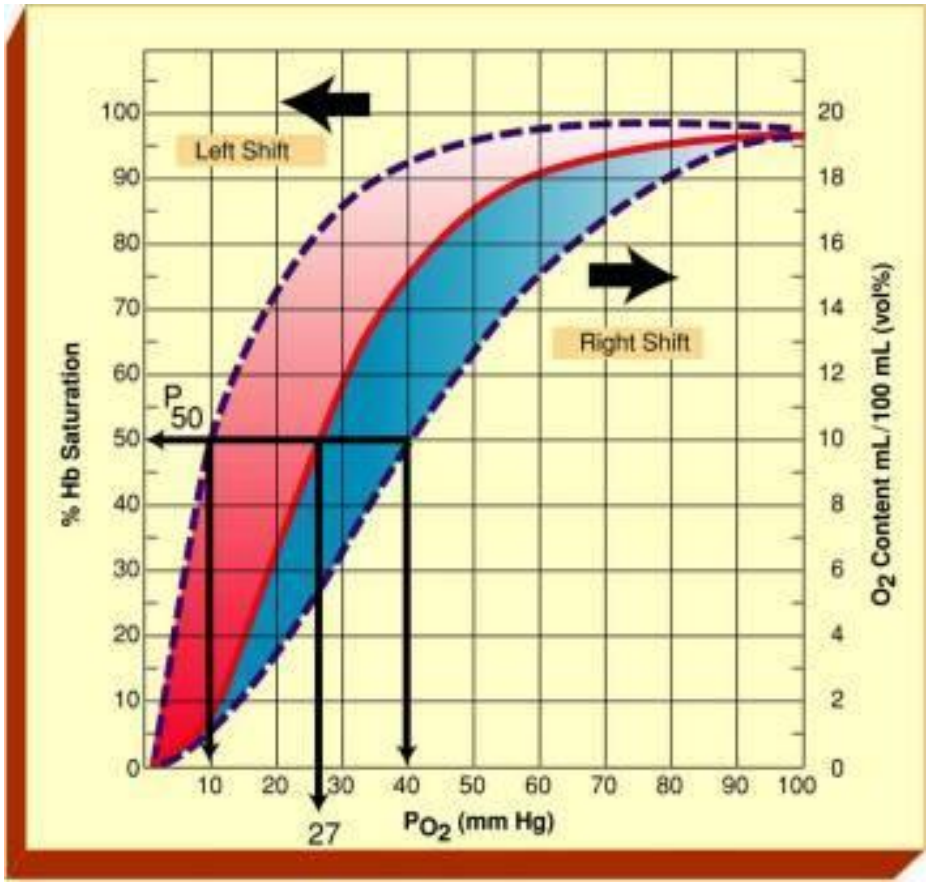
- Hypoventilation
  - Central
  - Obstructive
- V/Q mismatch
  - Asthma, ABPA
  - Infection
  - Pneumonitis
  - Pulmonary edema
  - Pulmonary hyptertension
  - Pulmonary embolus
- Other:
  - Low inspired oxygen
  - Technical error
  - Hemoglobinopathy
- Shunt
  - Intracardiac,
  - Intrapulmonary
    - Pulmonary AVM / HHT
    - Complete atelectasis, airway obstruction
- Diffusion abnormality
  - Interstitial Lung Disease
    - IPF
    - Connective Tissue disease
    - Sarcoidosis
    - chILD
    - IIP
      - COP

Diagnosis?

- Heterozygous Hb-Rothschild mutation
  - Reduced oxygen affinity

Oxygen-Hgb Dissociation Curve

- Normal p50: 27mmhg
- Left Shift (↓ O2 delivery)
  - ↑ pH
  - ↓ pCO2
  - Temp
  - ↓ DPG
- Right shift (↑ O2 delivery)
  - ↓ pH
  - ↑ pCO2
  - Temp
  - ↑ DPG

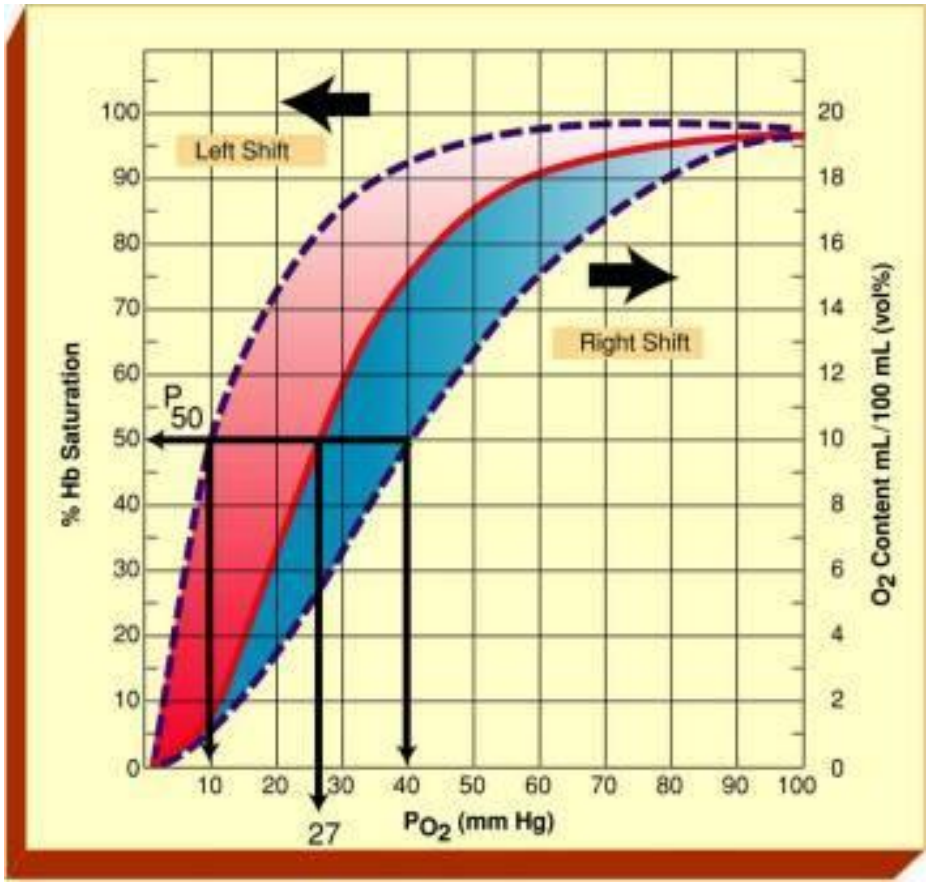


https://media.lanecc.edu/users/driscolln/RT127/Softchalk/Oxygen_transport_softchalk/Oxygen_Transport_Lesson4.html

Oxygen-Hgb Dissociation Curve

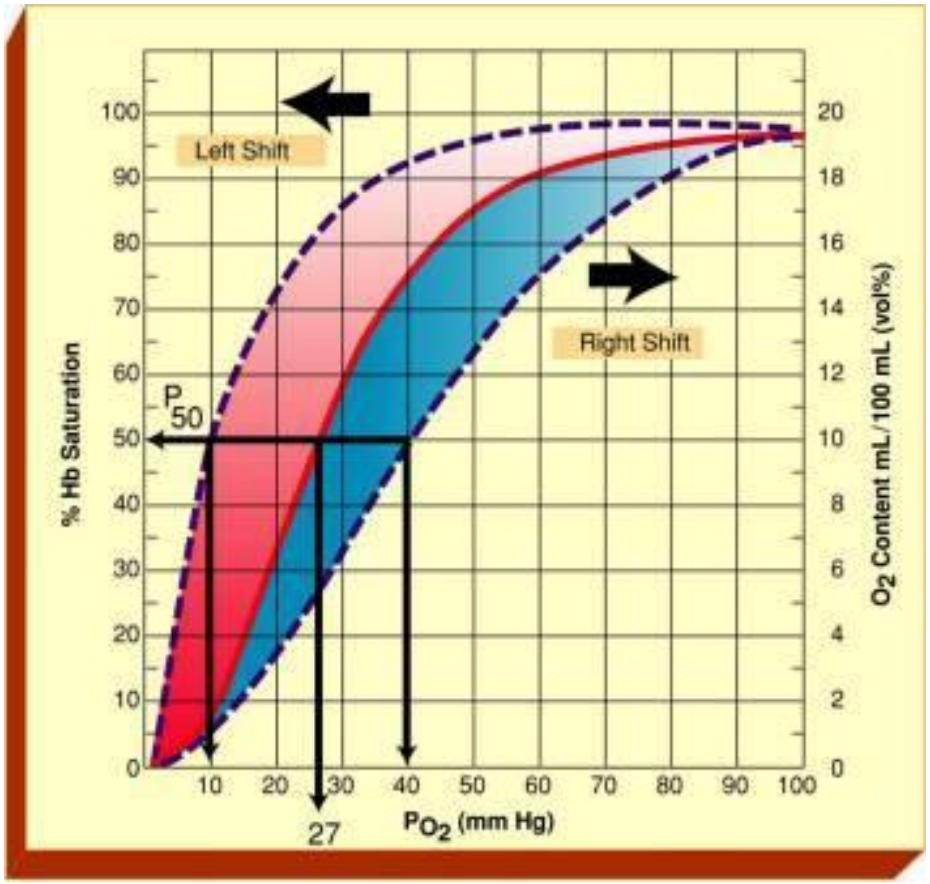
Hemoglobin variants

- HbS – Right
- HbF – Left
- MetHb – Right
- CoHb – Left
- Rothschild, Chico, Basset – Right



Oxygen-Hgb Dissociation Curve

- Normal p50: 27mmhg
- MM: VBG
  - PaO2 32.8
  - SaO2 46.0%
- Patient's p50: 34
  - Right-shift



Hemoglobin Variants and Desaturation

Mechanism of Low SpO2 Readings:

- True, low affinity Hb-variants
  - Rothschild, Bassett, Canebiere
- Absorption spectra of variant hemoglobins
  - Bonn, Cheverly, Koln
  - Methemglobin

7) Verhosek, et al. Erratum to: Unexpectedly low pulse oximetry measurements associated with variant hemoglobins: A systematic review. Am. J. Hematol. 86:722–725, 2011.

Algorithm

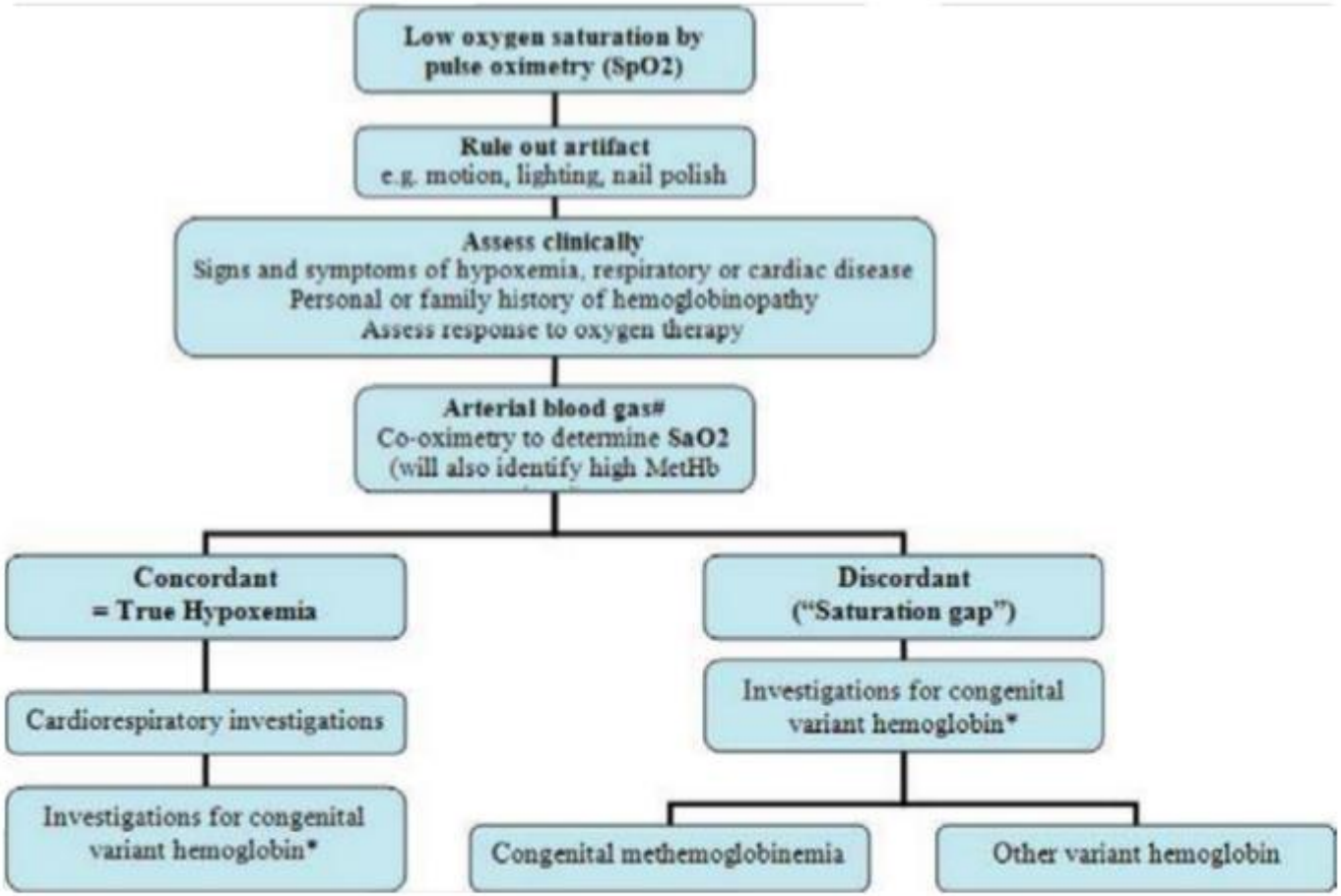


Figure 2. Algorithm for evaluation of low SpO2. MetHb = methemoglobin. # Arterial blood gas should be done on room air and with simultaneous SpO2 measurement. * Investigations could include hemoglobin analysis by various methods, and if necessary, DNA-based genotyping. [Color figure can be viewed in the online

7) Verhosek, et al. Erratum to: Unexpectedly low pulse oximetry measurements associated with variant hemoglobins: A systematic review. Am. J. Hematol. 86:722–725, 2011.

The Saturation Gap

- “Saturation Gap”
  - $SaO_2 – SpO_2 \geq 5\%$.
  - Suggests abnormal hemoglobin
    - Carbon Monoxide poisoning
    - Methemoglobinemia
    - Sulfhemoglobinemia
    - Other hemoglobin variants

8) Akhtar et al. Mind the gap. J Emerg Med. 2007 Aug;33(2):131-2. Epub 2007 Jun 5.

Absorption spectra of variants

Pulse oximetry calculates hemoglobin oxygen saturation based on light absorption at only two wavelengths

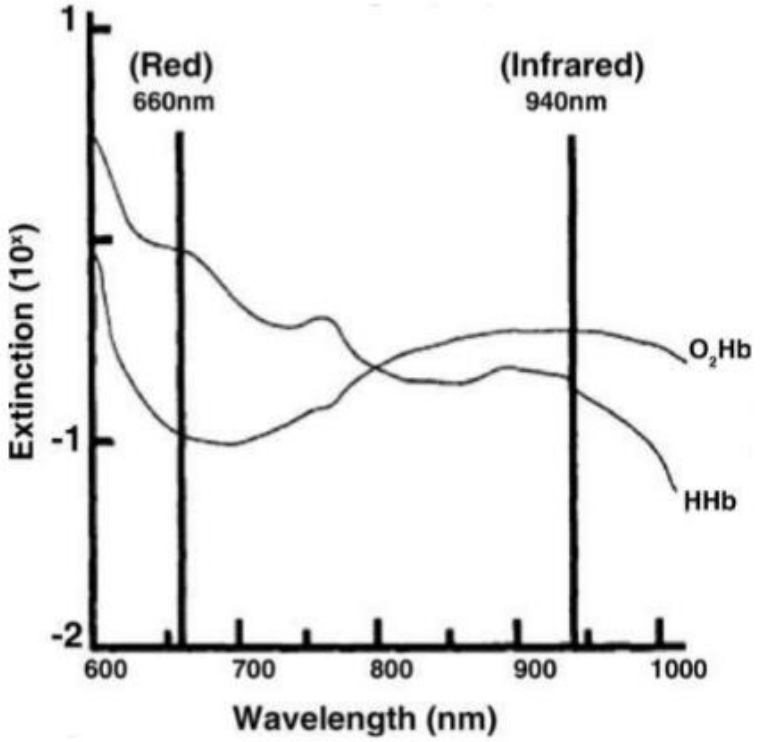
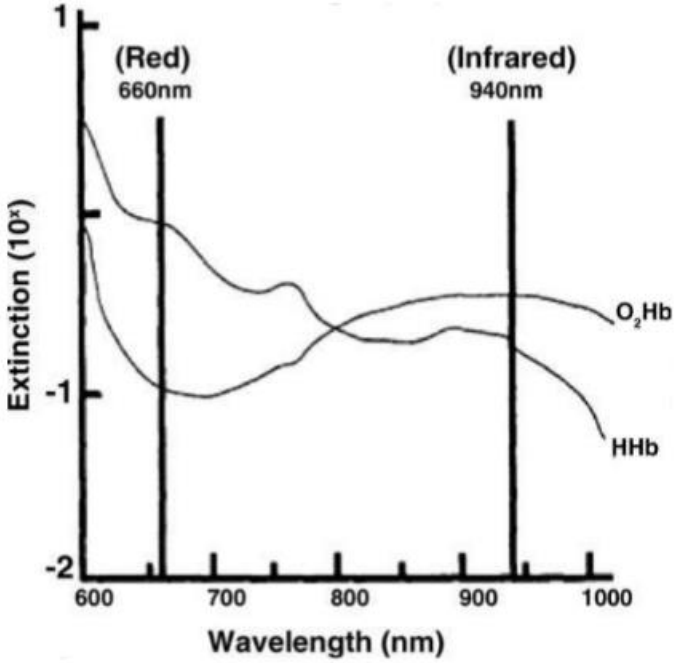


Figure 3. Hemoglobin extinction curve of normal adult oxyhemoglobin and normal adult deoxyhemoglobin. Figure from Sinex [36].

7) Verhosek, et al. Erratum to: Unexpectedly low pulse oximetry measurements associated with variant hemoglobins: A systematic review. Am. J. Hematol. 86:722–725, 2011.

Absorption spectra of variants

- Variant hemoglobins with abnormal absorption spectra compromise accuracy
- Methemoglobin
  - High absorption at 660, 940 nm → Unreliable
- Carboxyhemoglobin
  - Similar 660nm absorption, falsely elevated saturations



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Low Affinity Variants

- ↓SpO2, ↓SaO2
- Normal PaO2
- Right shifted p50

- Oxygen delivery NOT adversely affected
  - Right-shift: ↑ O2 delivery
  - Appropriate low-normal hemoglobin levels
- Desaturation α [Variant Hb]

Hemoglobin Rothschild

- Beta-chain mutation: Trp → Arg[9]
- Low-oxygen affinity variant
- P50: 34.75 – 35 mmHg[10]

Demonstration of Left Shift[11]

TABLE I. Effect of increased F_IO_2 on PaO_2, SaO_2 and predicted SaO_2

F_IO_2 (%)	PaO_2 (mmHg)	Measured SaO_2 (%)	Predicted SaO_2 (%)
21	94	84.2	97
50	169	91.3	99.4
100	589	96.1	100

9) Danish, et al. HB Rothschild (β 37 (C3) TRP → Arg): Clinical Studies. Hemoglobin. 6:1, 1982.
10) Hladik et al. Dyshemoglobinemias and Pulse Oximetry – A Therapeutic Challenge. J Pediatr Hematol Oncol. 30:11, 2008.
11) Bruns et al. Hemoglobinopathy Case Finding by Pulse Oximetry. American Journal of Hematology. 74:142-143, 2003.

Hemoglobin Rothschild

- Cannot be diagnosed via HPLC
  - Similar profile as Hemoglobin-D variant

Hb-Rothschild

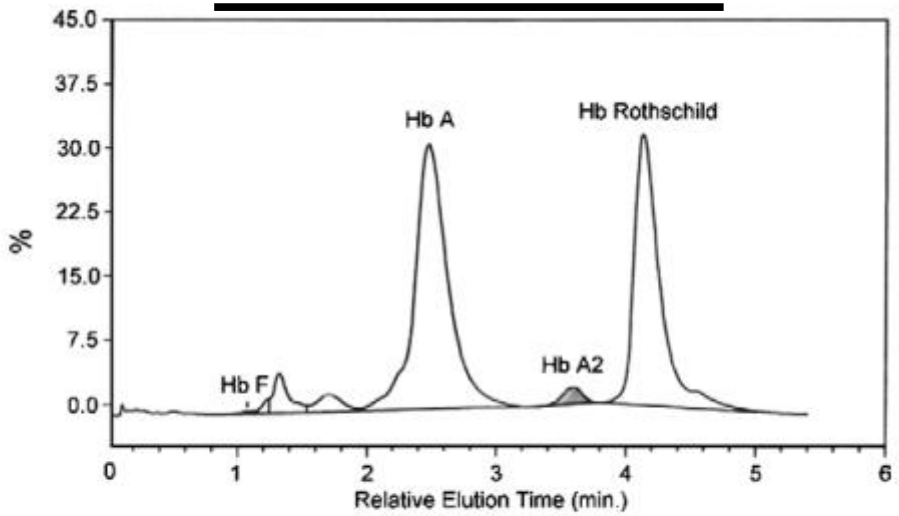

FIGURE 1. High-performance liquid chromatography analysis of proband's hemoglobin.

Hb-D

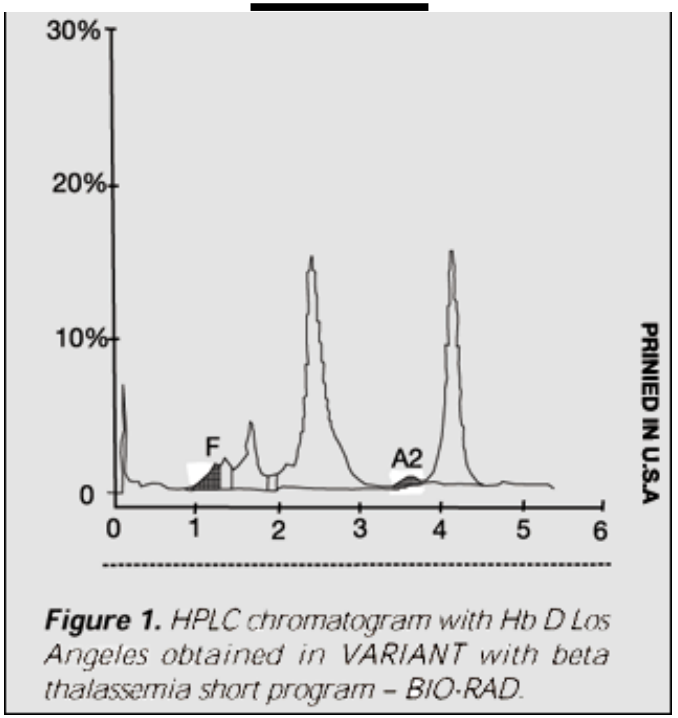

Figure 1. *HPLC chromatogram with Hb D Los Angeles obtained in VARIANT with beta thalassemia short program – BIO-RAD.*

10) Hladik et al. Dyshemoglobinemias and Pulse Oximetry – A Therapeutic Challenge. J Pediatr Hematol Oncol. 30:11, 2008.

http://www.scielo.br/img/fbpe/rbhh/v23n3/a04fig01.gif

Hemoglobin Rothschild

- Presentation:
  - Desaturation
  - Low-normal Hb
    - Appropriate vs. shorter $t_{1/2}$
- Natural History:
  - Unknown
  - Presumed normal life expectancy

Clinical Take Home Points

- Routine pulse oximetry
  - Record where oximetry is taken from
- Low SpO2 should be followed
- Do not ignore low SpO2 out of keeping with clinical picture


PET

ANY QUESTIONS??