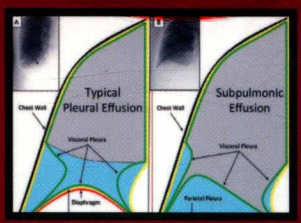
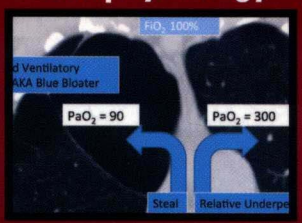
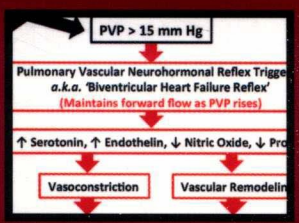
Judd W. Landsberg, MD

Clinical Practice Manual for Pulmonary and Critical Care Medicine

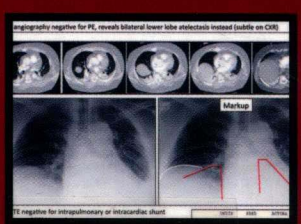
Pathophysiology

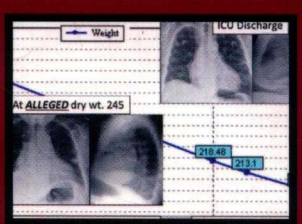


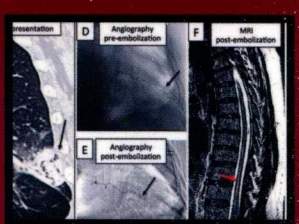




Illustrative Cases







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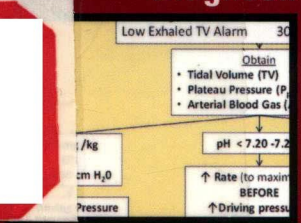

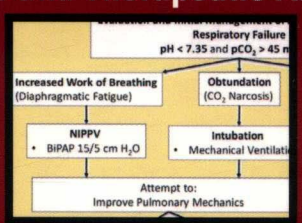

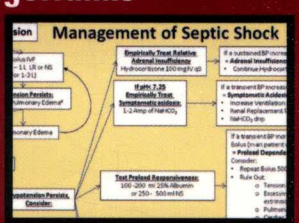

ELSEVIER

MANUAL FOR PULMONARY AND CRITICAL CARE MEDICINE

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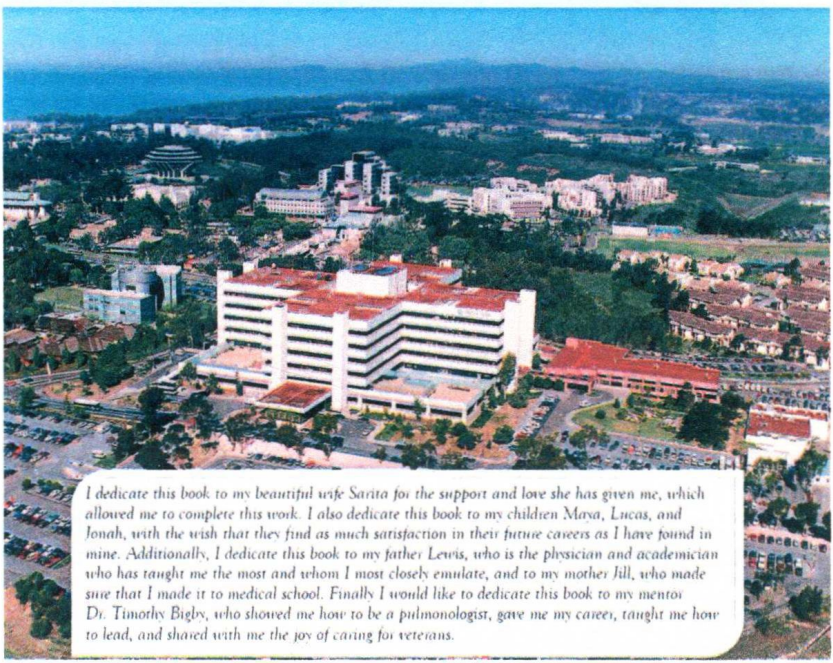
PREFACE

This book represents teaching materials and illustrative cases that have been compiled and refined over more than a decade, focused on basic topics that are taught poorly, fraught with misunderstanding, and for which no clear management algorithms exist. I wish I had this book when I started my training, and I am glad that I have it now to teach my trainees. My hope is that this book will help you every day in your clinical practice and your teaching.



I dedicate this book to my beautiful wife Sarita for the support and love she has given me, which allowed me to complete this work. I also dedicate this book to my children Maya, Lucas, and Jonah, with the wish that they find as much satisfaction in their future careers as I have found in mine. Additionally, I dedicate this book to my father Lewis, who is the physician and academician who has taught me the most and whom I most closely emulate, and to my mother Jill, who made sure that I made it to medical school. Finally I would like to dedicate this book to my mentor Dr. Timothy Bigby, who showed me how to be a pulmonologist, gave me my career, taught me how to lead, and shared with me the joy of caring for veterans.

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I want to individually acknowledge and thank **Dr. Philippe Montgrain**, my colleague and specialized content editor, who read every word of this book, on his own time, to ensure that I said what I meant and meant what I said. I also want to thank **Dr. Laura Crotty Alexander** and **Dr. Jess Mandel** for providing me the opportunities that ultimately resulted in this finished book. Finally I would like to thank the veterans who have taught me about service, longevity, and family and pulmonary disease, and who have allowed me to use our experiences together to teach others.

Special thanks go to the teaching attendings who have shaped my thoughts and practice of medicine:

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Angela Wang, MD
Aaron Waxman, MD, PhD
Jason Yuan, MD, PhD
Gordon Yung, MD

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I Pulmonary

II Critical Care

APPROACH TO OXYGENATION, HYPOXEMIA, AND HYPOXEMIC RESPIRATORY FAILURE

COMMON MISCONCEPTIONS AND MISTAKES

- Hypoxemia is a significant cause of dyspnea
- A cutaneous O_2 sat $\geq$92% predicts adequate oxygenation and is the appropriate target for O_2 orders
- 100% O_2 suppresses respiratory drive in CO_2 retainers
- O_2 supplementation for patients with COPD is given to improve exercise tolerance
- Confusing failure of oxygen delivery to tissues, hypoxia (the job of the circulatory system) with hypoxemia, and failure to maintain an adequate Pao_2 (the job of the respiratory system)

OXYGENATION

- **Normal oxygenation** (at sea level) predicts:
  - A partial pressure of oxygen (Pao_2) of 75–100 mm Hg with 21% Fio_2 (room air) and a Pao_2 of **~660 mm Hg** with **100% Fio_2**
- **Impaired oxygenation** exists on a spectrum from mild (abnormal A-a gradient) to severe (shunt):
  - $Pao_2 < 200$ mm Hg on Fio_2 of 100% = "shunt physiology"
  - **Without "shunt physiology"** an **$Fio_2 > 40\%$** (~ > 6 L/min via nasal cannula (NC)) should give a **$Pao_2 > 60$ mm Hg**, despite pathology causing an abnormally increased A-a gradient
- Patients demonstrating shunt physiology are at high risk for hypoxemic respiratory failure, necessitating a search for the underlying cause, as well as close observation and aggressive support (e.g. chest imaging, 100% Fio_2)
- What defines adequate oxygenation Pao_2, O_2 sat, or *it depends?* Correct answer, **Pao_2**:
  - Tissue oxygenation is a function of the circulatory system (primarily cardiac output (CO) and hemoglobin (Hb))
    - Systemic hypox**ia**, the result of failed oxygen delivery to tissue (e.g. distributive shock), leads to systemic lactic acidosis
      - Increasing Pao_2 does **not** meaningfully increase oxygen delivery to tissues or decrease lactate
  - The job of the respiratory system is to maintain a Pao_2 **>60 mm Hg**
    - When Pao_2 drops acutely to **<60 mm Hg** (hypox**emia**), organ specific symptomatic hypox**ia** may occur
      - Especially in the **brain, heart**, and **kidney** (high metabolic demand)
  - When treating hypoxemia hypox**emia** target, a **$Pao_2 > 60$ mm Hg**
- **Hypoxemic respiratory failure** is practically **defined as a $Pao_2 < 60$ mm Hg**
- An **acute drop in $Pao_2 < 60$ mm Hg** (but >54 mm Hg), ie, "mild hypoxemia," **may cause** a range of symptoms:
  - **Tachypnea** (hypoxic hyperventilation reflex)

- Designed to increase alveolar O_2 by decreasing alveolar CO_2, thereby increasing work of breathing
- Tachycardia
  - The right ventricle (RV) attempts to maintain CO in the face of rising pulmonary artery pressure (PAP) (hypoxic vasoconstriction) and decreased stroke volume (SV) by increasing heart rate (HR)
- **Mental status changes** (agitation, confusion, and decreased sensorium)
- **Increased left ventricular end-diastolic pressure (LVEDP)** (a.k.a. heart failure) from diastolic dysfunction
  - Hypoxia stiffens the left ventricle (LV) and tachycardia shortens diastole, both impairing ventricular filling
- **Decreased glomerular filtration rate (GFR)** from increased LVEDP (cardio-renal physiology) or hypoxic renal injury

- Additionally, **asymptomatic** patients with an acute drop in **Pao_2 (<60 mm Hg)** are at increased risk for sudden profound/life-threatening desaturations (steep portion of the hemoglobin–oxygen [Hb–O_2] dissociation curve)
- When patients in hypoxemic respiratory failure achieve a **Pao_2 > 60 mm Hg** (without hyperventilation) **no** further increase in respiratory support aimed at improving oxygenation is required
  - Efforts then focus on resolution of the underlying cause of hypoxemia
  - A low O_2 saturation, occurring with a **Pao_2 > 60 mm Hg**, indicates acidosis (causing Hb desaturation), **not** hypoxemic respiratory failure
    - Efforts then focus on resolving the acidosis (eg, renal replacement therapy)
- Symptomatic hypoxemia can be effectively ruled out by demonstrating a Pao_2 > 60 mm Hg
  - And, to a lesser extent, screened for by a cutaneous O_2 saturation (with a good wave form) >94%
- Pulse oximeter readings >92% (but <95%) may mask a Pao_2 < 60 mm Hg because of alkalosis or error (Figs. 1.1 and 1.2)

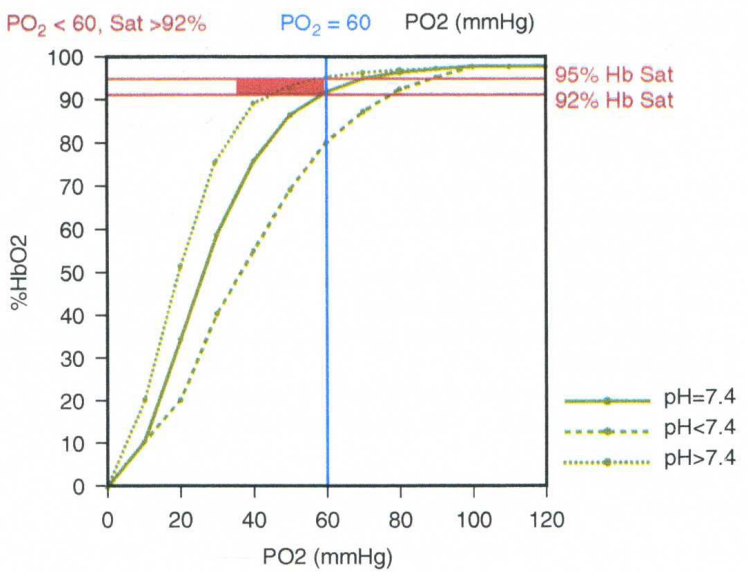
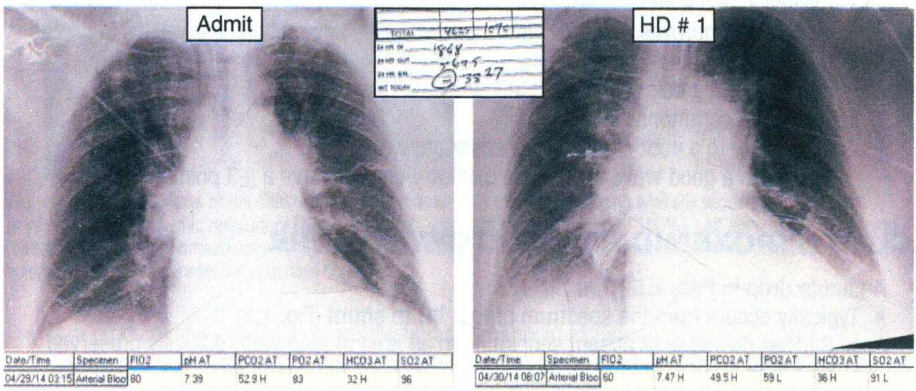
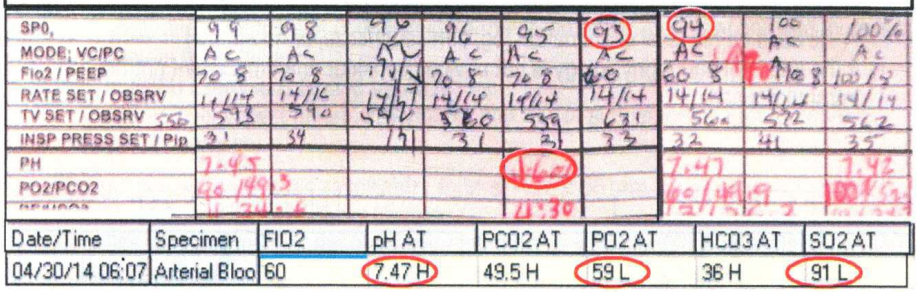


Fig. 1.1 Hemoglobin–oxygen dissociation curve. Shown is the Bohr effect (eg, shift in Hb saturation based on pH) where, for any given Pao_2 value, alkalosis promotes increased saturation and acidosis decreases it. The shaded area in red shows individuals whose cutaneous pulse oximetry readings will be >92% but whose Pao_2 values will be <60 mm Hg (because of alkalemia). Pulse oximetry readings of >94% ensure a Pao_2 > 60 mm Hg over a wide range of pH values, making it a more appropriate target for pulse oximetry orders (aimed at screening for hypoxemia, ie, a Pao_2 < 60 mm Hg)

- Patient admitted for heart failure with a preserved ejection fraction (HFpEF)
- Intubated for increased work of breathing and hypoxemia
- Admit CXR with increased interstitial markings, small effusions
- Despite a ~ 4L negative fluid balance over the first 24 hours the PT suffers ↓ oxygenation
- CXR on HD # 1 shows worsening pulmonary edema:
  - ↑Perihilar ground glass and interstitial edema with worsening effusions (L > R)
- EKG, troponins and a STAT cardiac echo were unchanged from admission
- Blood pressure overnight 150–160/80–85, HR: 60–90 sinus rhythm



- Inspection of the flow sheet shows the ↓ in FiO_2 to 60% at 4:30 am lead to hypoxemia
- Not recognized until a routine ABG was obtained at 6:00 am
- The hypoxemia was missed because of:
  - Pulse oximeter 3 point error despite a good wave form
    - Cutaneous O_2 sat 94%, calculated O_2 sat 91%
  - Alkalosis shifting the Hb–O_2 dissociation curve



- The hypoxemia caused worsening pulmonary edema by provoking diastolic dysfunction
  - Hypoxemia → subendocardial hypoxia → causing LV stiffing → impaired filling
- Leading to ↑ LVEDP and pulmonary edema despite a negative fluid balance
- Note, increased peak inspiratory pressures occurring during the same time frame indicative of pulmonary edema and worsening pulmonary mechanics

Fig. 1.2 Encapsulated case. Worsening pulmonary edema, despite aggressive diuresis because of diastolic dysfunction provoked by hypoxemia during oxygen weaning, targeting a cutaneous O_2 saturation of 92%. Because of error and alkalosis, the patient had Pao_2 values <60 mm Hg, leading to subendocardial hypoxia, left-ventricular (LV) stiffening, impaired filling, and increased left-ventricular end-diastolic pressure (LVEDP) physiology despite a 4 L negative fluid balance.

Teaching point: pulse oximetry readings should be used to screen for hypoxemia (Pao_2 values <60 mm Hg), and thus one should target cutaneous O_2 saturations >94%.

- Hb is designed to bind O_2 tightly (increase O_2 sat) in the alkalotic lungs and unload O_2 (decrease O_2 sat) in acidotic muscle
  - **Alkalemia elevates Hb sat** (steepening the Hb–O_2 dissociation curve, increasing the risk of rapid desaturation)
  - **Acidemia decreases Hb sat** (flattening the Hb–O_2 dissociation curve buffering against rapid desaturation)
- **Alkalosis** occurs commonly in:
  - Hypoxemia (hypoxic hyperventilation reflex)
  - Resolving acute on chronic hypercapnic failure (eg, posthypercapnic alkalosis), as ventilation improves and the previously compensatory metabolic alkalosis becomes the primary disorder
  - Aggressive diuresis (contraction alkalosis)
- **Error** occurs commonly:
  - Secondary to a poor signal (e.g. inadequate wave form)
  - Even with a good waveform, pulse oximetry devices have a ±3 point error range

ACUTE HYPOXEMIC RESPIRATORY FAILURE

- An acute drop in $Pao_2 < 60$ mm Hg
  - Typically occurs from the spectrum of **low VQ to shunt** (Fig. 1.3)
    - Sudden decrease or absent ventilation to an area of lung with relatively preserved perfusion
  - Confusion; tachycardia common; dyspnea (mild or absent) and work of breathing normal or mildly increased, unless the Pao_2 drop is severe (i.e. < 55 mm Hg)
- VQ mismatch (ie, low VQ) will respond to 100% Fio_2 (shunt will not)
  - With normal lungs 100% Fio_2 should lead to a $Pao_2 \approx 660$ mm Hg
  - A $Pao_2 < 200$ mm Hg on 100% Fio_2 implies shunt (physiologic more common than anatomic)
  - The **cause** of **shunt physiology** should be either:
    - Radiographically apparent (eg, diffuse alveolar filling, lung collapse [Fig. 1.4], or bilateral lower lobe atelectasis in the mechanically ventilated obese patient [Fig. 1.5]) or
    - Obvious on physical examination (eg, diffuse wheeze, or no airflow)
  - If the cause of shunt physiology is not obvious consider anatomic shunt (intracardiac or intrapulmonary)

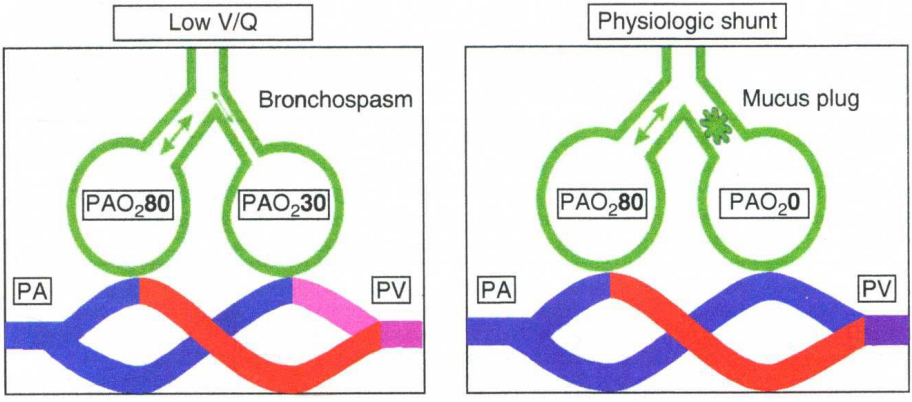


Fig. 1.3 Spectrum of low ventilation/perfusion (VQ) (a.k.a. VQ mismatch) to physiologic shunt. Schematic depicting two lung units (left and right). The left lung unit demonstrates normal aeration ($Pao_2 = 80$ mm Hg), and the right lung unit shows decreased aeration (bronchospasm) leading to low VQ or no ventilation (mucus plug) leading to physiologic shunt. Low VQ and physiologic shunt allow deoxygenated blood to mix with oxygenated blood, the major mechanism of hypoxemia.

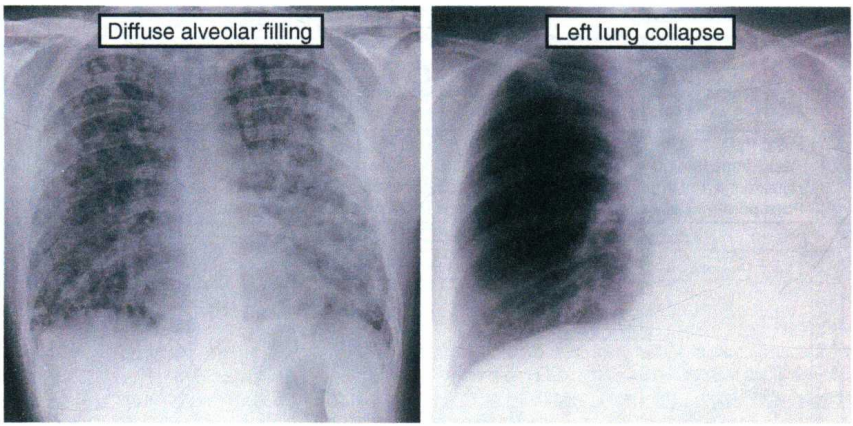


Fig. 1.4 Two frontal views of the chest showing the dramatically abnormal imaging typically associated with shunt physiology and hypoxemic respiratory failure (eg, a $Pao_2 < 60$ mm Hg despite Fio_2 of 100%). Left shows alveolar edema (either cardiogenic or noncardiogenic), and right shows complete lung collapse from endobronchial obstruction. Note the volume loss associated with the opacified hemithorax.

- A-a gradient screens for more subtle derangements in oxygenation, removing the confounding variable of CO_2 displacement in alveoli (as is seen in hypoventilation syndromes)

CHRONIC HYPOXEMIC RESPIRATORY FAILURE (PHYSIOLOGY AND UNDERLYING DISEASE)

- Mild chronic hypoxemic respiratory failure where Pao_2 falls gradually over time (typical Pao_2 values in the 55-59 range)
  - Caused by heterogeneous lung destruction, most commonly seen in chronic obstructive pulmonary disease (COPD)
    - Hypoxemia occurs from VQ mismatch (pink puffers) or hypoventilation (blue bloaters)
  - Causes mild symptoms of cognitive impairment (not exercise limitation), and increases the risk of heart failure
    - In COPD Exercise is limited by ventilation
  - Treat to prevent heart failure, arrhythmia, and risk of sudden death (not to improve exercise tolerance)
- Chronic severe hypoxemic respiratory failure, $Pao_2 < 55$ mm Hg
  - Commonly seen in pulmonary fibrosis
    - Fibrotic thickening of the pulmonary interstitium leads to diffusion limitation
  - Less commonly caused by small vessel pulmonary vascular disease (eg, idiopathic pulmonary arterial hypertension [IPAH])
    - Loss of vascular cross-sectional area from obliteration of small to medium pulmonary arterioles
  - In both cases, exercise limitation and dyspnea may be caused by profound hypoxemia (Fig. 1.6)

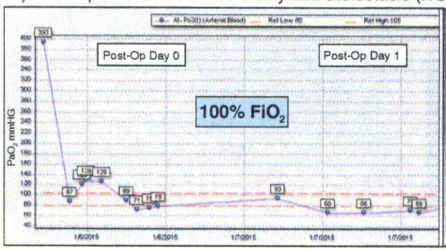
CLINICAL APPROACH TO ACUTE HYPOXEMIC RESPIRATORY FAILURE

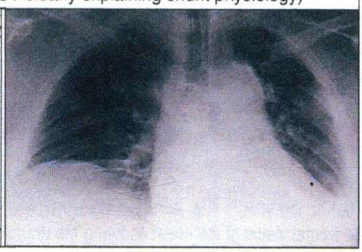
- Goal of O_2 support is a $Pao_2 > 60$ mm Hg **without** hyperventilation
  - Target an O_2 sat >94% or get an ABG to ensure $Pao_2 > 60$ mm Hg
  - Impending hypoxemic respiratory failure (ie, hypoxemia despite supplemental O_2 at ≥6 L/min) should be given 100% Fio_2
    - O_2 can be titrated down when a $Pao_2 > 60$ mm Hg is demonstrated, do not worry about O_2 causing CO_2 retention in patients with impending hypoxemic respiratory failure

Pulm Crit Resident H&P
CC: Hypoxic respiratory failure s/p sacral tumor resection
HPI:
BSM with h/o CAD s/p 3v CABG (2012), HFrEF (EF 40%), OSA on CPAP, and morbid obesity, here s/p sacral tumor resection, still intubated and noted to be hypoxic on 100% FiO2. On admission to the ICU, his ABG was 7.33 / 44 / 71 / 26 (on 100% FiO2 and 5 PEEP).

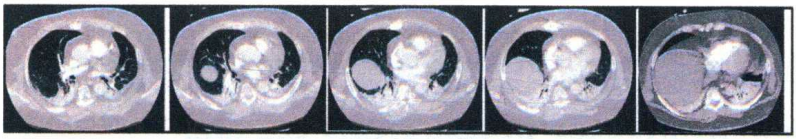
1) Initial PaO_2 393 mm Hg (100% FiO_2, PEEP of 5 cm H_2O)
2) PaO_2 drops to < 90 mm Hg during the surgery
3) Hypoxemia and shunt physiology persist on postoperative day # 1
4) Postoperative CXR shows only LLL atelectasis (**NOT** clearly explaining shunt physiology)

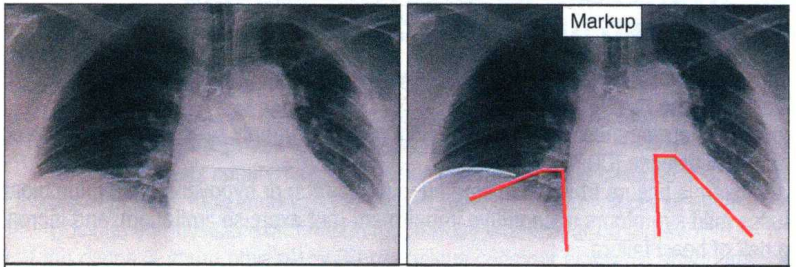
Wt (lbs):	302.5
BMI:	38.92





5) CT angiography negative for PE,reveals bilateral lower lobe atelectasis instead (subtle on CXR)



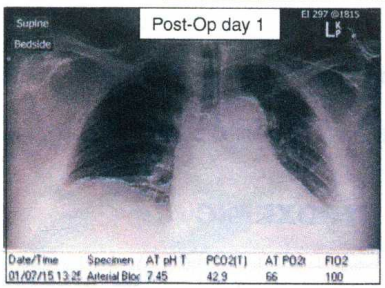


6) TTE negative for intrapulmonary or intracardiac shunt
7) Preop PFTS normal

Limited transthoracic echocardiogram
Agitated saline was used to assess for shunting.
A patent foramen ovale is not demonstrated with either color doppler or agitated saline contrast.

	UNITS	PRED	ACTUAL	%PRED
FVC	L	5.47	4.82	82.6
FEV1	L	4.20	3.48	82.8
FEV1/FVC	%	77.00	76.00	98.7
TLC	L	7.48	6.58	87.9
DLCO ADJ	mL/mmHg/min	32.20	27.10	84.2

Pre-discharge CXR and ABG (POD # 14) shows resolution of lower lobe atelectasis and shunt physiology



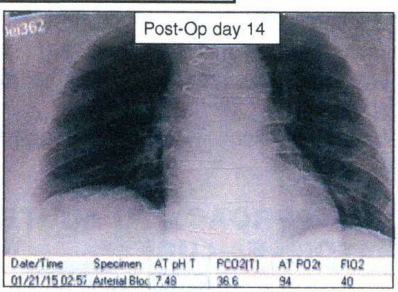


Fig. 1.5 Encapsulated case. Intraoperative and postoperative shunt physiology occurring in a morbidly obese individual undergoing general anesthesia and mechanical ventilation for an uncomplicated nonthoracic procedure. The patient had no underlying lung disease, evidence of anatomic shunt, or obvious radiographic explanation (by portable chest x-ray) for his profound hypoxemia, despite an Fio_2 of 100%. A computed tomography scan showed near complete bilateral lower

See the opposite page

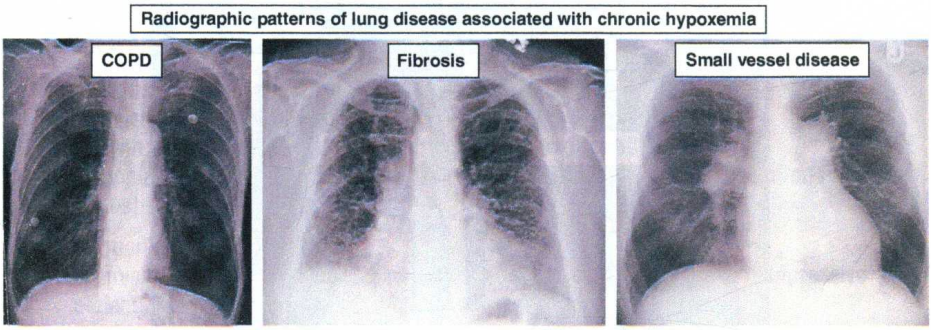


Fig. 1.6 Common radiographic patterns for patients with chronic hypoxemic respiratory failure. In chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary arterial hypertension (a.k.a. small vessel disease) the hypoxemia is caused by a loss of pulmonary arterial vascular cross sectional area. In pulmonary fibrosis, the hypoxemia is caused by diffusion limitation, secondary to a thickened pulmonary capillary interstitium.

- Deliver O_2 via high-flow system or reservoir device
  - Achieve ~100% Fio_2 by preventing entrainment of surrounding room air (when minute ventilation is high)
- A $Pao_2 < 60$ mm Hg on a 100% Fio_2 is life-threatening and mandates mechanical ventilation
  - Noninvasive (eg, Bi-level positive airway pressure [BiPAP]) or invasive (endotracheal intubation)
- Mechanical ventilation is used to increase mean airway pressure and recruit atelectatic lung (not primarily to ventilate)

CO_2 RETENTION AND HIGH Fio_2

- Patients with severe parenchymal disease and chronic CO_2 retention (ie, blue bloaters) *occasionally* increase their Pco_2 (~6 mm Hg) when given a high Fio_2
  - **Not** primarily by suppression of respiratory **drive**
    - Will not lead to progressive central hypercapnic respiratory failure
  - But rather by release of hypoxic vasoconstriction and subsequent steal phenomenon
    - Leading to an increase in dead space fraction
  - Ventilated units are suddenly underperfused as blood is "stolen" to poorly ventilated units (effectively increasing dead space) (Fig. 1.7)
- Average Pco_2 increase is ~6 mm Hg and is of little clinical significance (unlike hypoxemic respiratory arrest, which occurs when oxygen is withheld)
  - Anecdotally, **very rarely** a high Fio_2 and Pao_2 *may* suppress respiratory drive (**but this is *not* proven**) and should not dictate routine management

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Fig. 1.5, cont'd lobe atelectasis (subtle on chest x-ray). His hypoxemia improved with spontaneous breathing, and his shunt physiology ultimately resolved with extubation and resolution of his lower lobe atelectasis.

Teaching point: obese patients are vulnerable to shunt physiology from lower lobe atelectasis occurring when they receive general anesthesia and mechanical ventilation, likely from the collapsing forces of their abdominal and thoracic adipose tissue, no longer opposed by abdominal musculature (because of sedation). High positive end-expiratory pressure (PEEP) (possibly guided by esophageal manometry) and awake spontaneous breathing trials can often improve lower lobe aeration and oxygenation. It is likely that the shunt physiology in this case (and ones like it) is made worse by overdistention of lung apices (more complaint lung units). This overdistension decreases apical blood flow. The combination leads to extremely low ventilation/perfusion (VQ) physiology, where the lung apices receive most of the ventilation and the bases receive all of the blood flow.

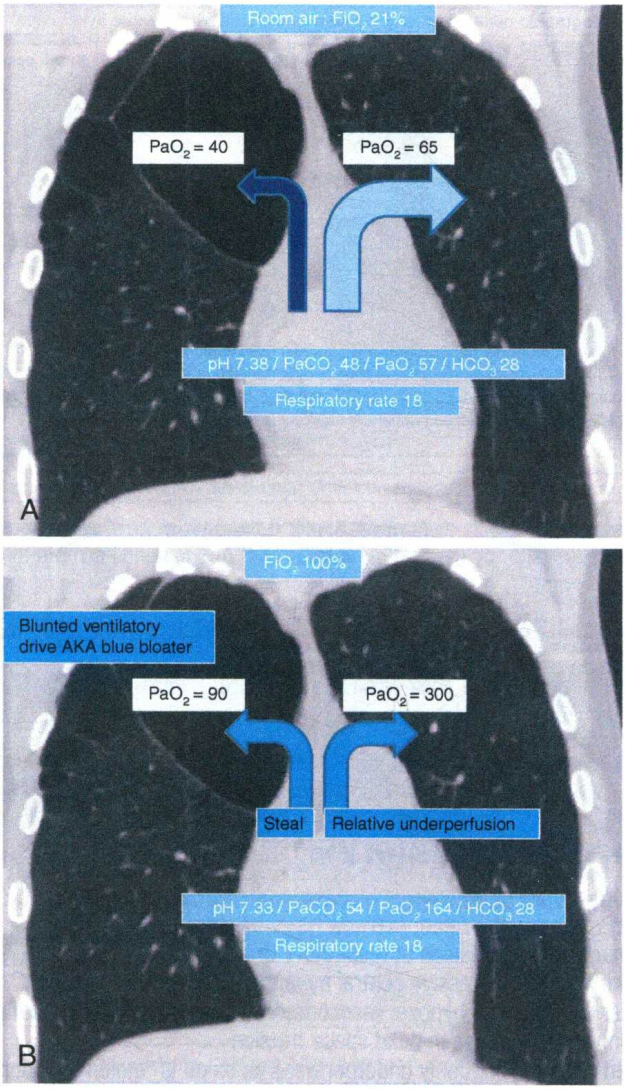

Fig. 1.7 Graphic depiction of the likely mechanism explaining acute CO_2 retention occurring in response to an increased Fio_2 in a patient with chronic obstructive pulmonary disease (COPD) and chronic CO_2 retention. (A)The heterogeneous ventilation and perfusion relationships between a diseased lung and a relatively normal lung in a patient with COPD while breathing room air. The profound hypoxemia in the bullae leads to a low Pao_2 in the pulmonary artery supplying the area. This causes hypoxic vasoconstriction, which attempts to improve ventilation/perfusion (VQ) matching in the lung by decreasing perfusion to the area of decreased ventilation and oxygenation (graphically depicted by the smaller darker blue arrow). (B) The same individual while breathing 100% Fio_2. Note, the oxygen level in the poorly ventilated bullae rises enough to increase the Pao_2 such that hypoxic vasoconstriction is released. This inappropriately "steals" blood from the normal lung to the diseased lung, effectively increasing dead space, as the increased blood flow to the right apex is **not** accompanied by increased ventilation. Because of this, the individual must either increase their minute ventilation (and work of breathing) or allow their Pco_2 to rise (and their pH to fall). Individuals with chronic CO_2 retention, ***by definition***, have a blunted ventilatory drive, such that the increased dead space causes an increase in Pco_2 and concomitant fall in pH, leading to an acute, uncompensated, respiratory acidosis that is nearly uniformly asymptomatic and of no clinical significance.

COMMON CAUSES AND INITIAL TREATMENT OF ACUTE HYPOXEMIC RESPIRATORY FAILURE

- Pneumonia (PNA)
  - VQ mismatch from alveolar filling, mucus plugging, and atelectasis
  - Rx with O_2, antibiotics, and pulmonary toilet (chest physiotherapy)
  - If supplemental O_2 fails, BiPAP may be difficult with copious secretions; often have to intubate
- Cardiogenic pulmonary edema
  - VQ mismatch from alveolar and interstitial edema, and effusions with compressive atelectasis
  - Common cause of shunt physiology
  - Rx with O_2, IV loop diuretics at adequate dose (eg, ≥ 80 IV Lasix, 2 IV Bumex)
  - BiPAP works great (rarely have to intubate)
- Noncardiogenic pulmonary edema (a.k.a. acute respiratory distress syndrome [ARDS])
  - VQ mismatch from diffuse alveolar filling (not believed to be secondary to HF)
  - Common cause of shunt physiology
  - Can be primary pulmonary inflammation vs. systemic infection or inflammation
  - Treat underlying cause, support and time, consider steroids, and avoid HF
  - Typically requires intubation (slow to resolve)
  - Common DDx (bronchoscopy useful):
    - Eosinophilic pulmonary inflammation (spectrum of acute to chronic eosinophilic PNA)
      - Bronchoscopy with significant bronchoalveolar lavage (BAL) eosinophilia (> then 25%, often 40–80%)
      - Responds well to steroids
    - Diffuse alveolar hemorrhage
      - Bronchoscopy with progressively bloody lavage
      - Search for underlying disease (eg, anti-glomerular basement membrane disease)
      - Treat provocative factors (eg, thrombocytopenia, PNA)
      - Consider steroids
    - Acute interstitial pneumonitis
      - Bronchoscopy shows a BAL with neutrophil predominance
      - Consider trial of high-dose steroids
- Bronchospasm
  - VQ mismatch from poorly ventilated lung
  - Rx with O_2, steroids, and β-agonists
  - Rarely requires intervention beyond supplemental O_2 **for hypoxemia**
- Large volume gastric aspiration
  - VQ mismatch from alveolar filling (initially pneumonitis)
  - Treat with O_2, often requires intubation, consider Abx; limited role for acute bronchoscopy
    - Urgent BAL does not mitigate the instantaneous injury of aspirated digestive contents
      - Should be reserved for segmental collapse and large particle removal
- Pulmonary embolism
  - VQ mismatch from atelectasis secondary to inflammatory mediator release (not increased dead space)
  - Rarely requires intervention beyond supplemental O_2 for hypoxemia
- Hypoventilation
  - Hypoxemia from CO_2 accumulation and displacement of O_2 from the alveoli
  - Seen commonly with blunted ventilatory drive (eg, obesity or narcotic effect)
  - Hypoxemia is easily reversed with supplemental oxygen