Pulmonary Gas Exchange

5

Vinod K. Bhutani and Vineet Bhandari

I. Introduction
   A. Pulmonary circulation plays a critical gas exchange function of the lung.
   B. Processes governing pulmonary vascular development, especially with regard to the origin, differentiation, and maturation of the various cell types of the pulmonary vasculature include factors which control development and also provide insight into the genetic diversity of these cells. The development of the pulmonary vascular system and the airways is closely coordinated and share similar branching patterns.
   C. The two major ways pulmonary vessels develop are vasculogenesis (de novo formation of blood vessels from endothelial cells) and angiogenesis ("sprouting" and/or "intussusceptive," i.e., formation of new blood vessels from existing ones). The extrapulmonary artery and acinar arteries develop at 34 and 44 days, respectively. The pre-acinar arteries develop at 5–15 weeks, the intra-acinar at 18–25 weeks, alveolar duct arteries at 25 weeks–18 months, followed by the alveolar capillaries from 30 weeks to 18 years.
   D. Environmental signals and signaling molecules contribute to the terminal differentiation of specific vascular cells at the local level, and which confer unique properties to these cells. Among the molecular signaling pathways implicated are those involving sonic hedgehog, vascular endothelial growth factor, angiopoietins, and Wnts, to name a select few.
   E. Model systems using temporal-specific genetic cell lineage tracing using Cre-loxP techniques as well as transgenic reporter mice will allow us to accurately mark and follow cell fates within the complex environment that obviously contributes to the ultimate phenotype of the pulmonary vascular cell of interest, as well as model systems where cell migration, cell-cell interaction, and proper environmental cues remain intact.

V. K. Bhutani (✉)
Department of Pediatrics, Lucille Packard Children's Hospital, Stanford University, Palo Alto, CA, USA
e-mail: Bhutani@stanford.edu

V. Bhandari
Department of Pediatrics, The Children's Regional Hospital at Cooper, Cooper Medical School of Rowan University, Camden, NJ, USA
e-mail: Bhandari-vineet@cooperhealth.edu

S. M. Donn et al. (eds.), *Manual of Neonatal Respiratory Care*,
https://doi.org/10.1007/978-3-030-93997-7_5

F. We will need to take into account the fact that angioblasts may arise from many distant sites and at certain stages of lung development could even come from the bone marrow-derived pool of circulating stem cells.
G. Because it is clear that oxygen tension plays such a critical role in directing development of many organs, we need to take into account the oxygen tension at which experiments are performed.
H. Further, we need to address the role that the nervous system may play in directing vascular development within the lung.
I. In doing all of the above, we will come to a better understanding of the unique origins of the macro- and microcirculations of the lung and may also provide new insight into the unique expansion and function of the selective cell types that play critical roles in many pulmonary diseases

II. Transition at Birth
A. Independent pulmonary gas exchange to replace the maternal placental gas exchange mechanism needs to be established within the first few minutes after birth.
1. In order to affect this transition, several physiologic changes occur
2. Adjustments in circulation
3. Pulmonary mechanics
4. Gas exchange
5. Acid-base status
B. Respiratory control
C. Upon transition, gas exchange takes place through an air-liquid interphase of alveolar epithelium with alveolar gas in one compartment and blood in the other (vascular) compartment. An understanding of gas laws, alveolar ventilation, and pulmonary vasculature are important in facilitating optimal pulmonary gas exchange.

III. Brief Outline of Cardiopulmonary Adaptations
A. Prior to birth, the fetus is totally dependent on the placenta (Fig. 5.1) and has made cardiopulmonary adjustments for optimal delivery of oxygen, whereas the maternal physiology has been adapted to maintain fetal normocapnia.
B. The salient features and sequence of events that occur during fetal to neonatal transition are listed in Table 5.1.

IV. Application of Gas Laws for Pulmonary Gas Exchange
A. There are fundamental laws of physics that pertain to the behavior of gases and thereby impact gas exchange.
B. An understanding of these laws is also specifically pertinent to the clinician in his/her ability not only to measure and interpret blood gas values but also to evaluate the impact on gas exchange during clinical conditions of hypothermia, high altitude, and use of gas mixtures of varying viscosities and densities.
C. A brief description of the pertinent and clinically relevant gas laws is listed in Table 5.2.
D. One of the most fundamental and widely used relationships to describe pulmonary gas exchange is summarized as:

$$PaCO_2 = 863\left(V_{CO2} / V_A\right)$$

where, in a steady state and with negligible inspired carbon dioxide, the alveolar pressure of carbon dioxide ($PaCO_2$) is proportional to the ratio of the rates of carbon dioxide elimination (V_{CO2}) and alveolar ventilation (V_A). This equation helps to summarize several of the gas laws. The applications of the laws are thus:

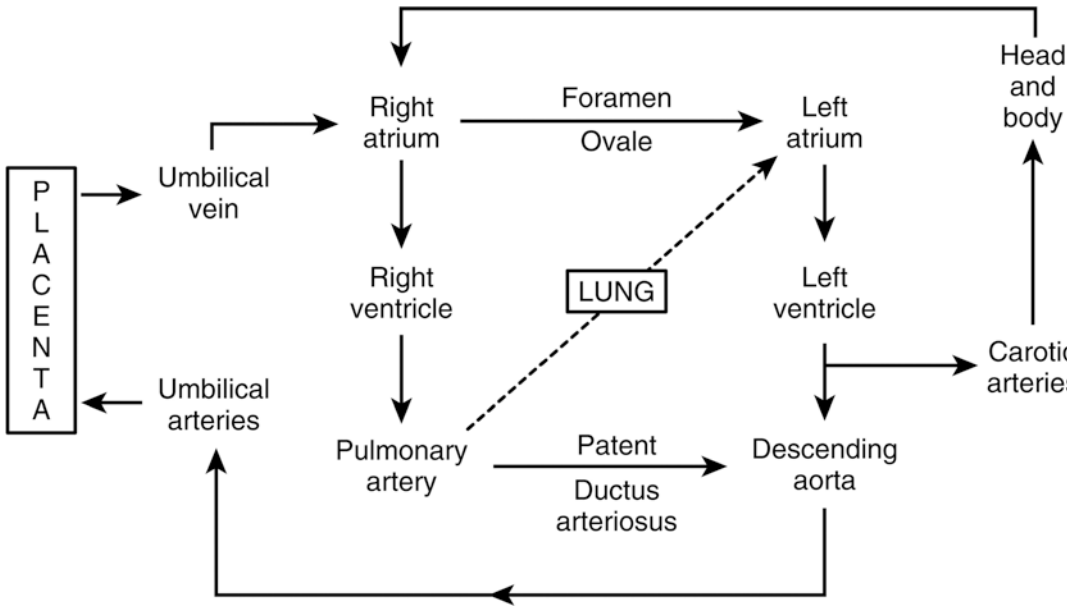

Fig. 5.1 Schematic representation of fetal circulation. (From Bhutani VK: Extrauterine adaptations in the newborn. Sem Perinatol 1997; 1:1–12, with permission)

Table 5.1 Salient features of extrauterine cardiopulmonary adaptations

Parameter	Mother (second trimester)	Fetus (before labor)	Newborn (before first breath)	Newborn (at about 6 hours)
PaO_2	80–95 torr	< 25 torr in pulmonary artery	16–18 torr	80–95 torr
$PaCO_2$	~ 34 torr	40–42 torr	45–65 torr	34 torr
pH	~ 7.45	7.35–7.40	7.10–7.30	7.35–7.40
Pulmonary blood flow	Equivalent to cardiac output	13–25% cardiac output	~ 25% cardiac output	90–100% cardiac output
Shunts	Placental shunts	Placental shunts Foramen ovale Ductus arteriosus	Foramen ovale Ductus arteriosus Intrapulmonary shunts	Foramen ovale closed Ductus arteriosus usually closed Intrapulmonary shunts
Pulmonary mechanics	Air-filled lungs Hyperventilation	Liquid-filled FRC at 30 mL/kg	Air and fluid (16–19 mL/kg) in the lungs	Air-filled FRC at 30 mL/kg
Control of respiration	Progesterone-mediated hyperventilation	Fetal breathing dependent more on stretch	First breath initiated by non-specific respiratory signals	Rhythmic respiratory cycles based on chemoreceptors

1. $PaCO_2$: when measured in dry gas as a percentage, Dalton's law needs to be applied to convert the value to partial pressure. The partial pressure of carbon dioxide, rather than its percentage composition, is the significant variable because Henry's law of solubility states that the gas is physically dissolved in liquid and in equilibrium with the gas phase at the same partial pressure.
2. 863: this peculiar number is derived from the need to standardize measurements from body temperature (310°K) to standard pressure and temperature (760 mm Hg•273°K). Based on the product 310 × (760/273), we obtain the value 863 (in mm Hg) providing the constant for the relationship in the above equation.

Table 5.2 Laws that describe gas behavior

Law	Description
Boyle's law	At constant temperature (T), a given volume (V) of gas varies inversely to the pressure (P) to which it is subjected
Charles's law	Gas expands as it is warmed and shrinks as it is cooled
Dalton's law	The total pressure exerted by a mixture of gases is equal to the sum of the partial pressure of each gas
Amagat's law	The total volume of a mixture of gases is equal to the sum of the partial volume of each gas at the same temperature and pressure
Henry's law	At constant temperature, any gas physically dissolves in a liquid in proportion to its partial pressure, although the solubility coefficient decreases with increasing temperature and differs from one gas to another
Graham's law	The rate of diffusion of a gas is inversely proportional to the square root of its density
Fick's law	The transfer of solute by diffusion is directly proportional to the cross-sectional area available for diffusion and to the difference in concentration per unit distance perpendicular to that cross section
Ideal gas equation	Summation of above laws: PV = nRT, where R is a numerical constant
Van der Waals's equation	Refinement of the ideal gas equation based upon the attractive forces between molecules and upon the volume occupied by the molecules
Barometric pressure and altitude	The decrease in barometric pressure is not linear with increasing altitude; weather, temperature, density of atmosphere, acceleration of gravity, etc. influence it

3. V_{CO2}/V_A: These values are measured at ambient temperature and pressure, saturated with water vapor (ATPS). Carbon dioxide output needs to be converted to STPD (standard temperature, pressure, dry) using Boyle's and Charles's laws, while alveolar ventilation has to be corrected to BTPS (body temperature, pressure, and saturated with water vapor).

V. Development of Pulmonary Vasculature.
   A. The main pulmonary artery develops from the embryonic left sixth arch.
      1. The sixth arches appear at about 32 days after conception (5 mm embryo stage) and give branches to the developing lung bud.
      2. Branches from the aorta that supply the lung bud and the right arch disappear subsequently.
      3. By 50 days (18 mm embryo stage), the adult pattern of vascularization has commenced.
   B. Before the main pulmonary veins are developed, the vessels drain into the systemic circulation of the foregut and trachea.
      1. These connections are lost as the main pulmonary vein develops.
      2. A primitive pulmonary vein appears as a bud from the left side of the atrial chamber at about 35 days.
      3. Starting as a blind capillary, it bifurcates several times to connect with the developing lung bud.
      4. Subsequently, the first two branches are resorbed to form the left atrium at about the seventh week.
   C. The branches of the pulmonary arterial system maintain a position next to the bronchial structures as both develop during the pseudoglandular and canalicular stages of lung development.
   D. By 18–25 weeks, there is a complete set of vessels that lead to the respiratory bronchioles, terminal bronchioles, and the terminal sacs.

VI. Onset of Pulmonary Gas Exchange.
  A. The physiologic processes that facilitate the onset of postnatal pulmonary gas exchange (described in the series of events depicted in Fig. 4.2).
    1. The effect of ventilation on reducing pulmonary vascular resistance (A).
    2. The effect of acidosis correction to enhance pulmonary blood flow (B).

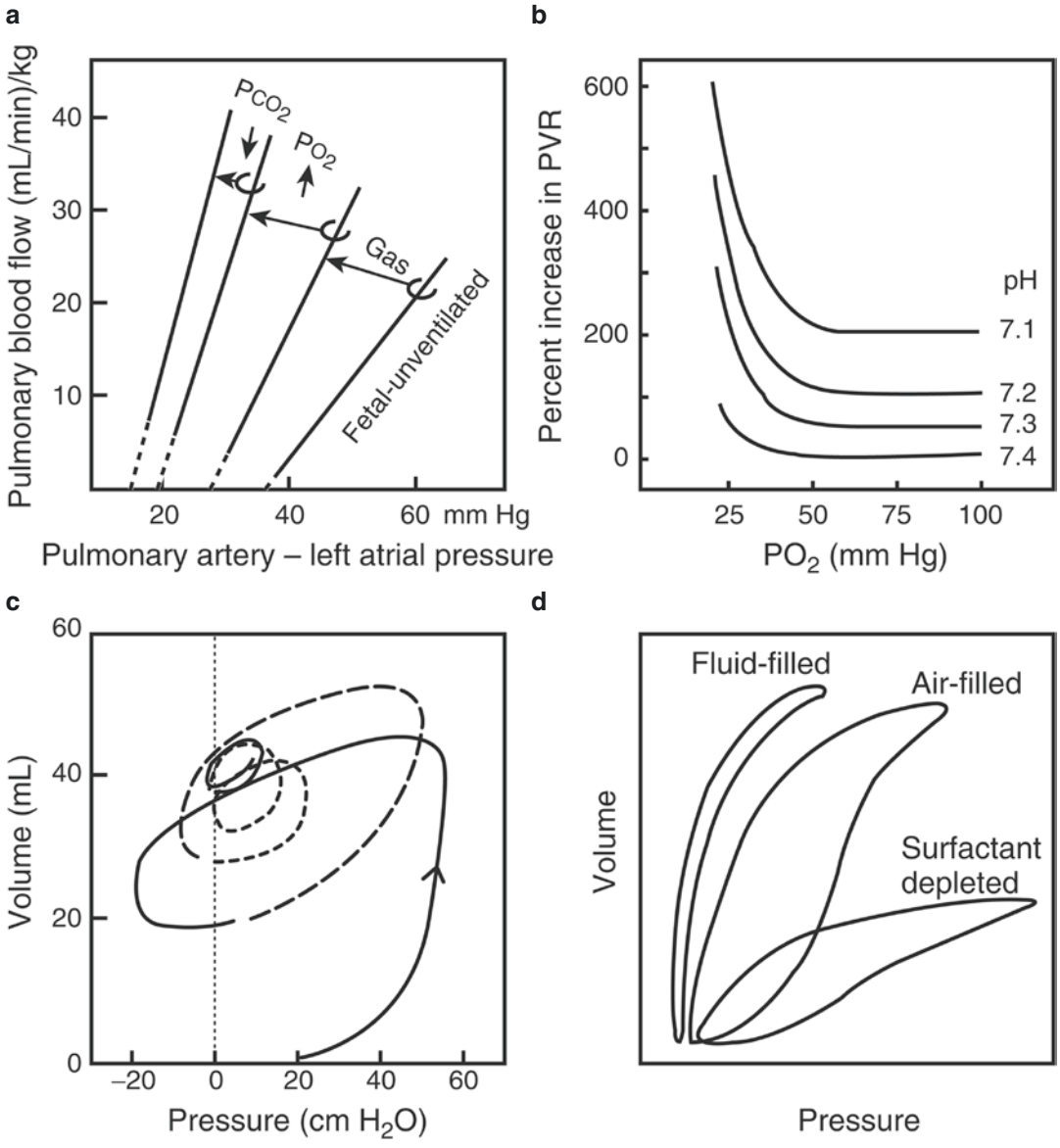

Fig. 5.2 Physiologic processes that facilitate onset of postnatal pulmonary gas exchange. (**a**) Effect of ventilation on reducing pulmonary vascular resistance (PVR). (**b**) Effects of acidosis correction on reducing PVR. (**c**) First breaths and establishment of optimal functional residual capacity. (**d**) Effect of driving pressure to maintain optimal tidal volume and work of breathing. (Modified from Bhutani VK: Differential diagnosis of neonatal respiratory disorders. In Spitzer AR [Ed.]: *Intensive Care of the Fetus and Neonate*. St. Louis, Mosby-Year Book, 1996, p. 500, with permission)

3. The effect of driving pressure and successful establishment of respiration during first breaths to achieve an optimal functional residual capacity (C).
4. The effect of driving pressure to maintain optimal tidal volume and achieve the least work of breathing (D).

B. These events highlight the other series of biochemical and physiologic events that concurrently occur to successfully establish and maintain the matching of ventilation to perfusion.

C. Maladaptation delays transition to adequate pulmonary gas exchange. (Maladaptation may result from central/peripheral nervous system abnormalities, as well as cardiopulmonary problems.)

D. Though it has been well established that a newborn is more likely to have events that lead to hypoxemia or maintain adequate oxygenation with an inability to compensate hemodynamically, it has also been realized that a newborn is more tolerant of hypoxemia than an adult. Reasons for occurrences of hypoxemic events:
1. Reduced FRC relative to the oxygen consumption.
2. Presence of intrapulmonary shunts that lead to V/Q mismatching.
3. A high alveolar-arterial oxygen gradient.

E. Hypercapnia that results from an inability to maintain adequate alveolar ventilation in the face of mechanical loads also results in lower alveolar oxygen tension.

F. From a hemodynamic perspective, impaired oxygen delivery may occur because of:
1. Low P_{50} values because of high oxygen affinity of the fetal hemoglobin.
2. Increased blood viscosity.
3. Lower myocardial response to a volume or pressure load.
4. Inadequate regional redistribution of the cardiac output.

G. The relationship between arterial oxygen and carbon dioxide values and how these relate to hypoxemia and respiratory failure are shown in Fig. 5.3.

H. The effect of oxygen inhalation on the composition of alveolar and blood gas tensions is shown in Table 5.3.

VII. Optimal Pulmonary Gas Exchange.

A. Failure to establish optimal pulmonary gas exchange leads to either oxygenation or ventilation failure.

B. Factors that impact on adequacy of neonatal gas exchange (especially a preterm newborn) are listed in Table 5.4.

C. Respiratory failure can initially lead to increased respiratory effort in an attempt at compensation, followed by an inability to ventilate, or apnea.

Table 5.3 Effect of oxygen inhalation (100%) on composition of alveolar and blood gas tensions

	Inspired dry gas		Alveolar gas		End pulmonary capillary blood		Arterial blood		End-systemic capillary blood	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
$P_{O2,}$ *torr*	1591	760	104	673	104	673	100	640	40	53.5
P_{CO2}, torr	0.3	0	40	40	40	40	40	40	46	46
$P_{H2O,}$ torr	0.0	0	47	47	47	47	47	47	47	47
$P_{N2,}$ *torr*	600.6	0	569	0	569	0	573	0	573	0
$P_{total,}$ torr	760	760	760	760	760	760	760	727	706	146.5[a]
O_2Sat (%)					98	100	98	100	75	85.5

[a]What happens to the total gas tension when a baby breathes 100% oxygen: the total venous gas tension is *now at 146.5 torr*

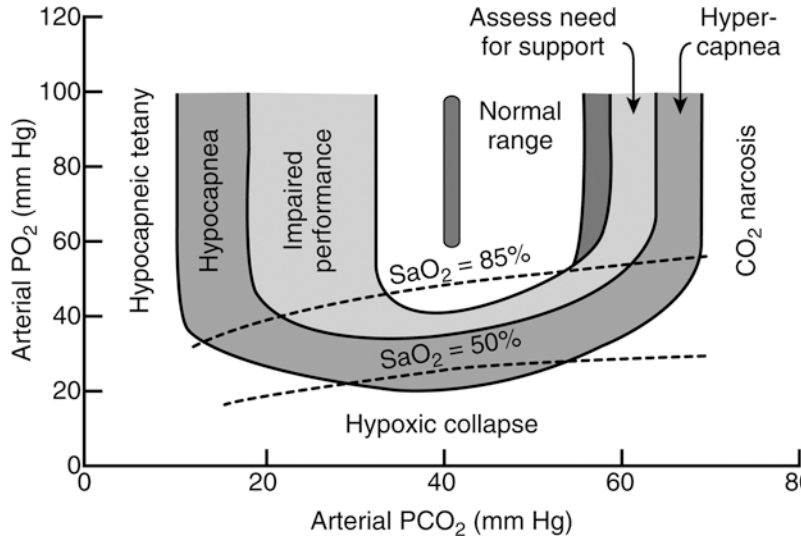

Fig. 5.3 The relationship between alveolar oxygen and carbon dioxide values and how these relate to hypoxemia and respiratory failure. (Modified from Bhutani VK: Differential diagnosis of neonatal respiratory disorders. In Spitzer AR [Ed.]: *Intensive Care of the Fetus and Neonate*. St. Louis, Mosby-Year Book, 1996, p. 501, with permission)

Table 5.4 Factors that impact on adequacy of neonatal gas exchange

Factors for gas exchange	Impact of prematurity
Neural control of respiration	Immaturity
Mechanical loads: elastic and resistive	High chest wall to lung compliance ratio
Stability of end-expiratory lung volume	Compliant airways with pre-end expiratory closure of airways
Ventilation-perfusion matching	Reactive pulmonary vasculature
Hemoglobin dissociation curve properties	Fetal hemoglobin characteristics
Match cardiac output to oxygen consumption	High neonatal oxygen consumption
Ability to maintain alveolar ventilation	Propensity for respiratory muscle fatigue

D. The concurrent changes in arterial oxygen and carbon dioxide gas tensions during both health and disease are shown in Fig. 5.3.

VIII. Physiologic Principles to Improve Pulmonary Gas Exchange.

A. The physiologic principles that may be utilized to improve oxygenation, enhance carbon dioxide elimination, and establish ventilation at optimal FRC (and thereby with the least baro- and volutrauma) are listed in Fig. 5.2a–d.

B. The clinically relevant interventional strategies are crucial to achieve optimal gas exchange.

C. It is also valuable to be reminded that in a healthy newborn, gas tensions are maintained in a narrow range by exquisitely sensitive feedback mechanisms of chemoreceptors and stretch receptors.

D. Moreover, during fetal development, the maternal physiology is significantly altered to maintain fetal normocapnia and neutral acid-base status.

E. Thus, as clinicians assume control of the newborn's ventilation with supportive technologies, the road map for optimal pulmonary gas exchange needs to be "quality controlled" from physiologic perspectives and with the least amount of baro- and volutrauma.