Amir A. Hakimi
Thomas E. Milner
Govind R. Rajan
Brian J-F Wong
Editors

Mechanical Ventilation Amid the COVID-19 Pandemic

A Guide for Physicians and Engineers

Springer

Mechanical Ventilation Amid the COVID-19 Pandemic

Amir A. Hakimi • Thomas E. Milner
Govind R. Rajan • Brian J-F Wong
Editors

Mechanical Ventilation Amid the COVID-19 Pandemic

A Guide for Physicians and Engineers

Springer

Editors
Amir A. Hakimi
Otolaryngology – Head and Neck Surgery
Medstar Georgetown University Hospital
Washington D.C., WA, USA

Govind R. Rajan
Anesthesiology & Critical Care Medicine
University of California, Irvine
Orange, CA, USA

Thomas E. Milner
Beckman Laser Institute and Medical Clinic
Irvine, CA, USA

Brian J-F Wong
Otolaryngology – Head and Neck Surgery
University of California, Irvine
Orange, CA, USA

ISBN 978-3-030-87977-8 ISBN 978-3-030-87978-5 (eBook)
https://doi.org/10.1007/978-3-030-87978-5

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The surge in COVID-19 cases leading to hospitalizations around the world quickly depleted hospital resources and reserves, forcing physicians to make extremely difficult life-or-death decisions on ventilator allocation between patients. Leaders in academia and industry have developed numerous ventilator support systems using both consumer- and industry-grade hardware to sustain life and to provide intermediate respiratory relief for hospitalized patients. This book is the first of its kind to discuss the respiratory pathophysiology underlying COVID-19, explain pulmonary and ventilator mechanics, provide and evaluate a repository of innovative emergency resuscitators conceived amid the pandemic, and explain both hardware and software components necessary to develop an inexpensive emergency resuscitator. The book serves both as a historical record of the collaborative and innovative response to the anticipated ventilator shortage during the COVID-19 pandemic and as a guide for physicians, engineers, and DIY-ers interested in developing emergency resuscitator devices.

Several mechanisms for these transitory emergency resuscitators or "bridge ventilators" have been proposed including automatic compression of resuscitation bags through various mechanical and pneumatic means, repurposing CPAP and BiPAP devices to function as ventilators, and noninvasive ventilation through oxygen helmets, snorkel masks, and more. Herein, the authors explore and appraise the functionality of each unique approach. Additionally, expert leaders behind several emergency ventilator designs provide a detailed review of resuscitation bag and motor mechanics and impart insight on their ventilator models. This resource provides a thorough framework for basic ventilatory support and guides readers toward developing their own bridge ventilators through evidence-based expert recommendations. We also encourage readers to go to our website www.bli.uci.edu/bvc or scan the QR code below to access supplemental videos and posts.

Washington, DC, USA — Amir A. Hakimi
Irvine, CA, USA — Thomas E. Milner
Orange, CA, USA — Govind R. Rajan
Orange, CA, USA — Brian J.-F. Wong

Contents

About the Editors

Amir A. Hakimi, MD is a resident in the Department of Otolaryngology-Head and Neck Surgery at MedStar Georgetown University Hospital. He received his Bachelor of Science degree in Neuroscience at the University of California, Los Angeles. He then graduated from Chicago Medical School at Rosalind Franklin University of Medicine and Science. During medical school, he became involved in clinical and translational research under the mentorship of Dr. Brian Wong. Dr. Hakimi has published numerous articles in peer-reviewed scientific journals, and he has developed a medical application for the iPhone to expedite the diagnosis of ocular injury.

Thomas E. Milner, PhD is Director of the Beckman Laser Institute and Medical Clinic and Professor of Biomedical Engineering and Surgery at the University of California, Irvine. He received his bachelor's and master's degrees from the Colorado School of Mines and his Ph.D. from the University of Arizona. Dr. Milner's research interests are in the fields of optical based therapeutics and diagnostic imaging, biomedical optics sensors, and optical tomography. He has published more than 180 journal articles, holds 55 issued US patents, and has started two technology companies. Dr. Milner is a fellow of the National Academy of Inventors, the American Institute for Medical and Biological Engineering, and the American Society for Lasers in Medicine and Surgery.

Govind R. Rajan, MBBS is an anesthesiologist in Orange, CA, and is affiliated with the UC Irvine Medical Center. He received his medical degree from Maulana Azad Medical College and has been in practice for 29 years. He also speaks multiple languages, including Hindi. He specializes in critical care medicine.

Brian J.-F. Wong, MD, PhD is Professor and Director of the Division of Facial Plastic Surgery in the Department of Otolaryngology-Head and Neck Surgery at the University of California Irvine Medical Center. Dr. Wong's clinical practice is based at both the UC Irvine Medical Center and the Beckman Laser Institute and Medical Clinic. He graduated summa cum laude with a bachelor's degree in biomedical

engineering from the University of Southern California and earned his medical degree from Johns Hopkins University. He also studied engineering at Oxford University as a Rotary Foundation Scholar and medical physics at the University of Amsterdam. Dr. Wong's research interests are in the field of biomedical engineering, with specific interests in medical device development and laser applications in medicine. He has more than 100 publications, and his research is funded by the National Institutes of Health, the Department of Defense, and the Health Science Partners.

Chapter 1
Establishment of the Bridge Ventilator Consortium

Amir A. Hakimi, Thomas E. Milner, Govind Rajan, and Brian J. F. Wong

The Bridge Ventilator Consortium (BVC) serves as a multidisciplinary organization linking industry, academia, government, nonprofit organizations, and community members who have voluntarily partnered to develop breathing devices for use if ICUs run short of conventional ventilators. Within days, we were able to recruit a motivated team of physicians, engineers, scientists, legal advisors, respiratory therapists, and manufacturers among others to combat the pandemic. There was a lot to learn about ventilators prior to delving into production. Our team

A. A. Hakimi (✉)
Department of Otolaryngology – Head and Neck Surgery, Medstar Georgetown University Hospital, Washington, DC, USA

Beckman Laser Institute & Medical Clinic, University of California – Irvine, Orange, CA, USA
e-mail: amir.a.hakimi@medstar.net

T. E. Milner
Beckman Laser Institute & Medical Clinic, University of California – Irvine, Orange, CA, USA

G. Rajan
Department of Anesthesiology and Perioperative Care, University of California – Irvine, Orange, CA, USA
e-mail: grajan@hs.uci.edu

B. J. F. Wong
Beckman Laser Institute & Medical Clinic, University of California – Irvine, Orange, CA, USA

Department of Otolaryngology – Head & Neck Surgery, University of California – Irvine, Orange, CA, USA

Department of Biomedical Engineering, University of California – Irvine, Irvine, CA, USA
e-mail: bjwong@uci.edu

A. A. Hakimi et al. (eds.), *Mechanical Ventilation Amid the COVID-19 Pandemic*,
https://doi.org/10.1007/978-3-030-87978-5_1

meetings intertwined the medical knowledge of anesthesiologists, critical care physicians, and respiratory therapists with the technical prowess of engineers from all backgrounds.

Our daily teleconference meetings were open forum, allowing participants worldwide to learn and contribute to this cause. Many individual groups within our team successfully developed emergency resuscitators, several of whom received or are in the process of receiving emergency use authorization from the United States Food and Drug Administration. The purpose of this textbook is to help guide readers toward a similar path in emergency resuscitator development. Experts from the BVC team have come together in this textbook to highlight the most essential medical, engineering, and regulatory concepts that we have learned throughout this process.

There is no doubt that improvements in the cost, availability, and function of ventilators are eminent. The need for ventilators and emergency resuscitators expands beyond the COVID-19 pandemic as many countries have long suffered a shortage of these lifesaving devices. It is our hope that the information in this textbook helps promote future works to advance ventilatory care.

Conflicts of Interest The authors have no relevant conflicts of interest to disclose.

Funding This work was not funded.

Part I
Lung Physiology and Ventilator Basics

Chapter 2
An Overview of Lung Anatomy and Physiology

Karen Katrivesis, Jennifer Elia, Brent Etiz, Keaton Cooley-Rieders, Sina Hosseinian, and Sean Melucci

Lung Anatomy

At the most basic level, normal human anatomy consists of two lungs. Each lung is divided into different lobes by separations known as fissures. The left lung consists of a superior and inferior lobe, separated by the oblique fissure located at the T4–5 vertebral level. The right lung is divided into superior, middle, and inferior lobes by the oblique and horizontal fissures. The right lung is larger and heavier, but also shorter and wider than the left lung. This is due to the diaphragm extending higher on the right and the heart bulging more to the left. The left and right lungs have different anatomical features. One of the most prominent features of the left lung is the cardiac notch which is an indentation on the anterior margin that allows for the leftward bulging of the heart. The right lung has vasculature grooves which allow for the passage of the superior and inferior vena cava.

Each lung has an apex, three surfaces, and three borders. The apex of the lung is the most superior aspect, ascending above the first rib into the root of the neck. The lung also has three surfaces: the costal surface, which is adjacent to the sternum and ribs; the mediastinal surface, which is found medially to the mediastinum and posteriorly to the vertebrae; and the diaphragmatic surface, which rests on the convex dome of the diaphragm. Each lung has an anterior, posterior, and inferior border.

The mediastinal surface includes the hilum of the lung, the medial aspect where structures enter and exit the lung. These structures form the root of the lung which has different orientations of structures for the left and right lungs. The most notable

K. Katrivesis (✉) · J. Elia
Department of Anesthesiology, Division of Critical Care Medicine, University of California, Irvine, CA, USA
e-mail: kkatrive@hs.uci.edu; jelia@hs.uci.edu

B. Etiz · K. Cooley-Rieders · S. Hosseinian · S. Melucci
Irvine School of Medicine, University of California, Irvine, CA, USA

A. A. Hakimi et al. (eds.), *Mechanical Ventilation Amid the COVID-19 Pandemic*,
https://doi.org/10.1007/978-3-030-87978-5_2

difference is the location of the main bronchus. In the left lung, the main bronchus is located inferior to the pulmonary arteries. In the right lung, the main bronchus is located posterior to the pulmonary arteries.

Both lungs are enclosed by a serous pleural sac that consists of two continuous layers of membranes, the visceral and parietal layers. Together, these layers are known as the pleurae. The visceral pleura fully covers the lungs and adheres to all its surfaces. The parietal pleura lines the pulmonary cavities, providing support for the lungs by adhering to the thoracic wall, mediastinum, and diaphragm. At rest, the inferior boundary of the lungs is at vertebral level T10, whereas during inhalation, the inferior boundary is at T12, the boundary of the pulmonary cavity. The pleural cavity contains two recesses: the costodiaphragmatic recess and the costomediastinal recess. The costodiaphragmatic recess is a bilateral recess that is bound by the lung superiorly and by the diaphragm inferiorly. The costomediastinal recess is a lateral recess that is located posterior to the sternum [1].

Trachea and Bronchi

The trachea, commonly referred to as the windpipe, is the airway that leads from the larynx to the large airways of the lungs known as the bronchi. Beginning at vertebral level C6, the trachea extends inferiorly to the carina, where it then bifurcates into the left and right main bronchi. The trachea is a tough airway surrounded by C-shaped cartilage rings.

The main bronchi extend inferolaterally and enter the lung at the hilum. It is one of the structures that form the root of the lung. The opposing sides of the bronchi have differing features. The right bronchus is wider, shorter, and more vertical than the left main bronchus. These bronchi branch into secondary bronchi: two secondary bronchi on the left and three on the right. Each secondary bronchus then divides into several tertiary bronchi that supply the bronchopulmonary segments. The right lung contains ten bronchopulmonary segments to supply three lobes. The left lung contains nine bronchopulmonary segments to supply two lobes.

Tertiary bronchi continue within the lung, dividing into smaller and smaller airways, termed as bronchioles. The tertiary bronchi continue as 20–25 generations of conducting bronchioles and terminal bronchioles. This represents the end of the conducting component of the airway. Terminal bronchioles extend as respiratory bronchioles, followed by alveolar ducts, sacs, and finally the alveoli, the main respiratory component of the lung.

Pulmonary Neurovasculature

Pulmonary arteries carry poorly oxygenated blood from the heart to the lung for oxygenation. They enter the lung at the hilum, descend to the main bronchi, and divide into several lobar and segmental arteries in a pattern similar to the main

bronchi. This ultimately allows for a branch to go into each lobe and segment of the lung. There are two pulmonary veins in each lung that carry oxygenated blood back to the heart to then be circulated to the rest of the body.

The innervation of the lungs and pleura is rather simple. Both are innervated by autonomic fibers derived from the pulmonary plexus. The pulmonary plexus consists of the vagus nerve (cranial nerve X) and fibers from the sympathetic trunk. The vagus nerve supplies parasympathetic fibers whereas the sympathetic trunk supplies sympathetic fibers. Parasympathetic innervation will dilate the pulmonary vessels, constrict the bronchioles, and excite glandular secretions. Sympathetic innervation will constrict the pulmonary vessels, dilate the bronchioles, and inhibit glandular secretions [2].

Lung Mechanics

Before discussing lung mechanics, we must first discuss pressure and how it is measured. It is commonplace in lung mechanics for units of pressure to be measured in cmH_2O. Historically, physiologists conducted experiments by applying air pressure to the lungs using columns of water. A column of water 50 cm high produces a pressure of 50 cmH_2O. 1033 cmH_2O is equal to one standard atmosphere, or to 760 mmHg. It is standard practice in lung mechanics and clinical settings to report pressures relative to atmospheric pressure. Thus, atmospheric pressure is equal to 0 cmH_2O.

There are four locations where air pressure is determined. First is alveolar pressure (P_{alv}) which is the pressure inside the alveolar regions. Second is the pressure at the airway opening (P_{ao}). Third is the pressure inside the chamber but outside the lung, the pleural pressure (P_{pl}). Fourth is the pressure outside of the system, or barometric pressure (P_B).

Much of what we know now about static lung mechanics is a result of physiology experiments conducted in the last century. Lungs removed from autopsies were studied by suspending them in a humidified chamber. The airways were connected to a pressure gauge and a syringe was used to inflate and deflate the lungs. An open pipe was placed in the chamber so that the chamber was always equal to atmospheric pressure. In one particular experiment, researchers discovered that the resting lung volume is roughly 1/5th of the total lung capacity. This experiment demonstrated that this volume, termed the residual volume (RV), is typically observed in normal human lungs. The pressure of lungs at rest is roughly measured at 2 cmH_2O [3].

Another important experiment was conducted in a similar manner. In this case, a syringe was placed on the pipe so that it is no longer completely open to the atmosphere. When the pressure is advanced to +5 cmH_2O, the lungs are at roughly 50% of the total lung capacity. This volume is referred to as the functional residual capacity (FRC). Since we are discussing static lung mechanics, there is no flow of air. As a result, the pressure in the airway and the alveolar pressure are the same value. In a human body, this is referred to as the mouth pressure.

If we were to continue to inflate the lungs to its maximum capacity, or the total lung capacity (TLC), the pressure would reach +25 cmH_2O. Further pressure on the system would not result in additional air inflation to the lungs but may result in rupturing of the lungs. In this scenario, a constant pressure must be applied to the syringe to keep it at +25 cmH_2O. If the syringe was let go, or disconnected, air will be expelled rapidly until the lung is approximately 1/10th of the total lung capacity. So, to maintain a given lung volume, there must be pressure continuously applied. As a result, researchers concluded that the lung generates an opposing pressure, termed the elastic recoil of the lung, which is working to expel air [3]. The elastic recoil is always acting to expel air from the lung at any lung volume.

In the previous experiments, the syringe and pressure gauge were connected to the airways. Although useful, these experiments failed to provide an accurate representation of lung mechanics in humans, as the pressure differential is not derived in such a manner. To account for this, researchers removed the gauge and syringe from the airways and instead attached them to the pipe that invaded the chamber, representing our pleural cavity. In this case, as in the case of a normal respiratory system, the airways and alveoli are open to the atmosphere. By pulling on the syringe, we create a negative pressure inside the chamber, and the lungs inflate. A chamber or pleural pressure of −2 cmH_2O would cause the lung volume to be approximately 1/5th of the total lung capacity [3].

Notice the similarities between this and the previous experiment. At total lung capacity in the first example, the pressure gauge read +25 cmH_2O, as that was the pressure being applied directly to the airway. In this example, the gauge would read −25 cmH_2O, as this subatmospheric pressure in the chamber still causes the lungs to fully inflate. An important note is that the elastic recoil of the lungs is the same in both experiments, and is +25 cmH_2O, as the elastic recoil is always positive.

These experiments set the basis for discussion of lung mechanics in the thoracic cavity. We previously discussed the FRC including that it corresponds to roughly ½ of the total lung inflation and is approximately +5 cmH_2O if one were to measure the pressure inside the lung, or −5 cmH_2O if one were to measure the pressure inside the pleural cavity. For our purposes, we will refer to pressure as pleural or chamber pressures, as is commonplace in literature. In a clinical setting, FRC is defined as the volume of air in the lungs at the resting expiratory level. In simple terms, it is the volume of the lungs when the glottis (vocal cords), or the airway to the atmosphere, is open and there is no airflow or effort to breathe. It is also the lung volume at the end of a quiet breath. Although muscular effort is required to inhale, no effort is required to exhale back to FRC, because the elastic recoil of the lungs does all the work. Thus, the pressure in the pleural cavity, at rest, is at −5 cmH_2O [3].

If the pleural region is sealed and intact, the respiratory system is stable at FRC. If air is introduced into the pleural space, the integrity of the system is compromised, and the pleural space is no longer at −5 cmH_2O, but now equal to atmospheric pressure. This causes the lung to deflate and collapse. Clinically, this is known as a pneumothorax.

Compliance and Elastance

To understand the basic physiology of the lungs, key biophysical concepts intertwining lung anatomy and mechanics must be outlined. Two of these concepts, which are inversely related, include compliance and elastance. Compliance refers to the propensity of the anatomic structure, in this case both the lung and the chest wall, to allow expansion of volume to accommodate pressure changes. Elastance, on the other hand, refers to the propensity of the lungs or chest wall to return to resting volume after being expanded. Mathematically, compliance can be represented by change in lung volume (DV) divided by the change in pressure (DP), while elastance can be represented by the reciprocal, DP divided by DV. Both of them must work in tandem for both the chest wall and the lungs themselves to maintain optimal inflation and deflation for adequate gas exchange [4]. Deviations to this lead to common lung pathologies, including restrictive interstitial lung diseases with reduced lung compliance and chronic obstructive pulmonary disease with diminished lung elastance [5].

Airway Resistance and Drive Pressure

The next key factor affecting the amount of air that enters the lung during inspiration and exits the lung during exhalation is airway resistance. As discussed earlier in the chapter, the airway progresses from the trachea down to the individual alveolar air sacs where gas exchange ultimately occurs. As air travels through this pathway, it experiences resistance to flow. For simplicity, this resistance can be represented through modeling of airflow as laminar flow. With that assumption, resistance to flow at a specific point along the airway can be modeled with the following parameters: air viscosity (m), length of the airway (L), and radius of the airway (r), with the overall resistance equation, $R = \frac{8\,\mathrm{mL}}{\neq r^4}$.

Using this model at specific points in the airway, it is clear that smaller diameter bronchioles have a much larger resistance to airflow than the larger diameter bronchi or trachea. However, as air travels down the airway, the trachea splits into two bronchi which continually branch further eventually leading to terminal bronchioles and ultimately alveoli. As the airway splits, it becomes a parallel resistance circuit leading to an overall decrease in resistance at the terminal small airways compared to the large airways (trachea, bronchi). Furthermore, when looking at inspiration versus expiration, the overall diameter of the airways is increased during inspiration compared to expiration, so the overall airway resistance is greater during exhalation [6].

Lastly, a key aspect of ventilation includes the drive pressure, which is the pressure gradient that provides the force behind the airflow during inspiration and expiration. Using the concepts discussed earlier, the drive pressure can be described by

the ratio between the tidal volume, which is the volume of air that goes into and out of the lung during a normal breathing cycle, and the overall compliance of the respiratory system, assuming a static overall compliance. This concept is key, because it attempts to quantify the pressure gradient needed to produce adequate volume expansion of the lungs. The ability to model and calculate this value can be used to guide therapy for patients. This will be useful later when mechanical ventilation strategies are discussed [7].

Work of Breathing

In normal physiology, to create the drive pressure needed to achieve the tidal volume, energy is required via adenosine triphosphate (ATP) to create mechanical changes through respiratory muscles moving the chest wall and the diaphragm. The amount of energy required for both inspiration and expiration can be quantified as work of breathing, expressed in units of energy (joules). To understand this in terms of respiratory physiology, the units can be manipulated to describe the energy expended in terms of a product of pressure and volume. Looking at the inspiratory work of breathing, several components discussed earlier are involved. First, work must be done to overcome the elastance or elastic recoil of both the chest wall and the lung. Second, work must be done to overcome the overall resistance from both the lung and chest wall tissue, as well as the airway resistance described above. The overall work for inspiration is the sum of these different components. As properties including elastance and resistance change, the work necessary to produce a specific tidal volume changes as well. This remains true when looking at the expiratory work of breathing. Overall, the drive pressure is generated through the contraction of respiratory muscles, which occurs using ATP created mainly from the metabolic pathway oxidative phosphorylation. Understanding the concept of the work of breathing will be necessary in subsequent chapters [8].

Gas Exchange

At the most fundamental level, the main function of the respiratory system is the exchange of oxygen (O_2) and carbon dioxide (CO_2) in a process known as gas exchange. As these gases are constantly produced and consumed during bodily reactions, there must be an efficient system for this exchange to occur. In the human body, gas exchange occurs in two predominant areas—the lungs and the peripheral tissues. The lungs provide the first location for gas exchange in a process known as ventilation while the peripheral tissues provide the second location for gas exchange in a process called oxygenation. The goal for the respiratory system is to bring atmospheric O_2 into the lungs for eventual distribution to the cells for cellular respiration. At the same time, these cells must rid themselves of their gaseous waste

product, CO_2, for removal via the lungs. Thus, the respiratory system functions as a circuit, bringing O_2 into the body while removing CO_2. We will begin our discussion of gas exchange by exploring the concepts of ventilation and oxygenation. Ventilation is the process of bringing O_2 from the atmosphere into the lungs whereas oxygenation is the uptake of O_2 in the lungs followed by O_2 delivery to the body. Oxygenation is the process that delivers oxygenated blood from our pulmonary and systemic circulation to the peripheral tissues.

Ventilation

Ventilation is a topic central to lung physiology that brings together foundational concepts of chemistry and physics. Simplistically, ventilation is the movement of gases in and out of the lungs. The impact of this seemingly simple process influences a number of systems, best understood beginning with blood flow to the lungs, following it as it interfaces with alveoli, and finally finishes at the tissue level in the body. Air enters the body via the upper respiratory tract which includes the nasal cavities, pharynx, and larynx. Along the upper respiratory tract, the air is humidified by mucus in the airway and heated from the blood traveling in adjacent blood vessels. Beyond the upper airway, the air continues into the lower respiratory tract which contains the trachea, bronchi, bronchioles, and alveoli. The upper airway, trachea, and bronchi predominantly function in the conduction of air and do not play a major role in gas exchange. Alternatively, the respiratory bronchioles and alveoli of the lower respiratory tract play a major role in gas exchange.

Once the now humidified and heated air reaches the terminal portions of the lower respiratory tract, it diffuses across the lung's air-filled sacs called alveoli. Each human lung contains roughly 150 million alveoli whose compact shape and distribution allow for roughly 50–75 m^2 of surface area for gas exchange. The alveolar epithelium is composed of simple squamous epithelium that enables efficient diffusion of gases. On the basal lamina of the alveoli, there is a very thin membrane (varying from 0.2 mm to 2.2 mm in thickness) known as the respiratory membrane. It is across this membrane that the O_2 diffuses from alveoli to the pulmonary capillaries. The alveolar respiratory membrane is separated from the pulmonary capillaries by only a tiny interstitial space, providing an advantageously small distance for gaseous diffusion into the capillary blood. CO_2 diffuses out of the pulmonary capillaries into the airway and is removed from the body via the respiratory tract [3].

Perfusion

Cardiac output from the heart is a mostly parallel circuit with equal quantities of blood delivered to both the systemic and pulmonary circulations. The delivery of blood and its "perfusion" to the lungs differ from that of systemic circulation in a number of ways.

First, the pressures within the pulmonary vasculature are low, with average systolic of 25 mmHg, diastolic of 8 mmHg, and mean of 15 mmHg, denoted with the syntax 25/8 (15). These numbers are approximately 1/4 to 1/5 that of systemic circulation [9]. Additionally, unlike systemic circulation where the majority of pressure loss in the system occurs at an arteriole level, instead in pulmonary vessels, this loss occurs directly at the capillary bed [10].

Also unique to pulmonary perfusion is its "capacitance" or ability to handle increases in cardiac output without a proportional increase in pressure. For example, during exercise, flow to lungs can increase 4–5 times that of baseline with relatively unchanged pressures. Systemic circulation significantly contrasts this, with increases in systolic pressure in excess of 50% during exercise. Consequently, when comparing both circulations, pulmonary resistance can be as much as ten times lower than that of systemic [9].

The capacitance of the pulmonary circuit can partly be described by a phenomenon where areas of the lungs, at rest, are unequally perfused. During times of increased cardiac output, recruitment of additional alveoli to participate in gas exchange as well as dilation of blood vessels occurs which is reflected in a large drop in resistance. "West zones" dividing the lung into base or 1, midportion or 2, and apex or 3 help describe the relationship between alveolar and arterial pressure with the result of lung bases being preferentially perfused (Fig. 2.1) [11].

Finally, a remnant of fetal physiology also has large impacts on lung perfusion. In utero, O_2 levels are much lower than those seen after birth and this results in vasoconstriction of pulmonary vasculature [11]. Aptly named "hypoxic

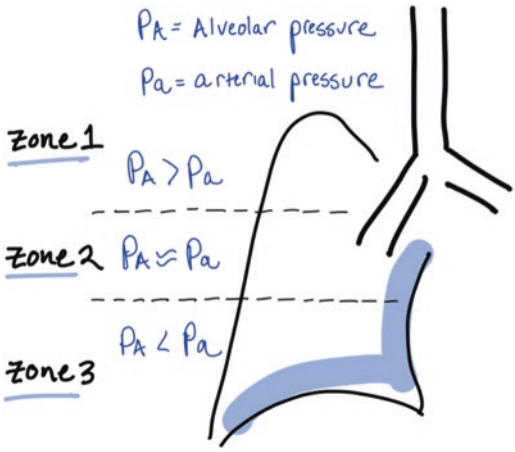

Fig. 2.1 Alveolar pressure (P_A) and arterial pressure (P_a) differences between the West zones of the lung

vasoconstriction," this mechanism persists beyond the womb. Alveoli not participating in gas exchange, for example during airway obstruction or external compression by a pneumothorax, experience lower levels of O_2, vasoconstriction of nearby vessels, and subsequently blood flow redirected towards areas of active gas exchange [12].

Dead Space

Understanding that areas of lung perfusion and ventilation are unequal brings up an important concept of ventilation called "dead space." Areas that are well ventilated, but poorly perfused, are central to this concept. Three types of dead space exist: physiologic, anatomical, and device related (Fig. 2.2).

Physiologic dead space is best seen at the apex of the lung or West zone 1. At rest these areas receive adequate movement of gases in and out of alveoli, however with minimal blood flow. This is normal physiology and varies based on cardiac output as previously described. The ratio of dead space to perfused alveoli can be calculated by the formula:

$$\frac{\text{Dead space}}{\text{Perfused}} = \frac{\left(\text{Alveolar partial pressure carbon dioxide}\right) - \left(\text{Exhaled partial pressure carbon dioxide}\right)}{\left(\text{Arterial partial pressure carbon dioxide}\right)}$$

Because it is nearly impossible to measure the partial pressure of CO_2 at the alveolar level, the arterial partial pressure of CO_2 is substituted instead [13].

Anatomical dead space exists within the airways where gases are transmitted from the atmosphere to alveoli but no gas exchange occurs. This includes all the volume from the trachea to the terminal bronchioles. The amount of anatomical

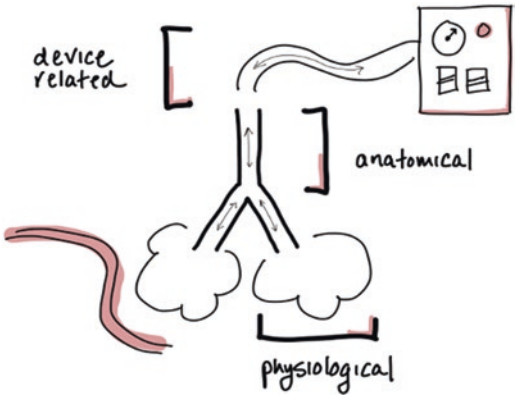

Fig. 2.2 Dead space may exist as related to the device, patient anatomy, or patient physiology

dead space is based on sex and height, and can be estimated at 1 mL/kg of ideal body weight [14].

Lastly, device- or apparatus-related dead space can exist. Mechanical ventilation requires tubes for delivering gases which exist outside of the body. These tubes contain a volume of gas that is considered dead space. This volume is generally clinically insignificant; however, it can become a problem with long circuits or small patients [15, 16].

Shunt

A related concept representing the opposite of "dead space" is "shunt" where blood travels from pulmonary to systemic circulations without gas exchange. This can occur within the lung where blood bypasses beyond areas of ventilated alveoli [17]. Additionally, blood can be "shunted" from pulmonary to systemic circulations at extrapulmonary locations which are seen in utero and congenital heart disease [18]. However, this extrapulmonary shunt physiology is complex and beyond the scope of this chapter.

A-a Gradient

As blood interfaces at the alveolar/endothelial basement membrane, gas exchange occurs. This process is primarily driven by diffusion. The volume of gas diffused is based on a number of factors including area, properties of gas, carrying capacity of blood/hemoglobin content, membrane thickness, and difference in partial pressures of gas from alveoli (Pa_{Alv}) to arterial (Pa_{Art}). These factors can be summarized in the following relationship [19]:

$$\text{Volume gas} = \frac{\text{Area} \times \text{Gas properties} \times \text{Hemoglobin content}}{\text{Thickness}} \times \left(Pa_{Alv} - Pa_{Art}\right)$$

The only part of this equation that is clinically relevant is the difference in alveolar to arterial partial pressures of gas or "A-a gradient" and their relative relationship to diffusion. Generally, this value is less than 10, but when elevated it can be helpful in diagnosing lung pathology [20].

For example, administering increasing amounts of O_2 to a patient with substantial shunt will result in a widened A-a gradient secondary to the relatively small area O_2 has to diffuse into the blood [21]. This is in contrast to instances where a diffusion limitation occurs such as with increased membrane thickness or decreased carrying capacity of the blood where administration of O_2 narrows the A-a gradient [22].

V/Q Mismatch

An additional cause of an increased A-a gradient that narrows with O_2 administration is "V/Q mismatch" or ventilation/perfusion mismatch [23]. Simplistically, this physiological condition represents areas of imbalanced ventilation and perfusion. This occurs under normal circumstances, described in previous sections by "West zones" where bases or zone 1 receives more perfusion than ventilation and apices or zone 3 experiences more ventilation than perfusion [24]. With approximately 4 L/min of ventilation and 5 L/min of perfusion to the lungs, the overall average V/Q ratio is 0.8 [25].

Pathologically this overall lung ratio can be decreased in instances of reduced ventilation such as obstructive lung disease, or increased with reduced pulmonary blood flow seen in pulmonary emboli [26].

Carbon Dioxide

The most important gas that diffuses at the alveolar/endothelial membrane and is central to ventilation is CO_2. This by-product of cellular respiration is used as a surrogate for the adequacy of ventilation, and its interaction with water is unique in that it contributes significantly to maintaining normal body pH.

The solubility of CO_2 into water is represented by the formula from Henry's law [27]:

$$\text{Dissolved carbon dioxide} = 0.0301\,mM\ /\ \text{mmHg} \times \text{Partial pressure of carbon dioxide}$$

With a normal partial pressure of this gas ranging from 35 to 45 mmHg, the total amount diffused in water is very small at approximately 1.2 mM.

However, CO_2 undergoes chemical change with water into the unstable intermediate of carbonic acid and then stable product bicarbonate, a weak acid. This reaction is represented in the equation $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO3^-$. As a weak acid, bicarbonate obeys the principles of the Henderson-Hasselbalch equation with its relationship to pH explained in the formula [28]

$$pH = 6.1 + \log\left[\frac{HCO3-}{\text{Pa}_{CO2} \times 0.0301}\right]$$

Using this formula, at physiologic pH of 7.4 with a partial pressure of CO_2 of 40 mmHg, approximately 24 mM of bicarbonate is soluble in water.

With this conversion to bicarbonate, a nearly 20 times increase in the capacity of water to carry CO_2 is seen beyond that of just dissolved gas. The acid base properties of this reaction also allow for relatively large amounts of CO_2 in the form of

bicarbonate to be transported with small changes in pH. However, these small changes become clinically significant as normal physiologic pH is tightly regulated between 7.35 and 7.45 [29]. Increases in the partial pressure of CO_2 beyond 45 mmHg can lower pH beyond physiological limits. The opposite is also true with decreases in the partial pressure of this gas to less than 35 mmHg, increasing pH to values outside of physiological limits.

The rate at which CO_2 is eliminated via ventilation is represented by the alveolar ventilation equation, which is a derivation of the ideal gas law. In this equation, minute ventilation, volume of CO_2, and partial pressure of CO_2 are related to each other in the following formula [30]:

$$\text{Minute ventilation} = \frac{\text{Volume}\, CO_2}{\text{Pa}_{CO_2}} \times K$$, where K equals 863 at a body temperature of 37 °C and 1 atmosphere.

The inverse relationship between minute ventilation and partial pressure of CO_2 is clinically useful in adjusting ventilation to match CO_2 production. For example, to halve a given partial pressure of CO_2, minute ventilation would have to double [31].

Bohr Effect

Emphasizing its importance to ventilation, the impacts of CO_2 extend beyond those of its influence on acid-base balance, and its clinical use to assess the adequacy of ventilation. At the tissue level, this gas has significant effects on the availability of O_2. The Bohr effect describes the elegant relationship between increasing levels of CO_2 and increased availability of O_2 gas that can be used in cellular respiration (Fig. 2.3) [32].

The mechanism of this process is a result of changes to the oxygen-hemoglobin dissociation curve, discussed in the below section. CO_2 reversibly interacts with the

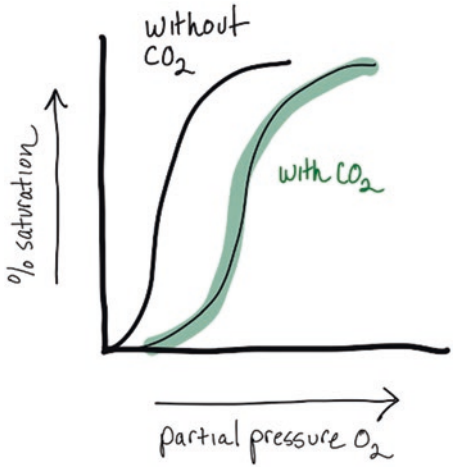

Fig. 2.3 Graphical representation of the Bohr effect

protein structure of hemoglobin, decreasing its affinity to O_2. This effectively shifts the overall oxygen-hemoglobin dissociation curve to the right [32].

The effect of this interaction is twofold. At the tissue level where CO_2 levels are high, it causes O_2 molecules to be "released" from hemoglobin. This stands in contrast to the conditions at the alveolar level where CO_2 gas is rapidly removed, increasing the affinity of hemoglobin to O_2. The overall net effect is an increase in the efficiency of oxygen transport to tissues [32].

O_2 Delivery to Tissues

Once in the blood, O_2 is carried in two forms: dissolved O_2 and O_2 that is reversibly bound to hemoglobin. During its journey to the tissues, dissolved O_2 accounts for roughly 2% of the total O_2 content in the blood while the remaining 98% of O_2 is reversibly bound to hemoglobin. Hemoglobin is a globular protein that contains four subunits. Each hemoglobin subunit is able to bind and transport one molecule of O_2 for a total of four molecules of O_2 per hemoglobin molecule. As we will go on to later explore, O_2 is able to dissociate from the hemoglobin molecule under different conditions. This dissociated O_2 is what exerts the partial pressure of O_2 within the blood, leading to important implications for O_2 delivery and gas exchange within the peripheral tissues.

The amount of dissolved O_2 in the blood abides by Henry's law regarding the concentrations of dissolved gases. In the context of blood as a solution, Henry's law states

$$Cx = Px \times \text{Solubility}$$

where Cx = concentration of dissolved gas (mL gas/100 mL blood), Px = partial pressure of gas (mmHg), and solubility = solubility of gas in blood (mL gas/100 mL blood per mmHg).

Henry's law demonstrates that the concentration of dissolved gas is directly proportional to the partial pressure of the gas and the solubility of the gas in the blood. The dissolved O_2 is solely responsible for exerting the partial pressure of O_2 in the blood. The partial pressure of O_2 is a crucial factor when it comes to establishing the gradient for oxygen's eventual exchange in the lungs and peripheral tissues.

Similar to the lungs, the capillaries within the peripheral tissues have thin membranes that allow for the rapid and efficient exchange of gases. O_2, bound to hemoglobin within the blood, is released for utilization by O_2-deprived tissues. At the same time, CO_2 is rapidly diffused from the peripheral tissues back into the capillaries for eventual removal by the lungs. In both ventilation and oxygenation, gas exchange occurs as a result of the underlying properties and laws that drive the movement of gases. We will now explore the underlying forces that drive the process of gas exchange.

The diffusion of O_2 and CO_2 in gas exchange is driven primarily by Fick's law for the diffusion of gases. Fick's law defines how the volume of gas transferred per unit time is affected by factors such as the diffusion coefficient of a specific gas,