Section I

General Principles

1

Cardiopulmonary Function

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A major function of the cardiopulmonary system is to deliver oxygen to tissues and eliminate carbon dioxide generated by tissue metabolism. To accomplish these functions, the respiratory and cardiovascular systems must act in close concert. Compromise of either system—or both systems—can adversely affect the outcome of animals undergoing thoracic surgery. The ability to quickly assess cardiopulmonary function and pinpoint the cause and severity of problems is firmly grounded in an understanding of cardiopulmonary physiology and pathophysiology. This ability is a core skill for those who undertake interventions in the thorax.

The Oxygen Pathway

The oxygen pathway is a clinically useful concept that provides a logical framework for evaluation and correction of disturbances in the cardiopulmonary system (Figure 1.1). It considers the transport of oxygen as a sequential, step-by-step process beginning with atmospheric oxygen and ending with oxygen delivery to tissues. Each step in the pathway is critically important and must be assessed independently to assure adequate overall cardiopulmonary function. The steps of the oxygen pathway can be viewed as a clinical checklist for monitoring cardiopulmonary function in animals before, during, and after thoracic surgery. Steps in the pathway include ventilation, pulmonary gas exchange, hemoglobin saturation, hemoglobin concentration, oxygen content, cardiac output, and oxygen delivery.

Ventilation

Ventilation is the mechanical process that causes air (a mixture of gases) to flow into and out of the lungs. Not all gas flow (L/min) into the respiratory system reaches areas of gas exchange; consequently, *total ventilation* or *minute volume* (V_T) is divided between *alveolar ventilation* (V_A), where gas exchange occurs, and *dead space ventilation* (V_D).

$$V_T = V_A + V_D \tag{1.1}$$

Anatomic dead space ventilation includes gas flow to anatomic areas not normally involved in gas exchange. Physiologic dead space includes anatomic dead space, as well as flow to alveoli that are ventilated but not receiving pulmonary blood flow. While anatomic dead space remains constant, physiologic dead space changes depending on the number of functioning alveoli. Furthermore, the ratio of V_D to V_A changes with the respiratory rate and *tidal volume* and cannot be easily determined clinically. For example, an animal that is panting increases V_T and V_D several-fold without necessarily changing V_A. Thus, the adequacy of V_A cannot be determined by just measuring V_T.

Carbon Dioxide Tension

The primary drive for alveolar ventilation is *arterial carbon dioxide tension* (P_aCO_2). Under physiologic conditions, the central respiratory center drives V_A to keep P_aCO_2 at about 40 mm Hg, regardless of the total amount of carbon dioxide produced (V_{CO_2}) based on the size, metabolism, and activity level of the patient. This relationship of P_aCO_2, V_A, and V_{CO_2} is described by Equation 1.2, where K is a conversion constant:

$$P_aCO_2 = \frac{V_{CO_2} \times K}{V_A} \tag{1.2}$$

By definition, *hypoventilation* is present when V_A fails to match V_{CO_2}, and as a result, P_aCO_2 increases (i.e., > 40 mm Hg for animals at sea level). Conversely, *hyperventilation* is present when V_A exceeds what is necessary to eliminate V_{CO_2} causing P_aCO_2 to decrease (i.e., < 40 mm Hg at sea level). Thus, in the

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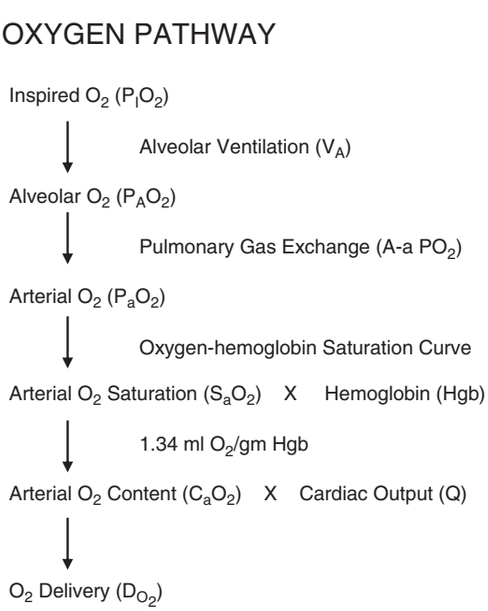


Figure 1.1 Oxygen Pathway

clinical setting, adequacy of ventilation is determined by P_aCO_2 from a blood gas analysis. If P_aCO_2 is normal based on the regional normal value, then ventilation to the gas exchange regions of the lung is considered adequate. (Note: The regional normal value of P_aCO_2 is altitude dependent because animals that reside at higher altitudes increase relative V_A to compensate for lower inspired oxygen tension.)

Alveolar Gas Equation

Because *arterial oxygen tension* (P_aO_2) cannot be higher than *alveolar oxygen tension* (P_AO_2), P_AO_2 is critically important to all subsequent steps in the oxygen pathway. P_AO_2 is not measured clinically, but can be estimated from the *alveolar gas equation:*

$$P_AO_2 = P_IO_2 - P_aCO_2/R \tag{1.3}$$

From above equation, it is apparent that P_AO_2 is a function of the *inspired oxygen tension* (P_IO_2), P_aCO_2 (and thereby V_A), and the *respiratory exchange ratio* (R). The respiratory exchange ratio is the ratio of *oxygen consumption* (V_{O_2}) to V_{CO_2}. The respiratory exchange ratio can be determined by indirect calorimetry, but this is not routinely done in the clinical setting. In a study of dogs evaluated by indirect calorimetry, R was found to be 0.76 in postoperative or post-trauma dogs compared to an R of 0.84 in normal dogs [1]. For purposes of the above calculation, R is generally assumed to be 0.8. The P_IO_2 is determined by the *fraction of inspired oxygen* (F_IO_2, 0.21 in ambient air), *barometric pressure* (P_B, 760 mm Hg at sea level), and the *vapor pressure of water* (P_{H_2O}, 47 mm Hg at 100% saturation and body temperature):

$$\begin{aligned} P_IO_2 &= F_IO_2\,(P_B - P_{H_2O}) \\ &= 0.21\,(760\text{ mm Hg} - 47\text{ mm Hg}) \\ &= 150\text{ mm Hg (at sea level)} \end{aligned} \tag{1.4}$$

Thus, the P_IO_2 of room air at sea level is approximately 150 mm of Hg. From the above equation, it can be seen that either barometric pressure or F_IO_2 can alter P_IO_2, and, in turn, the P_AO_2. Substantial change in barometric pressure is most likely to result from residence at altitude, whereas F_IO_2 is altered clinically by administration of supplemental oxygen. Increasing F_IO_2 to 40% nearly doubles P_IO_2 and increases P_AO_2 without changing V_A.

Alveolar ventilation is the other major determinant of P_AO_2. The alveolar gas equation predicts that an animal breathing room air at sea level with a P_aCO_2 of 40 mm Hg would have a P_AO_2 of approximately 100 mm Hg:

$$\begin{aligned} P_AO_2 &= F_IO_2(P_B - P_{H_2O}) - P_aCO_2/R \\ &= 0.21(760\text{ mm Hg} - 47\text{ mm Hg}) \\ &\quad - 40\text{ mm Hg} / 0.8 \\ &= 150\text{ mm Hg} - 50\text{ mm Hg} \\ &= 100\text{ mm Hg} \end{aligned} \tag{1.5}$$

A rule of thumb, for every 1 mm Hg elevation in P_aCO_2, there will be approximately a 1.25 mm Hg decrease in P_AO_2 (and P_aO_2).

Hypoventilation

Adequate ventilation requires central respiratory centers, spinal pathways, peripheral respiratory nerves, primary respiratory muscles, pleural-pulmonary coupling, and pulmonary mechanics to be intact or normal. Hypoventilation occurs when any component of this pathway is disrupted or abnormal. Important causes of hypoventilation include depression or injury of the central respiratory center, injury or disease of the neuromuscular apparatus of ventilation, disruption of pleural-pulmonary coupling (e.g., pneumothorax), and/or abnormal pulmonary mechanics that increase the work of respiration to levels that cannot be sustained by the patient. The major determinants of respiratory work are airway resistance and lung compliance. Obstructive airway disorders or restrictive lung conditions, or both, increase respiratory work leading to hypoventilation when they are severe.

Breathing Patterns

Clinical assessment of ventilation should include observation of breathing. The first indication that a patient is hypoventilating may come from the simple observation that ventilatory excursions are poor. Information about abnormal pulmonary mechanics is gained from observation of the pattern of breathing. Animals adopt a respiratory rate and pattern that minimizes respiratory work. Normal breathing balances the major elastic force of *lung compliance* with the major viscous force of *airway resistance*. Elastic forces in the lung are minimized by a *rapid and shallow* breathing pattern, whereas resistance forces in the lung are minimized by a *slow and deep* breathing pattern (Figure 1.2). Thus, animals with restrictive lung diseases (e.g., pulmonary edema, interstitial pneumonia, pulmonary fibrosis, pleural effusion) will adopt a rapid and shallow breathing pattern, whereas animals with airway obstruction (e.g., laryngeal paralysis, bronchoconstriction) will tend to adopt a slow and deep pattern of breathing. Obstructive breathing patterns can be further assessed by observing of the phase of respiration that produces the most ventilatory effort. Upper airway obstruction causes an exaggerated effort during inspiration, whereas lower airway obstruction causes an exaggerated effort during expiration.

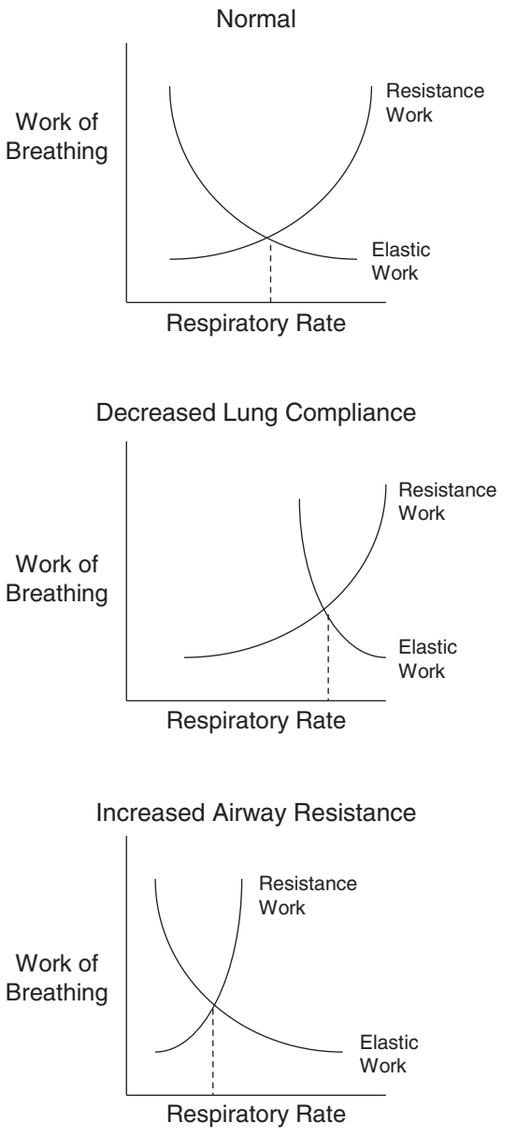


Figure 1.2 Work of Breathing

Tidal Volume and Minute Volume

Total ventilation can be measured directly with a respirometer attached to an endotracheal tube or tight-fitting mask. *Tidal volume* is the volume (mL) of gas expired during each breath and is normally at least 10 mL/kg of body weight. *Minute volume* (V_T) is the total volume of gas expired each minute (L/min). If tidal volume or minute volume are low, there is a good possibility that ventilation is inadequate. However, because V_T includes both V_D and V_A, measurement of a normal tidal volume or minute volume does not assure that V_A is adequate.

Arterial Carbon Dioxide Tension

Ultimately, clinical assessment of alveolar ventilation is based on the P_aCO_2. By definition, a patient is hypoventilating when *hypercapnia* (increased P_aCO_2) present. The most direct method of assessing P_aCO_2 is by arterial blood gas analysis. Alveolar ventilation should be considered inadequate when the P_aCO_2 is > 45 mm Hg for patients at or near sea level. Hypoventilation causes both hypoxemia and respiratory acidosis. Administration of supplemental oxygen (i.e., increasing the F_IO_2) corrects hypoxemia caused by hypoventilation by increasing the P_IO_2 and P_AO_2 (see the alveolar gas equation). Of course, administration of supplement oxygen does not correct the respiratory acidosis associated with elevated P_aCO_2, so it is important to correct the underlying cause(s) of hypoventilation even when animals are receiving supplemental oxygen.

End-Tidal Carbon Dioxide Tension

Because diffusion of carbon dioxide in the lung is highly efficient, P_aCO_2 and *alveolar carbon*

dioxide tension (P_ACO_2) are close to equal. The carbon dioxide tension of expired gas at the end of expiration closely approximates P_ACO_2 and is termed *end tidal carbon dioxide tension* ($P_{ET}CO_2$). The $P_{ET}CO_2$ is measured clinically with a capnograph that samples expired gas continuously and reports the peak carbon dioxide tension at the end of expiration. Measurement of $P_{ET}CO_2$ provides a clinical estimate of P_aCO_2, and therefore V_A.

Pulmonary Gas Exchange

Pulmonary gas exchange is the collective process by which oxygen and carbon dioxide are exchanged between the alveolus and blood. Exchange of oxygen is complex and dependent on diffusion across the alveolar-capillary membrane, matching of alveolar ventilation and perfusion, and the amount of venous admixture to arterial blood. Ideally, P_aO_2 should be nearly equal to P_AO_2 predicted by the alveolar gas equation (i.e., 100 mm of Hg under physiologic conditions at sea level). *Impaired pulmonary gas exchange* is present when P_aO_2 becomes substantially less than the predicted P_AO_2. Because P_aO_2 can be measured directly and P_AO_2 can be calculated from measurable values, the degree of gas exchange impairment can be quantified by the *alveolar-arterial oxygen difference* (A-a PO_2):

$$\begin{aligned} \text{A-a } PO_2 &= P_AO_2 - P_aO_2 \\ &= [F_IO_2(P_B - P_{H_2O}) - P_aCO_2/R] \\ &\quad - P_aO_2 \\ &= [0.21(760 - 47) - 40/0.8] - 98 \\ &= 100 - 98 \end{aligned} \tag{1.6}$$

The A-a PO_2 should be < 10 mm Hg for animals breathing room air. The normal A-a PO_2 gradient increases 5 to 7 mm Hg for every 10% increase in F_IO_2. There are three basic mechanisms of gas exchange impairment: *diffusion impairment*, *shunt*, and *ventilation-perfusion (V_A/Q) mismatch*.

Diffusion Impairment

Diffusion of oxygen across the alveolar-capillary membrane is directly proportional to the concentration gradient of oxygen across the membrane and the total membrane area; and inversely proportional to the membrane thickness. Adequate diffusion of oxygen is also a function of the time available to accomplish complete equilibration between the alveoli and blood. Under normal conditions, diffusion of oxygen in the lung is highly efficient and generally is complete by the time blood has traversed about one-fourth of the alveolar capillary bed. Thus, pulmonary disease must be severe before diffusion limits gas exchange. *Diffusion impairment* can result from diseases that affect the alveolar-capillary membrane such as pulmonary edema, interstitial pneumonia, or pulmonary fibrosis. However, because of the efficiency of gas diffusion, these conditions rarely cause hypoxemia by diffusion impairment in animals at rest.

The most important clinical cause of severe diffusion impairment is pulmonary thromboembolism (PTE), which impairs diffusion by decreasing the total membrane area available for oxygen diffusion. Because the cardiac output must be redirected to unobstructed pulmonary capillaries, the transit time available for diffusion is decreased, and this further contributes to diffusion impairment. A reciprocal consequence of pulmonary thromboembolism is an increase in dead space ventilation (V_D/V_T) resulting from the ventilation of unperfused alveoli. Dead space ventilation can be quantified by measuring the P_aCO_2 and mixed exhaled carbon dioxide tension (P_ECO_2):

$$\frac{V_D}{V_T} = \frac{P_aCO_2 - P_ECO_2}{P_aCO_2} \tag{1.7}$$

Determination of P_ECO_2 requires collection of expired gases into a collection bag and analysis of carbon dioxide tension with an infrared analyzer. This determination is rarely performed in clinical patients. In theory, the increase in dead space ventilation could lead to an increase in P_aCO_2. However, carbon dioxide diffuses across the alveolar-arterial membrane about 20 times more rapidly than oxygen and is rarely if ever limited by diffusion.

Administration of supplemental oxygen can be expected to correct hypoxemia caused by diffusion impairment. It does so by increasing P_AO_2, and therefore the concentration gradient of oxygen across the alveolar-capillary membrane that drives diffusion. This explains why hypoxemia due to diffusion impairment, including pulmonary thromboembolism, is so responsive to administration of supplemental oxygen. This response to supplemental oxygen serves as a useful clinical observation that supports an assessment that hypoxemia is the result of this mechanism (e.g., PTE).

Shunt

Shunt occurs when unoxygenated venous blood bypasses viable gas exchange areas of the lung and mixes with oxygenated arterial blood. The resultant *venous admixture* produces hypoxemia. Shunt results from either a *right-to-left cardiac shunt* or *pulmonary shunt*. Examples of right-to-left cardiac shunt

include ventricular septal defect with suprasystemic pulmonary hypertension and Tetralogy of Fallot. Pulmonary shunt results from perfusion of completely collapsed or fluid-filled alveoli. Shunt is an important cause of clinically significant hypoxemia. The magnitude of hypoxemia caused by shunt is a function of the ratio of shunt flow to total cardiac output, termed the *shunt fraction* (Q_s/Q). Because venous admixture has no opportunity for gas exchange, hypoxemia arising purely from shunt is unresponsive to administration of supplemental oxygen. This physiologic reality distinguishes shunt from other causes of hypoxemia and serves as a useful clinical finding for diagnosing shunt as a contributing or sole mechanism of hypoxemia.

Shunt does not affect the P_aCO_2 until it becomes very severe. Thus, shunt usually does not result in hypercapnia. In fact, animals with shunt often have a low P_aCO_2 as a result of hypoxia-driven hyperventilation.

Ventilation-Perfusion Mismatch

Ventilation-perfusion (V_A/Q) mismatch occurs when ventilation and blood flow are not closely matched in gas exchange units. The result is inefficient gas exchange and hypoxemia. If regions of the lung are ventilated but poorly perfused (i.e., high V_A/Q), the functional result is wasted ventilatory effort that does not benefit gas exchange. Because regions of high V_A/Q are associated with complete gas exchange, regions of high V_A/Q do not directly contribute to impaired pulmonary gas exchange and hypoxemia. It does make gas exchange inefficient. In regions of the lung that are perfused but poorly ventilated (i.e., low V_A/Q), the functional result is inadequate bulk flow of oxygen to alveoli to fully oxygenate blood as it flows through these regions. This results in admixture of poorly oxygenated blood from these exchange areas with blood that is more fully oxygenated from normal regions. The net result is overall hypoxemia. *Low V_A/Q mismatch* is an important cause of hypoxemia in animals with pulmonary disease. Any pulmonary condition that disrupts ventilation but maintains blood flow to alveoli will result in low V_A/Q mismatch and global arterial hypoxemia. Because alveoli are still at least partially ventilated in the setting of low V_A/Q mismatch, the resultant hypoxemia is responsive to the administration of supplemental oxygen, depending on the magnitude of low V_A/Q. In reality, pulmonary diseases that cause low V_A/Q mismatch are usually accompanied by an increase in pulmonary shunt, explaining why many pulmonary conditions are only partially or poorly responsive to supplemental oxygen.

Alveolar-Arterial PO_2 Gradient

The A-a PO_2 can be calculated by measuring P_aO_2 and P_aCO_2 by blood gas analysis and inserting these values into Equation 1.6. The calculated A-a PO_2 for animals breathing room air is normally < 10 mm of Hg. A calculated A-a PO_2 of 30 mm of Hg or greater in animals breathing room air suggests significant impairment of gas exchange. Because the normal valve of A-a PO_2 is affected by F_IO_2, the above normal valves do not apply to animals breathing supplemental oxygen. While normal values of A-a PO_2 are reported for various levels of F_IO_2, it is often difficult to determine an accurate F_IO_2 in the clinical setting. Thus, blood gas analysis and calculation of A-a PO_2 is most revealing when performed in animals breathing room air. The A-a PO_2 has been shown to be an important predictor of survival in critically ill dogs [2].

Shunt Fraction (Q_s/Q)

The magnitude of shunt can be determined by calculation of the shunt fraction from the oxygen saturation of arterial blood (S_aO_2), mixed venous blood (S_vO_2), and pulmonary capillary blood (S_cO_2) during breathing of pure oxygen:

$$\frac{Q_s}{Q} = \frac{S_cO_2 - S_aO_2}{S_cO_2 - S_vO_2} \tag{1.8}$$

The S_cO_2 is not measured directly, but is assumed to be 100% during breathing of pure oxygen. Ideally, the S_vO_2 sample should be obtained from a catheter in the pulmonary artery. Alternatively, the S_vO_2 can be approximated from a sample obtained from a central venous catheter. Shunt is the only mechanism of impaired gas exchange that persists during administration of 100% supplemental oxygen. A calculated Q_s/Q > 10% is abnormal and indicates clinically important gas exchange impairment in animals breathing supplemental oxygen.

Oxygen Saturation and Oxygen Content

The P_aO_2 reflects the amount of oxygen dissolved in plasma. Dissolved oxygen is of course insufficient to meet metabolic demand for oxygen. Hemoglobin greatly increases the oxygen carrying capacity of blood. *Arterial oxygen saturation* (S_aO_2) is defined as the fraction or percent of total hemoglobin binding sites that are bond to oxygen in the arterial blood. The P_aO_2 is the principal determinant of S_aO_2.

The relationship between P_aO_2 and S_aO_2 is described by the *oxygen-hemoglobin saturation curve*

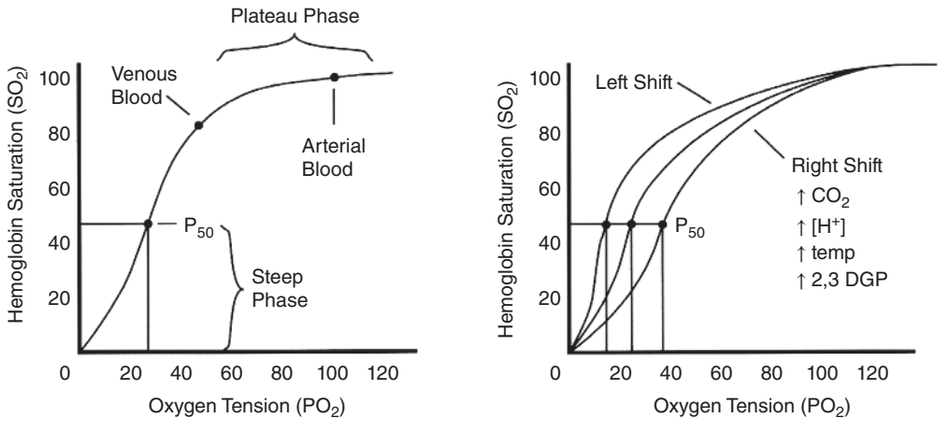


Figure 1.3 Oxygen-Hemoglobin Saturation Curve

(Figure 1.3). The affinity of hemoglobin for oxygen increases as more oxygen binds to it which gives the oxygen-hemoglobin curve its sigmoid shape. The shape of the oxygen-hemoglobin curve has important physiologic and pathophysiologic implications. The plateau phase of the curve causes hemoglobin to remain saturated over a wide of range oxygen tensions. The S_aO_2 is approximately 97% when the P_aO_2 is 97 mm of Hg. The S_aO_2 cannot be increased substantially by higher than normal P_aO_2 values. The steep phase of the oxygen-hemoglobin curve allows for efficient oxygen release in the peripheral tissues where oxygen tension normally decreases. A pathophysiologic implication of the steep phase of the curve is that small changes in P_aO_2 can have profound changes on S_aO_2 when arterial hypoxemia is present.

The oxygen-hemoglobin curve can "shift" to the right or left reflecting changes in the overall affinity of hemoglobin for oxygen. A shift of the curve to the right decreases overall oxygen affinity of hemoglobin, whereas a shift to the left increases hemoglobin oxygen affinity. Conditions that shift the curve to the right include increased CO_2 (Haldane effect), increased hydrogen ion concentration (Bohr effect), increased temperature, and increased 2,3-diphosphoglyerate. Interestingly, conditions that decrease hemoglobin affinity prevail in the peripheral tissues where unloading of oxygen is desirable. Because shifted curves converge in the plateau phase, a shift in the oxygen-hemoglobin curve has a more profound effect on the steep phase than on the plateau phase of the curve. For this reason, shifts in the curve have a greater physiologic effect on unloading of oxygen in the peripheral tissues than on loading of oxygen in the lung. Shifts in the oxygen-hemoglobin curve are quantified by measurement of the oxygen tension at which hemoglobin is 50% saturated (P_{50}). Even though shifts in the oxygen-hemoglobin curve can have an important effect on pulmonary function, they are generally not assessed clinically. Nevertheless, it is useful for clinicians to be mindful of the possibility for such effects in their patients.

Arterial oxygen content (C_aO_2) is the total oxygen present in arterial blood measured in units of mL O_2/100 mL (dL). Each gram of hemoglobin (Hgb) is capable of carrying 1.34 mL of molecular oxygen when fully saturated. Thus, the amount of oxygen bound to hemoglobin can be calculated by multiplying 1.34 (mL O_2/gm), the hemoglobin concentration of blood (gm/dL), and S_aO_2 (%). Dissolved oxygen can be calculated from the P_aO_2. At sea level, dissolved oxygen is equal to 0.003 mL O_2/dL blood/mm Hg P_aO_2. Thus, C_aO_2 is calculated as shown in Equation 1.9:

$$\begin{aligned} C_aO_2\,(\text{mL } O_2/\text{dL}) = {} & S_aO_2(\%) \times \text{Hgb (gm/dL)} \\ & \times 1.34\,(\text{mL } O_2/\text{gm}) \\ & + P_aO_2(\text{mm Hg}) \\ & \times 0.003\,(\text{mL } O_2/\text{dL/mm Hg}) \end{aligned} \tag{1.9}$$

For an animal at sea level with a P_aO_2 of 97 mm of Hg, a S_aO_2 of 97%, and a hemoglobin concentration of 15 gm/dL, the C_aO_2 would be:

$$\begin{aligned} C_aO_2(\text{mL } O_2/\text{dL}) = {} & 0.97 \times 15\,\text{gm/dL} \\ & \times 1.34\,\text{mL } O_2/\text{gm} \\ & + 97\,\text{mm Hg} \times 0.003\,\text{mL} \\ & O_2/\text{dL/mm Hg} \\ = {} & 19.5\,\text{mL } O_2/\text{dL} + 0.3\,\text{mL } O_2/\text{dL} \\ = {} & 19.8\,\text{mL } O_2/\text{dL} \end{aligned} \tag{1.10}$$

From this calculation, it is apparent that the contribution of dissolved oxygen to overall C_aO_2 is negligible and for clinical purposes can largely be ignored. Thus, the principal clinical determinants of C_aO_2 are S_aO_2 and hemoglobin concentration. Polycythemia

and anemia can have an important impact on C_aO_2. Within limits, polycythemia is an important adaptive mechanism for physiologic (e.g., altitude) or pathophysiologic causes of chronic hypoxemia. Conversely, anemia substantially decreases C_aO_2. The effect that anemia has on C_aO_2 is sometimes under appreciated. In animals with a relatively normal cardiovascular system, deficits in C_aO_2 caused by anemia can be compensated for by an increase in cardiac output. However, if the cardiovascular system is compromised, as is often the case in critical patients, anemia can have an important adverse effect on O_2 delivery. Thus, as a general rule, it is important to keep the hematocrit ≥ 30% in patients undergoing thoracic interventions.

Oxygen Delivery, Oxygen Consumption, and Oxygen Extraction

Oxygen delivery (D_{O_2}) is the mL O_2 delivered to the peripheral tissues each minute and is the product of C_aO_2 and cardiac output (Q):

$$D_{O_2}(\text{mL } O_2/\text{min}) = C_aO_2(\text{mL } O_2/\text{dL}) \times Q(\text{dL/min}) \quad (1.11)$$

Thus, maintenance of adequate D_{O2} requires adequate pulmonary function (P_aO_2), hemoglobin concentration, and cardiovascular function (Q). When hypoxemia (low P_aO_2) or low hemoglobin concentration cause low C_aO_2, oxygen delivery can be maintained by increasing cardiac output assuming that the cardiovascular system is capable. When D_{O_2} is limited by low cardiac output, compensation is more difficult. Within limits, D_{O_2} can be increased by increasing the hemoglobin concentration (e.g., *polycythemia*) or by increasing oxygen extraction.

Oxygen consumption (V_{O_2}) is the mL O_2 consumed by tissues each minute and can be calculated by multiplying the difference between C_aO_2 and mixed venous oxygen content (C_vO_2) with cardiac output:

$$V_{O_2}(\text{mL } O_2/\text{min}) = [C_aO_2 - C_vO_2(\text{mL } O_2/\text{dL})] \times Q\ (\text{dL/min}) \quad (1.12)$$

From the relationship in Equation 1.12, it can be seen that, in the setting of a low cardiac output, V_{O_2} can be maintained by increasing the $C_aO_2 - C_vO_2$ difference (i.e., increasing oxygen extraction).

The *oxygen extraction ratio* is the proportion of oxygen consumed (V_{O_2}) to oxygen delivered (D_{O_2}):

$$O_2 \text{ extraction} = \frac{V_{O_2}}{D_{O_2}} = \frac{(C_aO_2 - C_vO_2) \times Q}{C_aO_2 \times Q} \quad (1.13)$$

Because cardiac output is in both the numerator and denominator, it cancels out. Thus, determination of O_2 extraction ratio does not require actual measurement of cardiac output. Also, hemoglobin concentration can be assumed to be the same in arterial and mixed venous blood. As a result, calculation of O_2 extraction can be simplified to:

$$O_2 \text{ extraction} = \frac{S_aO_2 - S_VO_2}{S_aO_2} \quad (1.14)$$

Because the O_2 extraction accounts for any deficits in SaO_2 in the delivery of O_2 to tissues, it becomes primarily an index of the adequacy of cardiac output. The utility of the O_2 extraction is that it is independent of the patient size and does not require actual measurement of cardiac output. As such, the oxygen extraction ratio is a clinically useful method of assessing the adequacy of cardiac output. Under physiologic conditions at rest, oxygen extraction is about 0.25. When cardiac output becomes inadequate to meet the demands of the patient, O_2 extraction increases. An O_2 extraction ratio of > 0.4 suggests that cardiac output is inadequate.

Cardiac Output

The principal function of the cardiovascular system is the delivery of blood to the pulmonary and systemic circulations. This function is accomplished by pumping an adequate volume of blood to the pulmonary and systemic circulations (i.e., pulmonary and systemic cardiac output) and maintaining adequate pulmonary and systemic perfusion pressures.

Cardiac Output, Blood Pressure, and Vascular Resistance

The relationship of cardiac output (Q), mean arterial pressure (MAP), atrial pressure (AP), and vascular resistance (R) are described by:

$$Q = MAP - AP/R \quad (1.15)$$

This relationship shows that cardiac output is a direct function of the pressure difference that drives flow. In the pulmonary circulation this is the difference between mean pulmonary arterial pressure and left atrial pressure. In the systemic circulation this is the difference between mean systemic pressure and right atrial pressure. Cardiac output is inhibited by pulmonary and systemic vascular resistances in the pulmonary and systemic circulations, respectively.

Rearranging this relationship demonstrates the determinants of mean arterial pressures for the pulmonary and systemic circulations

$$MAP = (Q \times R) + AP \quad (1.16)$$

Vascular resistances are not measured directly, but can be calculated from Q, MAP, and AP:

$$R = (MAP - AP)/Q \quad (1.17)$$

As predicted by the Law of Poiseuille, vascular resistance is determined by the collective total cross-sectional vascular radius of resistance arteries (i.e., degree of vasoconstriction and vasodilation) and the viscosity of blood (i.e., hematocrit). The pulse pressure (P_p) is the difference between the systolic and diastolic blood pressures around the mean arterial pressure. The P_p is the principle determinant of the "strength" of a patient's peripheral pulse on palpation. The P_p is a direct function of the SV and inverse function of the collective compliance of the large elastic arteries (C_A):

$$P_p = SV/C_A \quad (1.18)$$

The most common cause for a diminished P_p or a "weak" pulse is a poor SV. Poor compliance or "stiffening" of the elastic conducting arteries can have the effect of elevating the P_p. Conditions such as patent ductus arteriosus or aortic insufficiency that allow rapid diastolic "run off" of blood dramatically lower diastolic blood pressure and thereby elevate the P_p. Together, the mean arterial pressure and pulse pressure determine the systolic arterial pressure, which is the major determinant of cardiac afterload.

Pressure-Volume Relationship

The cardiac cycle encompasses the electrical, pressure, volume, flow, and valve motion events that occur during one complete cardiac systole and diastole. During each cardiac cycle, the heart accomplishes two fundamental kinds of external work. It generates pressure (i.e., potential energy) and it ejects volume (i.e., kinetic energy). The relationship of these two events is illustrated by plotting instantaneous ventricular pressure and volume against each other to generate a ventricular pressure-volume plot (Figure 1.4). Pressure-volume plots form the basis of current understanding of cardiac physiology. Each loop of a pressure-volume plot represents one complete cardiac cycle and consists of the rapid diastolic and atrial filling phases, isovolumetric contraction phase, ejection phase, and isovolumetric relaxation phase. The important pressure endpoints are *ventricular end-diastolic pressure* (EDP) and *ventricular systolic pressure* (P_s). The principal volume endpoints are *end-diastolic volume* (EDV) and *end-systolic volume* (ESV). The difference between EDV and ESV is the *stroke volume* (SV). The area inside in pressure-volume loop represents the external work done by the heart in one cardiac cycle. The *ejection fraction* is the SV divided by EDV.

Stroke Volume (Preload, Afterload, Contractility)

Cardiac output is the product of stroke volume and heart rate. Stroke volume is critically important to the maintenance of adequate cardiac output. Stroke volume, in turn, is determined by three important

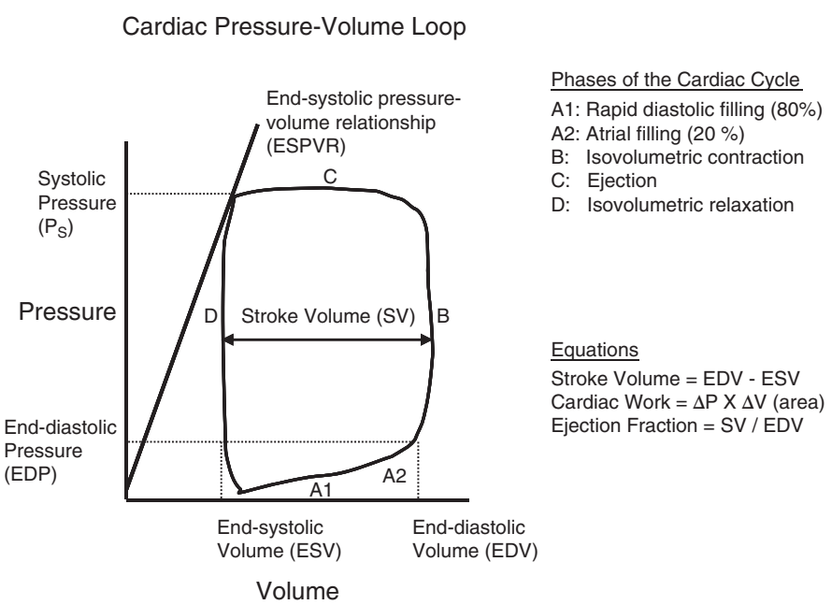
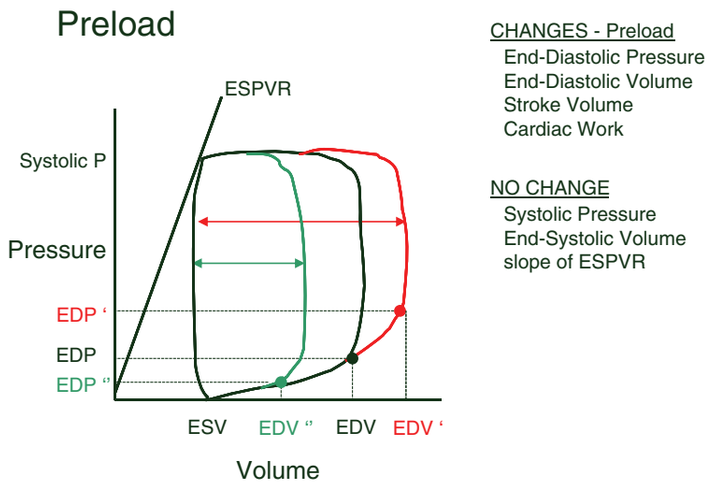


Figure 1.4 Cardiac Pressure-Volume Relationship

Figure 1.5 Cardiac Preload



independent variables: preload, afterload, and contractility. Preload encompasses the Frank-Starling principle of the heart. On a cellular basis, preload is determined by the amount of diastolic strain on each cardiomyocyte. Within limits, the greater the diastolic strain, the more forceful the cardiac contraction. On a whole heart basis, preload is reflected by the EDV and EDP (Figure 1.5). On a beat-to-beat basis, the greater the EDV and EDP, the greater the preload. Since ESV does not change with preload, the net result of an increase in preload is an increase in stroke volume, and vice versa. Factors that determine preload are the *mean filling pressure* of the circulation and the vascular resistance. The mean filling pressure of the circulation is the pressure in the cardiovascular system at zero flow and the theoretical pressure that drives flow of venous blood back to the heart. Mean filling pressure is largely determined by blood volume and venous vascular tone. The mean filling pressure has a direct relationship with preload. Vascular resistance has an inverse relationship with preload. Increases in vascular resistance decrease venous return to the heart and therefore decrease preload and stroke volume. Thus, the determinants of preload reside within the circulation, not in the heart. Afterload is the systolic stress that the ventricular wall must overcome before it can eject volume. The determinants of ventricular systolic wall stress, and therefore cardiac afterload, are predicted by the LaPlace relationship:

$$\text{Wall stress}_s = \frac{\text{Systolic pressure } (P_s) \times \text{Ventricular radius (r)}}{\text{Ventricular wall thickness (h)}} \quad (1.19)$$

On a beat-to-beat basis, afterload is a function of P_s. On a chronic basis, cardiac remodeling (e.g., ventricular dilation and/or wall thickening) also affects afterload. Thus, beat-to-beat afterload is determined by events outside of the heart (i.e., mean arterial pressure and pulse pressure). Afterload has an inverse relationship with stroke volume (Figure 1.6). As afterload increases, stroke volume deceases, and vice versa. In theory, changes in afterload have a minimal effect on external cardiac work (area within the pressure-volume loop). A way to think about afterload is that it reflects the distribution of external cardiac work between generation of pressure and ejection of volume. As the heart is required to generate a higher systolic pressure (i.e., higher afterload), less work is leftover for the ejection of stroke volume.

Contractility, also known as inotropic state, represents the intrinsic contractile state of the heart independent of preload and afterload. On a beat-to-beat basis, contractility is largely a function of the amount of sympathetic (β) influence on the heart. Contractility is also affected by the diseases of the myocardium, cardiac drugs, and cardiac mass. Changes in cardiac mass through cardiac hypertrophy have a direct effect on the global contractility of the heart. Contractility has a direct relationship with stroke volume (Figure 1.7). The greater the contractility or inotropic state, the greater the stroke volume. On a pressure-volume loop, contractility is reflected by changes in the slope of the end-systolic pressure-volume relationship (ESPVR). The net result is a change in the ESV for given loading conditions.

Through the effects of preload, afterload, and contractility, maintenance of cardiac output is a complex interaction of acute and chronic physiologic and pathophysiologic changes in the heart and circulation (Figure 1.8). Understanding these interactive relationships is important for troubleshooting and managing cardiovascular function in the clinical setting.

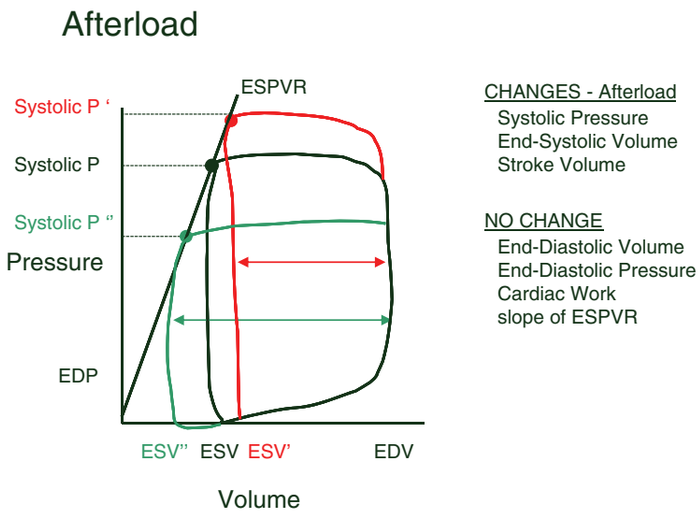


Figure 1.6 Cardiac Afterload

Heart Failure

Heart failure is present when cardiac output is inadequate despite adequate ventricular end-diastolic pressures or when adequate cardiac output can only be maintained at the expense of elevated end-diastolic pressures. Heart failure results from the combined effects of acute or chronic cardiac insufficiency and compensatory neuroendocrine mechanisms. Heart failure manifests as either organ dysfunction secondary to low cardiac output (termed *low output heart failure* or *forward heart failure*) or congestion of organs behind the heart (termed *congestive heart failure* or *backward heart failure*), or both (Figure 1.9). Congestion is manifested behind the left heart by pulmonary edema or pleural effusion; or behind the right heart as ascites, peripheral edema, or pleural effusion.

The stretch or load on myocardial fibers just prior to contraction profoundly influences the degree of myocardial fiber shortening. This load or stretch prior to contraction is the cellular basis of preload. *End-diastolic pressure* in the heart reflects the amount of stretch or preload on the ventricle prior to contraction and in turn are an important determinant of cardiac output. The *Frank-Starling curve* describes the direct relationship between cardiac output and end-diastolic pressures in the heart.

Cardiac output and ventricular end-diastolic pressure are not only functionally related, but are the physiologic parameters directly responsible for the two adverse manifestations of heart failure; namely,

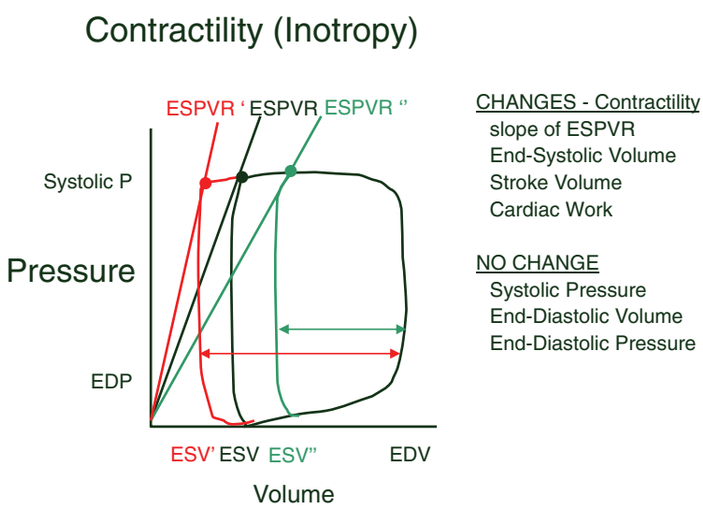


Figure 1.7 Cardiac Contractility

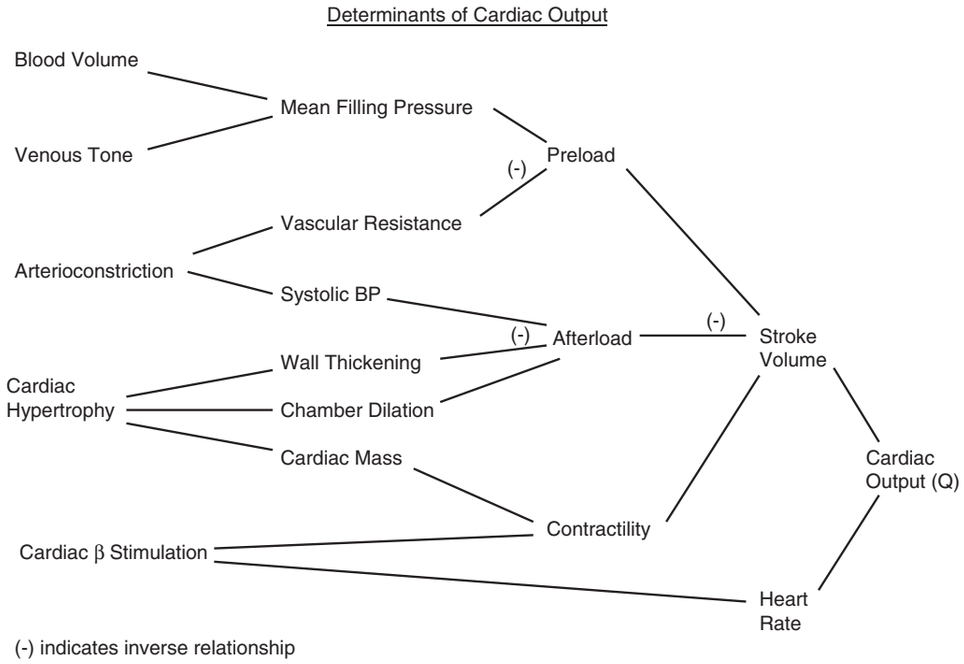
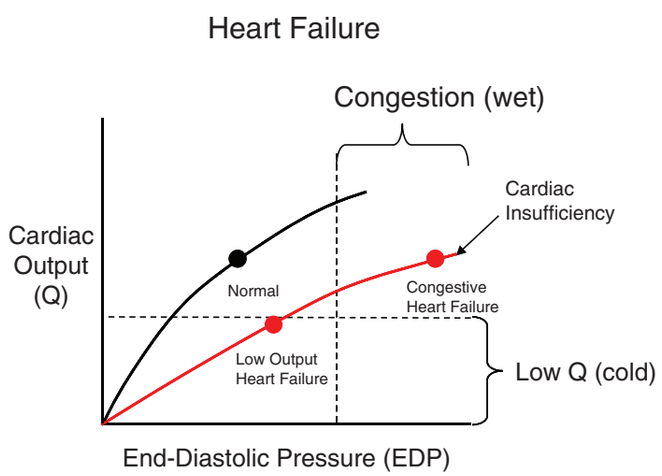


Figure 1.8 Determinates of Cardiac Output

inadequate perfusion and congestion. Initially, impaired cardiac function narrows the cardiac reserve (i.e., the ability to increase cardiac output during activity or exercise). The clinical manifestation is exercise or activity intolerance. Eventually, cardiac output can become low enough that it fails to meet metabolic needs of organ systems and tissues even at rest. If this happens acutely, the patient may manifest low output heart failure. Organ and tissue dysfunction become apparent. The patient is "cold" rather than "warm." While ventricular end-diastolic pressure exerts a positive influence on cardiac output, it also is the effective downstream pressure that resists venous return to the heart. Congestion occurs when end-diastolic pressure elevates capillary hydrostatic pressure to the point where a net efflux of water from capillaries to the interstitial space occurs. The result is edema of the organs and tissues behind the failing heart. The patient is "wet" rather than "dry."

Cardiac insufficiency is caused by one or a combination of four basic mechanisms: *primary myocardial failure*, *hemodynamic overload*, *diastolic dysfunction*,

Figure 1.9 Heart Failure



or *cardiac arrhythmias*. Progression of heart disease can be arbitrarily divided into three phases. The first phase of heart disease occurs when an initiating cardiac injury or insufficiency is present. If the initiating cardiac insufficiency is acute and overwhelming, then *low output heart failure* may ensue. More often in animals the cardiac insufficiency is not initially overwhelming or lethal, but rather slowly progressive. In this case, the presence of heart disease may be signaled only by the presence of physical findings such as abnormal heart sounds or murmurs, and not be associated with overt symptoms of heart failure other than possible activity or exercise intolerance.

The second phase of heart disease is hallmarked by activation of the *neuroendocrine response* to cardiac insufficiency. This neuroendocrine response ensures that blood pressure and cardiac output are maintained principally through the retention of vascular blood volume and the constriction of arteries and veins. *Cardiac hypertrophy* generally begins during this phase, particularly when the initiating cardiac insufficiency results from hemodynamic overload. The type of cardiac hypertrophy depends on the nature of the cardiac insufficiency. During this phase, clinical evidence of cardiac insufficiency in the form of cardiomegaly occurs, although overt signs of heart failure still may not present. Symptoms would still be mostly associated with reduced activity or exercise capacity.

Although the neuroendocrine response is initially adaptive, ultimately this response becomes maladaptive. This is the third phase of heart failure. During this phase, the neuroendocrine response "overcompensates," producing high end-diastolic pressures primarily through the retention of blood volume. The result is congestion in the form of tissue and organ edema. Inappropriate arterioconstriction is also present during this phase, contributing to poor tissue perfusion. This state is termed *congestive heart failure*. It is possible in advanced cases of cardiac insufficiency for both congestive heart failure and low output heart failure to be present.

Summary

Adequate cardiopulmonary function is dependent on sequential physiologic processes to achieve the ultimate goal of delivering oxygen to tissues. Derangement of any of these physiologic processes can result in inadequate oxygen delivery. Success in thoracic surgery often depends on quickly pinpointing and correcting disruptions in oxygen delivery. Fortunately, techniques for determining the cause(s) and magnitude of pathophysiologic disruptions in the cardiopulmonary system are readily available to the clinician with an understanding of these processes.

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