CHAPTER 134  OXYGEN THERAPY
AND BASIC RESPIRATORY CARE
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THE CHEMISTRY OF OXYGEN

Oxygen in air exists in a diatomic molecular form (O₂), molecular weight [MW] 16 g/mol; that, at standard temperature and pressure, is a colorless, odorless gas. The diatomic molecular state is the form that we administer to our patients as a respiratory gas, either pure oxygen or in mixtures with air or helium (heliox), and is that form most commonly referred to as oxygen. While the gaseous state of oxygen is most clinically relevant, it can be found in a liquid and solid state as well under appropriate conditions. However, molecular oxygen has additional chemical states that expand its impact on human physiology. The diatomic form ("oxygen") is essential for aerobic metabolism in animals but is toxic to obligate anaerobic organisms (a fact exploited in hyperbaric oxygen therapy). The triatomic form, ozone, is produced continuously by ultraviolet (UV) radiation in the upper layers of the atmosphere, and serves to shield the earth’s surface from UV radiation. However, ozone is also produced by the immune system as an antimicrobial defense. Finally, singlet oxygen (several different forms exist) is a high-energy state of molecular oxygen in which all the electron spins are paired, resulting in extreme instability and exceptional reactivity toward common organic molecules. Such oxygen-free radicals, as they are collectively termed, have varied and increasingly important physiologic roles; therefore, their role in both normal and pathologic processes must be recognized and understood to allow the correct application of oxygen therapy.

In this chapter, we will discuss the various modalities for oxygen delivery in the critical care setting. In addition, we will address oxygen’s diverse physiologic and possible pathologic effects, but in our discussion of oxygen-free radicals, we will confine it to their role in oxidative lung injury, while being cognizant of their potential impact on all tissues.

OXYGEN THERAPY DEVICES

Oxygen therapy is one of the basic modes of respiratory care. Yet, despite the fact that oxygen has been delivered to patients with lung disease for almost a century, it is commonly delivered in imprecise concentrations. Because oxygen is “invisible,” it has often been downgraded to a position considerably less than the powerful drug that it is.

Delivery devices for oxygen therapy are typically classified into two groups: variable flow or fixed-flow equipment. The term variable flow relates to the fact that as the patient’s respiratory pattern changes, delivered oxygen is diluted with room air. This results in a widely inconsistent and fluctuating fraction of inspired oxygen concentration (FiO₂). In fact, despite some commonly published figures for delivered FiO₂ at given flow rates, the actual FiO₂ delivered to the patient by various devices is neither precise nor predictable. Variable flow devices include nasal catheter, nasal cannulae, transtracheal oxygen catheter, and various oxygen masks.

Fixed-flow equipment, on the other hand, provides the entire patient’s inspired gas with a precisely controlled FiO₂; when applied appropriately, the FiO₂ delivered to the patient is therefore constant, regardless of ventilatory pattern. Fixed-flow devices include air-entrainment masks, large-volume aerosol systems, and large-volume humidifier systems.

The following describes various oxygen delivery equipment and their proper placement, possible problems, and overall performance.

Variable Flow Equipment

Nasal Catheter

Description. The nasal catheter is the simplest oxygen delivery device. It is a soft, plastic, blind-end tube with numerous side holes at the distal tip. Nasal catheters typically come in French sizes, which is a reference to the outside diameter (OD) of the device. A French (Fr) size is three times the OD in millimeters, with typical adult sizes being 12 Fr to 14 Fr. Oxygen is delivered to the nasal catheter from a bubble humidifier through the oxygen tubing.

Placement. Before use, the catheter should be liberally lubricated with a water-soluble lubricant. The catheter is placed in the external naris and advanced along the floor of the nasal cavity into the oropharynx, stopping just behind the uvula. The appropriate size can be determined by inspection of the external naris and by measurement of the distance between the tip of the nose to the ipsilateral external ear.

To achieve proper placement, use a tongue blade and flashlight to observe the posterior pharynx, and then advance the catheter into the nasopharynx until it appears below the uvula. After identifying the catheter tip, withdraw the catheter until the tip of the catheter is no longer seen. Once proper placement is achieved, the catheter should be secured to the nose with tape.

Problems. Pain and discomfort during insertion have been described. In the presence of nasal pathologic conditions, including nasal polyps, deviated septum, and nasal congestion, placement may be particularly traumatic or impossible. Bleeding
can occur resulting from mucosal irritation. For this reason, patients with coagulation disorders should not have a nasal catheter placed.
When in place, routine changing of the catheter is required to prevent blockage of the side holes with secretions in addition to subsequent reduction of oxygen flow.

Performance. Nasal catheters have been used for adults as well as infants (1). In adults, nasal catheters provide a relatively low FiO₂. The increase in FiO₂ through the nasal catheter is directly related to gas flow, and is enhanced at low flow rates by using the nasopharynx and oropharynx as a reservoir for oxygen. Accordingly, at flow rates of 6 to 10 L/minute, an FiO₂ of 0.69 to 0.82 can be delivered to the patient (2). However, like all variable performance equipment, delivered FiO₂ will vary with a change in respiratory rate or tidal volume.
The major advantage of using a nasal catheter is that it can be securely placed in obtunded patients. However, due to a long list of disadvantages, including discomfort, difficulty in insertion, and bleeding, nasal catheters are infrequently used today.

Nasal Cannula
Description. The nasal cannula is the most frequently utilized oxygen delivery device. It consists of a blind-end tube with two protruding “nasal prongs” that rest in the external nares. Cannulae come in a variety of designs for more comfortable or subtle application. Regardless of the design, the principle of oxygen delivery is the same. Cannulae are connected to an oxygen flowmeter through oxygen tubing without a humidification device for flow less than 4 L/minute and with a bubble humidifier for higher flow rates to prevent nasal drying (3).

Placement. Nasal cannulae are easily placed regardless of the type and brand.

Problems. The nasal cannula is relatively problem free. However, short-term use can result in drying of the nasal mucosa, while long-term use can cause pressure sores above the ears, under the chin, and above the upper lip. Gauze or foam padding can be placed between the cannula and irritation sites to limit this complication.

Performance. A nasal cannula is used with oxygen flow rates of 1 to 6 L/minute in adults and as low as 0.16 L/minute in infants. The exact FiO₂ delivered with a nasal cannula has been measured and estimated using a variety of methods and, as expected, yielded a variety of results.

An earlier method to predict FiO₂ through variable performance equipment and using a host of assumptions demonstrated a wide range of FiO₂ values delivered by nasal cannula at any given constant flow of oxygen (4). Another study in FiO₂ delivery through the nasal cannula utilized a model of the respiratory system (5). The model consisted of a lung placed inside a rigid container and attached to a rubber test lung through tubing that approximated tracheal volume. A ventilator producing a sine wave was connected to the container, and inspiratory flow varied from 12 to 40 L/minute at a constant rate and volume. The study illustrated that delivered FiO₂ varied 13% to 40% at a given oxygen flow when inspiratory flow varied from 12 to 40 L/minute.

The nasal cannula is commonly used as the first means to deliver oxygen to patients requiring long-term therapy. In theory, the nasal cannula increases FiO₂ by 0.08 for every liter of oxygen flow. Flow is typically set between 1 and 6 L/minute. Flow above 6 L/minute adds little to increased FiO₂ and may induce patient discomfort, including nasal mucosa dryness and bleeding.

Oxygen-conserving Devices
The wide use of nasal cannulae led to recognition of an important device limitation. Since there is lack of synchronization between the patient ventilation and continuous flow of oxygen through the cannula, there is wasted oxygen flow to the room during expiration. In an attempt to eliminate this waste and reduce the cost of oxygen delivery, several device modifications have been developed. However, the mechanism of oxygen conservation has centered on two main concepts.

Reservoir Cannula
Description. These devices use a mechanical reservoir that fills with 100% oxygen during exhalation and empties the oxygen into the lungs early in inspiration. This was achieved through the use of a collapsible chamber that empties on inspiration and fills during exhalation.

Moustache-style Cannula. This is among the most widely available reservoir devices. The cannula contains a soft, inflatable reservoir with a volume of approximately 20 mL. During patient exhalation, oxygen flow fills the expandable reservoir. Then, during early inspiration, the patient inspires first from the reservoir, causing the reservoir to begin to empty, and from the continuous flow once the reservoir is depleted.

Placement. The reservoir cannula rests directly beneath the nose.

Problems. The moustache-style cannula is larger, heavier, and more obvious than the traditional cannula. Hence, it is more obtrusive, and many patients in need of O₂ therapy at home may prefer not to wear it in public.

Performance. As expected, the reservoir cannula can achieve oxygenation equivalent to a conventional nasal cannula, but at a lower flow rate.

Pendant Reservoir Cannula
Description. The pendant reservoir cannula (Fig. 134.1) uses a pendant-like reservoir that is worn on the chest with a larger-diameter cannula and connecting tubing. The pendant contains an inflatable reservoir with a volume of approximately 40 mL that forces gas up the cannula tubing during expiration. Subsequently, during early inspiration, the gas stored in the tubing acts as a reservoir of oxygen, but as inspiration continues, the cannula begins to function like a conventional cannula.

Overall, most of the benefit appears to be derived from the oversized tubing between the patient and the pendant (6).
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FIGURE 134.1. Pendant reservoir cannula.

Placement. The pendant reservoir is placed to the patient in a manner similar to a conventional cannula.

Problems. Tubing size makes the pendant cannula more prominent but less so than the moustache-style cannula.

Performance. Like the moustache-style cannula, the pendant reservoir cannula is capable of providing similar or higher oxygenation at the flow used with a conventional cannula (6). The cannula reservoir contains close to 80% oxygen at a flow rate of 0.5 L/minute, but increases to nearly 100% oxygen at a flow rate of 1 L/minute (7,8). In addition, at an inspiratory-to-expiratory ratio of 1:2 and a respiratory rate of 20 breaths/minute, the most efficacious FiO$_2$ delivery will occur during the first 0.5 seconds of the inhalation (7,8).

Various studies compared the efficacy of reservoir cannulae with that of standard cannulae, and consistently indicated that the reservoir cannula at flow rates of 0.5, 1, and 2 L/minute will yield an FiO$_2$ equivalent to that delivered by flow rates of 2, 3, and 4 L/minute by the standard nasal cannulae, respectively (7,8).

Electronic Demand

Pulsed-dose Oxygen Delivery

Description. Pulsed-dose oxygen therapy can be used in conjunction with a cannula, reservoir cannula, or transtracheal catheter. Pulsed-dose oxygen systems work by detecting patient effort and only provide gas during the early portion of inspiration (9,10).

During expiration, the demand device is referenced to the atmospheric pressure. Once the flow sensor detects patient effort, a solenoid valve opens and provides a “pulsed dose” of oxygen at the preselected flow setting. The pulsed dose is usually set to begin with every inspiratory effort or every second or third breath. The goal of these devices is to reduce oxygen usage while maintaining inspired oxygen concentration at a level that provides adequate oxygen saturation.

One of the major concerns about such devices is the effect of exercise and tachypnea on oxygen saturation. A device that produces adequate oxygen saturation while the patient is at rest may not produce adequate oxygen saturation when the patient is walking or becomes ill.

Placement. Pulsed-dose devices can be connected to any oxygen outlet, including cylinders and liquid oxygen systems. The device takes the place of a standard flowmeter or incorporates the flowmeter into the design.

Problems. Possible problems with such devices include displacement and improper sensing of patient effort. However, the device design incorporates an automatic alarm and default mechanism to allow continuous flow if patient effort is not sensed over a designated period. Also, the cost for the device can be a concern and must be weighed against the potential savings in oxygen usage.

Performance. Depending on the size and frequency of the oxygen pulse, the savings of such a device could be 4 to 1 or 7 to 1 compared with continuous flow oxygen. Equivalent oxygenation can also be accomplished at lower flow rates (10). On the other hand, it is important to remember that desaturation may occur in many patients during exercise. Hence, to ensure adequate oxygenation, they should be tested during various activities.

Transtracheal Oxygen Catheters

Description. Transtracheal oxygen catheters deliver oxygen directly into the trachea through small-bore catheters (Fig. 134.2). Direct delivery into the trachea prevents dilution of oxygen with room air, as seen with other appliances, and fills the upper respiratory tract with oxygen.

Placement. Under sterile technique and local anesthesia, a small incision is made in the skin. A tracheal stent is advanced through the incision into the trachea. This stent remains in place for 7 to 10 days to facilitate a permanent tract formation. Afterward, the stent is removed over a guidewire and a 9 Fr (3.0-mm OD) catheter is inserted over a guidewire and secured in place with external flange.

Problems. Problems may include subcutaneous emphysema, infection, hemoptysis, and malposition. However, the most common problem is mucous obstruction with a mucous ball at the tip of the catheter. Routine cleaning of the catheter with instillation of saline and a cleaning rod can help in avoiding such problem.

Performance. Transtracheal systems have been shown to increase oxygenation compared with conventional oxygen...
therapy with a nasal cannula at equivalent flow rates, or can provide equivalent oxygenation at lower flow rates (11). Patient acceptance is also reportedly improved because of the relatively hidden appearance of the equipment. Reduced oxygen usage, reduced costs, and increased life of portable gas sources have all been reported with transtracheal oxygen therapy. The use of transtracheal oxygen therapy can reduce required oxygen flow by close to 50% (12). The latter may even be enhanced with the additional use of demand pulsed-dose oxygen that can further increase the savings.

Masks

Simple Mask

Description. The simple mask is a disposable, lightweight plastic that increases FiO$_2$ by increasing the available reservoir by adding the volume of the mask. Oxygen is delivered to the mask through standard oxygen tubing at a flow rate of 5 to 12 L/minute. The mask allows room air to be drawn in around the mask edges and through side ports. A bubble humidifier may be used to provide comfort, especially with prolonged use.

Placement. Simple masks are held in place over the patient’s nose and mouth with an adjustable elastic strap.

Problems. Patients wearing a mask may complain of claustrophobia or pain at the site of mask application. Also, it can interfere with eating and drinking.

Performance. Since it is a variable performance device, the actual FiO$_2$ delivered varies with mask fit, oxygen flow, and certainly patient respiratory effort. This was first suggested in a study by Bethune and Coffis (13), who investigated the relation of the flow and rebreathing of carbon dioxide (CO$_2$). They were able to demonstrate that, at flow rates of 1 to 8 L/minute and tidal volume of 500 mL, an FiO$_2$ of 0.21 to 0.60 can be delivered. However, at the same flow rates but at a tidal volume of 1,200 mL, only an FiO$_2$ of 0.21 to 0.43 was delivered. It is generally stated that a minimum flow of 5 L/minute is necessary to prevent rebreathing of CO$_2$ (14).

Partial Rebreathing Reservoir Mask

Description. Partial rebreathing reservoir masks are simple masks that are fitted with an additional 600- to 800-ml reservoir that extend below the patient’s chin. Oxygen flow is provided from a bubble humidifier at a flow that keeps the reservoir bag at least half full during inspiration (usually 8–15 L/minute). In addition, during expiration, the first third of expired gas enters the reservoir bag, hence the term, partial rebreather. This is gas from the anatomic reservoir, so it is high in oxygen and contains little CO$_2$. As the bag fills from the oxygen flow and first third of expiration, the remaining expired gas exits the exhalation openings of the mask.

Placement. The partial rebreathing reservoir mask is held in place over the patient’s nose and mouth with an adjustable elastic strap.

Problems. As stated above, flow must be adjusted as patient demand changes to ensure minimal FiO$_2$ delivery.

Performance. At flow rates of 6 to 10 L/minute, the partial rebreathing mask delivered FiO$_2$ values from 0.35 to 0.70 (15).

Nonrebreathing Reservoir Mask

Description. The Nonrebreathing Reservoir Mask incorporates one-way valves over one of the mask side ports and above the reservoir bag. The one-way valve over the reservoir bag prevents expired gas from entering into the bag. In addition, the one-way valve over the side port limits further entrainment of room air during inspiration, except if gas flow is inadvertently disconnected.

Placement. The nonrebreathing mask is held in place over the patient’s nose and mouth with an adjustable elastic strap.

Problems. In addition to previously mentioned shortcomings of masks, the combined effects of time and moisture can cause one-way valves to stick in either the open or closed position.

Performance. The nonrebreathing mask requires minimum oxygen flow of 10 to 15 L/minute to prevent the reservoir bag from collapsing during inspiration. With that flow rate, it is estimated that an FiO$_2$ of 0.60 to 0.80 is delivered with a nonrebreathing mask (15). A FiO$_2$ of 0.57 to 0.70 is delivered when oxygen flow can be set greater than the patient minute ventilation. Contrary to common belief, FiO$_2$ values near 1.0 cannot be achieved using the commonly available disposable nonrebreathing masks.

Fixed-performance Devices

Air-entrainment Masks

Description. An air-entrainment mask consists of the mask, a jet nozzle, and entrainment ports. Oxygen under pressure is
The mask is secured to the patient's face with an adjustable, elastic band.

**Problems.** The most important problem associated with the air-entrainment mask is obstruction of the entrainment port by various objects. This decreases total flow perceptibly and increases FiO₂.

**Performance.** The air-entrainment mask requires FiO₂ values <0.30 to maintain total flow 30% greater than peak inspiratory flow and continue to function as a fixed-performance system. At higher FiO₂, the total flow falls below 40 L/minute, and the air-entrainment mask becomes a variable performance device. The latter may occur if patient demand for flow increases and room air is drawn in around the mask (18). Thus, the air-entrainment mask is intended for patients with high or changing ventilatory demands, such as patients with chronic lung disease who may hypoventilate when exposed to high FiO₂ values.

**The OxyMask**

**Description.** The OxyMask is a recently introduced oxygen face mask for both hospital and home use. It uses a small diffuser to concentrate and direct oxygen toward the mouth or nose. This unique design enables the OxyMask to deliver oxygen more efficiently than a Venturi mask, especially in patients with chronic hypoxemia.

**Placement.** The mask is secured to the patient’s face with a comfortable oxygen delivery (Fig. 134.3). The oxygen diffuser can be directed toward the nose or mouth; however, it does not come in contact with either one. Consequently, the OxyMask will not interfere with various activities such as eating and talking.

**Performance.** A recent study compared the OxyMask versus the Venturi mask in 26 oxygen-dependent patients with chronic, stable respiratory disease in a randomized, single-blind, cross-over design (20). Oxygen delivery was titrated to maintain an oxygen saturation (SaO₂) 4% to 5% and 8% to 9% above baseline for two separate 30-minute periods of stable breathing. Oxygen flow rate, partial pressure of inspired and expired oxygen (PO₂), and transcutaneous PCO₂ were recorded. The study reported lower oxygen flow rates, higher inspired PO₂, and lower expired PO₂ while using the OxyMask. In addition, minute ventilation and inspired and expired PCO₂ were significantly higher while using the OxyMask, whereas transcutaneous PCO₂, heart rate, and the ratio of nasal to oral breathing did not change significantly throughout the study. The study concluded that oxygen is delivered safely and more efficiently by the OxyMask than by the Venturi mask in stable oxygen-dependent patients.

**Table 134.1**

<table>
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<th>FiO₂ Setting</th>
<th>Minimum Oxygen Flow (L/min)</th>
<th>Entrainment Ratio O₂:AIR</th>
<th>Total Flow (L/min)</th>
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<tr>
<td>0.70</td>
<td>12</td>
<td>1:0.6</td>
<td>19</td>
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</tbody>
</table>

**FIGURE 134.3.** The OxyMask.
Large-volume Aerosol and Humidifier Systems

Description. Large-volume aerosol systems use air-entrainment nebulizers alone or in tandem to provide gas to face masks, T-pieces, and tracheostomy collars. Nondisposable aerosol systems usually offer FiO$_2$ values of 0.40, 0.60, and 1.0, whereas disposable systems offer continuous adjustments, with six to eight settings calibrated from 0.28 to 1.0. These systems use a constant jet nozzle with a changeable size entrainment port to modify FiO$_2$.

Placement. Placement varies with the device used. Most systems use an elastic band that attaches the device around the head or neck, while the T-piece connects directly to the artificial airway.

Problems. The most common problem with the system is inadequate flow. Other common problems include the presence of water condensation in the delivery tubing that prevents room air entrainment and increases delivered FiO$_2$. In general, if mist from the aerosol escapes the oxygen delivery device during inspiration, flow is generally considered sufficient.

Performance. Under conditions of high patient ventilatory demand, these systems become variable performance devices (22). With decreased flow, room air becomes entrained in the mask, and therefore, despite the increase in set FiO$_2$ values, delivered FiO$_2$ decreases. Accordingly, when precise FiO$_2$ values are necessary at a high flow rate, a high-volume humidifier system is preferred. If delivery of oxygen is required in excess of 100 L/minute, a blender, air–oxygen flowmeter, or even a Venturi system can be used and directed through a heated humidifier. A reservoir is usually placed between the humidifier and the patient.

MIXING AIR AND OXYGEN

Oxygen Flowmeters and Blenders

Various commercially available oxygen flowmeters (Fig. 134.4) can be used to deliver precise oxygen concentrations. Gas is delivered from air and oxygen flowmeters and passes through a humidifier before being delivered to the nasal cannula or mask.

Air–oxygen blenders (Fig. 134.5) are more expensive compared with using two flowmeters, but with a 50-psig (pounds-force per square inch gauge) source, they can deliver more precise FiO$_2$ values. In general, blenders have three separate compartments where different functions are performed: the alarm, pressure-balancing, and proportioning compartments.

Air and oxygen enter the alarm compartment from two separate inlets. If the pressure differences between the two inlets are greater than 10 psig, the accuracy of FiO$_2$ will be compromised and a high-pitched alarm will sound (23). The pressure-balancing compartment will then use a diaphragm to balance the air and oxygen pressures. Finally, at the proportioning compartment, air and oxygen at similar pressures are adjusted in proportion to the desired FiO$_2$.

Postextubation Respiratory Therapy

Postextubation pulmonary complications are major causes of morbidity and mortality among intensive care unit (ICU) patients, especially after thoracic or upper abdominal surgeries. During normal respiration, healthy individuals inspire approximately ten times each hour and take large intermittent breaths—“sighing”—that are three times the normal tidal volume (24). However, postoperatively, such deep breaths are absent and replaced with a shallow, monotonous breathing pattern that decreases ventilation to the dependent lung regions, contributing—with the use of postoperative higher FiO$_2$—to the development of atelectasis. Factors such as residual
anesthetic effects and incisural pain promote decreased resting lung volume. Furthermore, assuming a prolonged postoperative recumbent position, the diaphragmatic movement is limited and the functional residual capacity (FRC) decreased (25). The diminishing expiratory lung volume decreases lung compliance and eventually increases the elastic work of breathing. To minimize this work, patients take shallow, frequent breaths, which may further decrease lung volume (23). The primary goal of postoperative respiratory therapy is to increase FRC, reducing pulmonary atelectasis and their related complications.

A slight elevation of temperature and decrease in breath sounds over the lung bases may be useful in diagnosing atelectasis. However, these means are insensitive in detecting decreases in FRC. In addition, the large decline in the amount of air that can be maximally forced out of the lungs after a maximal inspiration (forced vital capacity [FVC]) and the forced expiratory volume in the first second (FEV₁) that occur after upper abdominal operations are patient effort dependent and cannot accurately predict a decrease in FRC. The same can be true regarding the interpretations of portable chest roentgenography in ICU patients, which is useful for identifying patients with atelectasis but does not predict FRC.

The use of postextubation positive pressure devices has been part of respiratory therapy management since intermittent positive pressure breathing (IPPB) was first introduced over 50 years ago (26). In addition to the incentive spirometer (IS), there are many positive pressure devices from which to choose; these include IPPB, continuous positive airway pressure (CPAP), positive expiratory pressure (PEP), and nasal intermittent positive pressure ventilation. In this section, we will review the physiologic effects and limitations relating to the use of the IS and IPPB. However, the use of CPAP and noninvasive intermittent positive pressure ventilation will be discussed in detail elsewhere in this textbook.

Incentive Spirometer

Description. Compared to many other therapeutic maneuvers and devices that have been used to prevent postoperative pulmonary complications, the IS has gained the most popularity for its simplicity, and currently is a common mode of postoperative respiratory therapy worldwide. The IS is designed to mimic natural sighing or yawning by encouraging the patient to maximally inflate the lungs and sustain that inflation. This is accomplished by using a device that provides patients with visual or other positive feedback when they inhale at a predetermined flow rate or volume and inspiratory time, the latter usually targeted at 3 seconds (27). The prolonged and forced lung inflations open collapsed alveoli, preventing or resolving atelectasis. Since the re-expanded alveoli remain inflated during expiration, the FRC increases.

Placement. The IS mouthpiece is placed in the mouth with the lips tightly sealed around it. The IS should be used five to ten times a day (27). Problems. The IS use may lead to discomfort secondary to inadequate incisural pain control and hypoxia secondary to interruption of prescribed oxygen therapy if a face mask or shield is being used. Furthermore, the IS is generally ineffective unless closely supervised or performed as ordered. In addition, although uncommon, it might result in barotrauma in patients with severely emphysematous lungs.

Performance. Four trials with 443 participants contributed to a recent Cochrane Database of Systematic Review about the benefits of the IS (28). In that review, there was no significant difference in pulmonary complications (atelectasis and pneumonia) between treatment with the IS and treatment with other positive pressure breathing techniques (CPAP, bilevel positive airway pressure [BiPAP], and IPPB), regardless of preoperative patient education. In addition, patients treated with the IS had worse pulmonary function and arterial oxygenation compared with positive pressure breathing (CPAP, BiPAP, IPPB). However, in view of the small number of patients in the included studies and the multiple methodologic and reporting shortcomings, these results should be interpreted cautiously.

Intermittent Positive Pressure Breathing

Description. IPPB is used in clinical practice, primarily to improve the lung volumes and to decrease the work of breathing. However, its role in clearing excessive secretions from the lungs is questionable and controversial. Commercially available devices are most commonly used for the delivery of IPPB. In general, all these devices are powered by compressed gas—either air or oxygen (29). Short-term humidification can be added to the driving gas. Since IPPB is a pressure-cycled device, the operator can select the pressure and flow rate of the gas and the sensitivity for the patient to trigger the system. Upon inspiration, a negative pressure is generated in the circuit, and inspiratory flow proceeds until the preset pressure is attained when flow ceases and the patient expires passively. The operator should adjust the machine settings until a desired maximal volume is delivered to the patient, in general “reyehalled” (to 1 inch of chest excursion or approximately 6 to 8 mL/ideal body weight in kilograms (30,31).

Placement. The patient is connected to IPPB through a mouthpiece. The patient needs to be cooperative and spontaneously breathing to trigger the machine using the mouthpiece. Occasionally, a full face mask may be used for less conscious patients, as it is generally tolerated only for a brief period of time.

Problems. IPPB has been shown to increase tidal volume, and consequently minute ventilation, by passively ventilating the patient and hence improving arterial blood gases (29). However, this may lead to a decline in cardiac output as a result of increased intrathoracic pressure during delivery and decreased venous return.

Performance. A large body of literature has been published examining the efficacy of IPPB in different patient populations. The efficacy of IPPB in the management of chronic obstructive pulmonary disease (COPD) was found to be mainly unsupported (29). This can be partly explained by an inappropriate choice of patient populations, the frequency of IPPB used, and other confounding effects of concurrent chest physiotherapy techniques (32).

Another largely studied use of IPPB was in the prevention or management of postoperative respiratory complications (33). The comparative efficacy of IPPB with IS, deep breathing exercises, blow bottles, and physiotherapy has been studied.
Although this literature is overwhelmed by various methodologic problems, their outcomes demonstrated that the use of IPPB conferred no added benefit to patients following abdominoal or cardiac surgery when compared to the other modalities (29). However, it is conceivable that in patients with excessive secretions, IPPB may need to be combined with gravity-assisted drainage and chest wall vibrations for more effective upward clearing of secretions (29).

The use of IPPB has declined over the past two decades, partly due to controversial research outcomes and partly as a result of the introduction of newer modes of positive pressure support. However, IPPB may still have a role—though reduced—in the management of patients with reduced lung volumes and respiratory insufficiency who cannot cooperate well with the use of IS.

**OXYGEN: THE PHYSIOLOGIC IMPACT**

**The Fate of Oxygen in the Body**

The predominant metabolic pathway for oxygen is as an electron acceptor in oxidative phosphorylation within the mitochondria (34). Oxidation of glucose and fatty acids shuttles electrons to special molecular carriers, which are either pyridine nucleotides or flavins within the mitochondria. The reduced forms of these carrier proteins, in turn, donate their high-potential electrons to molecular oxygen by means of an electron transport chain located in the inner membrane of the double-enveloped mitochondria. The transmembrane proton gradient generated as a by-product of this electron exchange and associated liberation of a large amount of free energy drives the synthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and inorganic phosphate (P). Of the four protein complexes that form the electron transport chain, complex IV, also known as cytochrome c oxidase, is responsible for the transfer of four electrons, along with four hydrogen ions, to reduce molecular oxygen to two molecules of water. Cytochrome c oxidase has an extremely complex structure and contains 13 subunits, two heme groups (cytochrome a and cytochrome a3), and multiple metal ion cofactors (three atoms of copper, one of magnesium, and one of zinc).

Although the transfer of four electrons and four protons reduces oxygen to water, the transfer of one or two electrons produces superoxide anion ($\bullet O_2^-$) and peroxide ($O_2^{2-}$), respectively. This occurs in about 1% to 2% of all cases (35). Superoxide anions need an additional electron to make them more stable, so they steal an electron from the nearest source such as mitochondrial DNA, the mitochondrial membrane (lipid peroxidation), protein, reductants such as vitamins C or E, or nonenzymatic antioxidants such as glutathione or thioredoxin. If too much mitochondrial damage occurs, the cell undergoes apoptosis, or programmed cell death (Fig. 134.6). The majority of superoxide anions produced is converted to hydrogen peroxide in the mitochondrial matrix or cytosol by one of three versions of superoxide dismutase. Hydrogen peroxide ($H_2O_2$) is a more stable compound; however, it also can cause cellular damage as a result of its further reduction to hydroxyl radicals ($\bullet OH$) by a series of iron-catalyzed reactions (36).

Oxygen-free radicals are produced in pulmonary smooth muscle cells, endothelial cells, alveolar cells, and leukocytes residing in the lungs. They are produced by both enzymatic and nonenzymatic (auto-oxidation) reactions. Enzymes capable of forming superoxide radicals include xanthine oxidase,

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**FIGURE 134.6. Oxidant and antioxidant systems.**
arachidonic acid peroxidases, nitric oxide synthase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and nicotinamide adenine dinucleotide (NADH) oxidase (37,38). All of these enzymes are essential to the biochemical function of the cell. Phagocytic cells in the lung, such as neutrophils and alveolar macrophages, can form large quantities of superoxide anions during “respiratory bursts” (39,40). The most significant sources of free radicals in lung tissue are the mitochondria and endoplasmic reticulum, the sites of many of the aforementioned enzyme reactions.

The Antioxidants

To combat the excess accumulation of intracellular oxygen radicals, a system of enzymatic and nonenzymatic antioxidants exists in the lungs to prevent their formation and to facilitate the eradication of these reactive species (41,42). There are three primary enzymatic antioxidant systems, although other compounds serve as opportune scavengers. First is superoxide dismutase (SOD), which is found both intra- and extracellularly (42,43). It is present in the cytosol and the mitochondria on the plasma membrane surface, and in the extracellular plasma (44). The cytosolic form of SOD (CuZnSOD), which contains zinc and copper, is associated with pulmonary and endothelial vascular smooth muscle cells (45). The manganese-containing mitochondrial form (MnSOD) is abundant in pulmonary arterial smooth muscle and endothelium, and is felt to be the most active defense during times of pulmonary oxidative stress, catalyzing the dismutation of $\ddot{O}_2$ to $H_2O_2$.

Catalase and the glutathione antioxidant systems are the primary mechanisms for the reduction of hydrogen peroxide. Catalase is a hemoprotein found in peroxisomes that catalyzes the reduction of hydrogen peroxide to water. Its limited cellular distribution suggests that it has a specific role in managing hydrogen peroxide excess during inflammatory responses. The sulfur-containing antioxidant, glutathione, has a much broader distribution than catalase, and has been measured in the cytosol at millimolar concentrations (46). Exogenously administered glutathione has little effect on intracellular levels. However, N-acetylcysteine is a glutathione analogue capable of crossing the plasma membrane and enhancing glutathione activity, which may account for its purported beneficial effects in various forms of cellular injury. Glutathione peroxidase plays a role in eliminating lipid peroxides formed from free radical–altered lipid membranes (46). Glutathione peroxidase enhances the reduction of $H_2O_2$ by first oxidizing glutathione (in its reduced form, GSH) and donating the pair of electrons to hydrogen peroxide to form water. The oxidized glutathione disulfide (GSSG) is subsequently reduced in a reaction that transfers the protons from NADPH + $H^+$ (Fig. 134.7) (47). Glutathione reductase activity is dependent on NADPH generated from the hexose monophosphate shunt (48). The activity of the glutathione peroxidase enzyme in humans is also dependent on the trace element selenium. The absence of selenium in the diet will markedly reduce the efficacy of the glutathione peroxidase system.

![FIGURE 134.7. Hyperoxic cell death.](image-url)
Other elements with antioxidant capacity include the lipid-soluble vitamin E and the water-soluble vitamin C. Vitamin E (α-tocopherol) is a plasma membrane constituent thought to play a role in inhibiting oxidative cell membrane injury, possibly by interfering with surfactant synthesis (49). Its deficiency in critically ill patients may lead to a susceptibility to pulmonary oxygen toxicity. Vitamin C, or ascorbic acid, is found primarily in the extracellular space and, given its water solubility, is best suited to protecting the respiratory airway mucosa from pollutant oxidants. Other purported nonenzymatic antioxidants include uric acid, β-carotene, taurine, α-lipolic, and bilirubin. Newly discovered families of proteins, the thioredoxins, are located in the inner mitochondrial membrane of the airway epithelium. They may scavenge reactive oxygen species in response to oxidative stress and activate other intramitochondrial antioxidant systems such as MnSOD (50).

Pulmonary Oxygen Toxicity

It may appear paradoxical that oxygen could be a pulmonary toxin at nearly any concentration (51). The lung is well-prepared to cope with the insult when relatively low partial pressures of oxygen (e.g., 160 mm Hg at standard temperature and pressure (STP)) are breathed by virtue of the presence of abundant antioxidants. However, when these defense mechanisms are overwhelmed or depleted by prolonged exposure to an elevated POₐ, a progressive and potentially lethal inflammatory reaction takes place in the lungs (52).

Reactive oxygen species are cytotoxic to nearly all cells that constitute the respiratory system. This toxicity stems from two primary mechanisms. The first major mechanism, already mentioned, is lipid peroxidation, and the second is DNA damage. Polyunsaturated fatty acids are a major constituent of the plasma membrane and mitochondrial membrane envelope. Hydroxyl-free radicals derived from molecular oxygen destroy these fatty acids by cleaving hydrogen atoms. Protonated hydroxyl radicals form the radical intermediates, peroxides and peroxynitrites. Peroxides and peroxynitrites subsequently re- move hydrogen atoms from other fatty acids, initiating a destructive chain reaction that renders the plasma membrane porous (53,54).

Cellular DNA is at risk in the presence of reactive oxygen species. Hydroxyl radicals also damage DNA by directly hydroxylating guanine (55). Additionally, oxidant stress depletes nicotinamide nucleotides and disrupts the cellular cytoskeleton (56). Free radical attacks on DNA are known to produce nearly 100 lesions that include oxidation of bases and sugars, depurination, deoxyribonucleoside, and phosphodiester single- and double-strand breaks (57). It is controversial whether DNA strand breaks result directly from the attack of reactive oxygen species on DNA or are a consequence of nuclease activated during programmed cell death. Regardless, the reactive lipid compounds formed during lipid peroxidation by hydroxyl-free radicals are capable of cross-linking DNA proteins, compromising structural integrity (58). Such reactions induce cell death by a combination of apoptosis and cell necrosis, and interfere with protein synthesis and cell replication (59-61). Superoxides may also modify gene transcription by the activation of a potent regulator of gene transcription, the ubiquitous nuclear factor-κB (NF-κB) (62). It is unclear what impact this has on any specific protein synthesis, although one study provided some evidence of a negative feedback mechanism by inducing the expression of superoxide dismutase (63).

An additional primary target of oxygen-free radicals is pulmonary artery smooth muscle, resulting in vasoconstriction. Pulmonary artery smooth muscle contractility is affected through a variety of pathways, although most involve either the release of calcium from the sarcoplasmic reticulum or its sequestration via the enhanced activity of ATP-dependent Ca²⁺ uptake transporters. Superoxide anions also destroy nitric oxide produced by endothelial cells, in effect eliminating one of the most potent vasodilatory regulators in the lung (35).

A biphasal response to oxygen toxicity is seen in the lung. Initially, there is a proliferative phase where pulmonary artery endothelial cells replicate rapidly in response to the presence of superoxide anions. Superoxide anion production and release by these stimulated endothelial cells is far greater than that of quiescent endothelium. Thus begins a vicious cycle of superoxide radical generation and increased levels of exposure of surrounding lung parenchyma resulting in further DNA strand breakage, depletion of ATP, and enhanced membrane lipid peroxidation (64). This produces the inhibitory phase of endothelial proliferation. Other pulmonary cells such as bronchial and type I alveolar epithelial cells are also early victims in oxidant injury. Type I alveolar cells are replaced by hyperplasia of type II alveolar epithelial cells, resulting in the typical thickening of the alveolar epithelium seen in electron micrographs. Clara cells, which are nonciliated epithelial cells distributed throughout the airways and rich in cytochrome P450, are particularly sensitive to oxidant stress (65).

The Clinical Manifestations of Pulmonary Oxygen Toxicity

It is common to treat hypoxemia with supplemental oxygen to increase the inspired PO₂. However, the clinical consequences of continuous exposure to high partial pressures of inspired O₂ (PO₂) are directly related to the inflammatory reactions resulting from the cellular injury described above. While studies in animal models have clearly shown the damage to alveolar epithelial and vascular endothelial cells, the results in humans have been less conclusive. It is very likely that, in addition to species differences, there are genetic, environmental, and pathologic processes that modify the susceptibility to oxygen-related lung damage in humans that have not yet been elucidated.

Initial attempts to delineate the threshold for oxygen toxicity had their basis in military diving applications and during attempts to develop cabin atmospheres for manned space flight and underwater habitats in the 1960s and 1970s. In a series of experiments in hyperbaric chambers during this period, healthy divers were subjected to 28 to 30 days of breathing air under increased ambient pressure, with a target PO₂ of 0.31, 0.57, and 0.81 atmospheres (66). Of note, the air at sea level provides a PO₂ of 0.21 ATM. The results of many such studies suggested that the threshold for signs and symptoms of pulmonary oxygen toxicity occurred at approximately a PO₂ of 0.60 (67,68); thus arose the clinical dictum that an PO₂ of <0.60% should be the limit for prolonged oxygen therapy (69). However, it may not be accurate to extrapolate such studies in healthy divers

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to sick patients with pre-existing parenchymal disease or the systemic inflammatory response syndrome (SIRS).

Normal individuals breathing 100% O2 experience symptoms of tracheobronchitis within 12 to 24 hours (69). This initial phase of oxygen toxicity is marked by a decline in tracheobronchial clearance of particulates, substernal chest discomfort, tachypnea, and a nonproductive cough. Associated systemic symptoms include malaise, nausea, headache, and anorexia. While the decrease in particulate clearance may begin as early as 6 hours after such exposures, by 24 hours the vital capacity begins to decline significantly. Within 48 hours of exposure to 100% oxygen, decrements in static lung compliancex and carbon monoxide-diffusing capacity are measurable. In a study of patients with irreversible brain damage and ventilated with 100% FiO2, the alveolar-arterial gradient increased rapidly after 40 to 60 minutes. Continued exposure of the lungs to high partial pressures of oxygen ultimately contributed to the development of the acute respiratory distress syndrome (ARDS) accompanied by severe dyspnea and subsequent pulmonary fibrotic changes. Chest radiographic findings are nonspecific and show increased interstitial markings or alveolar consolidation similar to a number of other causes of diffuse alveolar damage.

Hypercapnia

The wisdom of administering high partial pressures of oxygen to patients with chronic hypercarbia continues to be a source of debate among clinicians. The concern has been that the patient with CO2 retention (e.g., COPD) relies predominantly on a hypoxic ventilatory drive and that increasing PaO2 by the administration of oxygen will result in depression of this stimulus and a dangerous drop in minute ventilation with a rise in PaCO2. PaCO2 has been observed to rise in a subset of these patients suffering acute exacerbations of their COPD when treated with 100% O2 (60). However, there have been several studies in both stable COPD and those with acute exacerbations that demonstrate only a transient decline in minute ventilation inadequate to explain the accompanying rise in CO2 (70–72). Another explanation for the rise in PaCO2 includes rightward displacement of the CO2-hemoglobin dissociation curve in the presence of increased oxygen saturation, and a consequent reduction in carboxyhemoglobin formation and transport—the Haldane effect. More likely, there are relative increases in dead space ventilation via alterations in hypoxic pulmonary vasoconstriction. Hanson et al. modeled ventilation and perfusion in a computer simulation of the lung, and demonstrated that it was possible to account for the change in PaCO2 by oxygen-induced relaxation of hypoxic pulmonary vasoconstriction (73). This pulmonary vascular response to hypoxia is capable of redirecting blood flow from alveoli that are poorly ventilated to those with a higher PaO2. Blunting this response by artificially increasing the PaO2 prevents appropriate matching between ventilation and pulmonary perfusion, and permits a rise in CO2.

A recent study examined a cohort of CO2-retaining COPD patients recovering from an acute exacerbation after they had been weaned from mechanical ventilation to a baseline FiO2 of 0.3 to 0.4 (72). Patients were re-exposed to an FiO2 of 0.7 for 20 minutes, and no statistically significant changes in respiratory rate, tidal volume, dead space, or PaCO2 were reported. Robison et al. compared two groups of patients with acute COPD exacerbations, dividing them into CO2-retaining and nonretaining groups (74). They found only modest declines in minute ventilation, with a rise in PaCO2 averaging about 3 mm Hg in the CO2 retaining group upon exposure to 100% O2 face mask. The dispersion of alveolar ventilation/perfusion ratios increased nearly equally in both groups upon oxygen exposure, suggesting that hypoxic pulmonary vasoconstriction was affected equally in both groups. From these experiments, one must conclude that the mechanisms generating hypercapnia in individuals with COPD treated with supplemental oxygen are varied and complex. Close monitoring of respiratory parameters, including arterial oxygenation and carbon dioxide, is mandatory when oxygen therapy is employed to reverse severe hypoxemia.

Absorption Atelectasis

An individual spontaneously breathing a high inspired concentration of oxygen results in replacement of nitrogen with oxygen within the alveoli. This may cause absorption atelectasis secondary to oxygen diffusing into the alveolar capillary blood more rapidly than nitrogen can diffuse into the alveoli and inhaled oxygen can replace the lost volume (75). This may be more theoretical than practical, certainly in the short term where nitrogen will continue to diffuse into the blood from all tissues, and to some degree into the alveoli to re-establish an equilibrium. Nonetheless, it is potentially a problem in those regions of the lung experiencing low ventilation/perfusion ratios and subjected to large compressive forces (e.g., lower lobes from abdominal contents or weight of the heart in the supine individual). The rate of alveolar collapse may potentially be greater in those circumstances where there are increased metabolic demands and rates of oxygen uptake. Although the mechanism has not been fully elucidated, decrements in vital capacity of up to 20% have been recorded after exposure to 100% oxygen in patients, although oxygen-induced tracheobronchitis was presumed (76).

SUMMARY

The management of airway, breathing, and oxygen therapy in critically ill patients continues to be a challenging task. A comprehensive understanding of the various oxygen delivery modalities is of utmost importance in not only delivering the highest quality of care to the critically ill patients, but also avoiding major oxygen therapy-related consequences, including increased morbidity and even mortality.

References


