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Chapter 2

Pathophysiology of Apnea, Hypoxia, and Preoxygenation

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Abstract

Because intubation becomes a long procedure as potential, arterial oxygen (O_2) desaturation should be taken into account during the intubation. Since oxygen reserves are not always sufficient to meet the duration of intubation, preoxygenation should be routine before anesthetic induction and tracheal intubation. Surveys show that maximal preoxygenation increases oxygen reserves in the body and significantly delays arterial hemoglobin desaturation and hypoxia. In cases of respiratory insufficiency oxygenation can be improved by positive end expiratory pressure (PEEP) or pressure support. Effective technique and FeO_2 monitoring can increase the effectiveness of preoxygenation and thus increase the safety margin. Preoxygenation failures have to be identified and alternative oxygenation methods must be readily available in order to be applied quickly and easily. Although genetic and environmental factors play a role in diseases such as heart attack, stroke and cancer, which have become the cause of the worst death in the twenty-first century, the underlying problem in the development of these pathological conditions is hypoxia. Better understanding of hypoxic areas in ischemic tissues or growing tumors as well as increased knowledge of hypoxia cellular and molecular responses will allow possible applications in the treatment of major diseases associated with tissue hypoxia.

Keywords: apnea, hypoxia, preoxygenation, anesthesia, intubation

1. Introduction

In this chapter, factors affecting the formation of severe hypoxemia during apnea, pathophysiology of oxygen delivery and preoxygenation, pathophysiologic responses to hypoxemia will be discussed.

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In an anesthetized patient, oxygen consumption (VO_2) remains fairly constant at 250 mL/min. This is delivered to the tissues by hemoglobin whose oxygen is then replenished, on return to the pulmonary circulation, by the diminishing store of oxygen within the lungs. Alveolar partial oxygen pressure (PAO_2) is constantly reduced not only due to oxygen uptake by the lungs but also due to the severe negative intrathoracic pressure produced by this oxygen uptake, if the airway is occluded at the same time. However, the arterial partial pressure of oxygen (PaO_2) drops directly to PAO_2, while arterial hemoglobin oxygen saturation (SpO_2) remains above 90% as long as hemoglobin can be oxygenated again in the lungs. SpO_2 begins to fall only when the oxygen stores in the lungs are empty and PaO_2 is 6–7 kPa. Their subsequent declines are constant and fast at around 30% per minute. At the beginning of this rapid decline, SpO_2 is still around 90–95%. This bending point can be defined as "critical hypoxia." Since oxymetry detects the fall in SpO_2 before any obvious clinical sign, it has an important place in helping clinical applications to detect and avoid critical situations.

Preservation of oxygenation during intubation is essential because lack of control of O_2 intake can cause life-threatening complications. Anesthesia induction usually leads to apnea. In this case, tissue oxygenation is maintained by the use of oxygen reserve and continuous O_2 administration. In some cases, adequate oxygenation cannot be achieved due to pulmonary disease, inadequate mask ventilation or difficulties in intubation. These critical situations are often predictable and can be avoided by alternative oxygenation methods by following a valid algorithm [1].

2. Pathophysiology of oxygen delivery

Oxygenation during anesthesia mostly depends on three parameters: alveolar ventilation (VA), ventilation-perfusion distribution and VO_2.

2.1. Oxygen reserves

Tissue oxygenation during apnea is usually sustained at the expense of body O_2 reserves that are present in the lungs, plasma, and hemoglobin [2]. When the ambient air is breathing, the lung O_2 reserve is calculated as: 0.21 × 3000 = 630 mL for 3000 mL functional residual capacity (FRC). After full preoxygenation, FAO_2 is close to 0.95 and the reserve increases as follows: 0.95 × 3000 mL = 2850 mL. These theoretical figures are the maximum values; in practice, the rate of ventilation-perfusion is lower than that of FAO_2 because of the heterogeneity. In a subject inhaling ambient air (PaO_2 = 80 mmHg) and a plasma volume of 3 liters, plasma oxygen reserve is calculated as 0.003 × 80 × 3 × 10 = 7 mL. At 500 mmHg PaO_2, this plasma reserve reaches 45 mL. The hemoglobin O_2 reserve is calculated in the ambient air (SpO_2 = 98%) for a hemoglobin concentration of 12 g/100 mL and a total blood volume of 5 L as follows: 1.34 × 0.98 × 12 × 10 × 5 = 788 mL. This value increases to 804 mL for 1 FiO_2 (SpO_2 = 100%). In cases of anemia, hyperoxic ventilation increases the availability of O_2 by replicating solute O_2 [3]. Considering the basic physiological O_2 reserves, while the ambient air is inhaled, the total O_2 reserve is approximately 1450 mL and reaches approximately 3700 mL in the pure O_2 solution.

This increase (approximately 2250 mL) is mainly due to the rice FAO_2 in FRC. Several factors influence O_2 availability: the initial rise in $PaCO_2$ (Haldane effect), FRC, FAO_2, fraction of shunt, VO_2, hemoglobin concentration, and cardiac output. Replacement of nitrogen by O_2 in the lung reservoir during preoxygenation obeys an exponential law [2]. The change in O_2 reserve over time is linear in both blood and tissue compartments.

2.2. O_2 consumption

The VO_2 value of an awake person is about 300 mL/min and falls about 15% in old aged people. After ventilation in ambient air, O_2 reserves allow apnea for up to 3 minutes without serious eff on O_2 transport. This time can be doubled with the correct applied preoxygenation. The duration of apnea tolerated is additionally decreased if O_2 reserves are low due to decreased FRC, low PAO_2 and/or high VO_2 and the O_2 reserves are reduced due to low FRC, PaO_2 and/or high VO_2.

2.2.1. Ventilation/perfusion incompatibility

Preoxygenation leads to an increase in shunt and microatelectasis after induction of anesthesia [4]. The inspired high O_2 fraction (FiO_2) is not the only responsible mechanism; atelectasis was also observed when FiO_2 was used as 0.4 [5]. The use of 0.8 FiO_2 does not inhibit the emergence of microatelectasis and results in a considerable shortening of the time limit before critical desaturation compared to the use of 100% oxygen [6]. Microatelectasis are reversible with alveolar engraftment (>30 cmH_2O tracheal pressure for 15 seconds) and can be prevented by the addition of 10 cmH_2O positive end expiratory pressure (PEEP) [7]. In morbidly obese patients and in parturients, shunt can exceed 20% and even increasing FiO_2 to 1 does not provide correction of the hypoxemia. Implementation of a microatelectasis prevention strategy of alveolar recruitment maneuvers and PEEP limits the extent in elderly and obese patients [8, 9].

2.3. Epidemiology of arterial desaturation during anesthesia induction and intubation

Arterial O_2 desaturation occurs if O_2 reserves are insufficient to support O_2 consumption during apnea. There are three responsible mechanisms: quantitative reduction in the reserve (decline in FRC, deterioration in gas exchange), VO_2 increase (birth, fever), and prolonged apnea.

It is especially important to mention the four high-risk situations:

- Rapid induction sequence in which mask ventilation increases the risk of inhalation of gastric fluid.
- Prediction of difficult ventilation with face mask.
- Anatomical abnormality and prediction of difficult intubation with specific technical assessments (such as double-lumen tube).
- Obesity and pregnancy.

After rapid sequence induction, spontaneous ventilation reinitiation does not occur rapidly after an unsuccessful intubation procedure and saturation falls below 90% in 11% of patients [10]. Administration of succinylcholine (0.56 and 1 mg/kg) after induction with propofol (2 mg/kg) and fentanyl (μg/kg) has increased desaturation risk and apnea duration compared to placebo [11]. In a pharmacodynamic study with succinylcholine (0.3–1 mg/kg), it found that the intubation conditions were excellent at doses above 0.5 mg/kg, but the delay in resumption of spontaneous breathing rose from 4.0 to 6.16 minutes after administration of 0.6 and 1 $mg.kg^{-1}$, respectively [12]. Reversal of deep neuromuscular block (induced by high-dose rocuronium) with sugammadex (16 mg/kg) used for rapid sequence induction is significantly faster than spontaneous recovery of succinylcholine (6.2 ± 1.8 versus 10.9 ± 2.4 minutes) [13]. Reversal with sugammadex following rapid sequence induction with rocuronium allows earlier restoration of spontaneous respiration compared to succinylcholine (216 versus 406 seconds) [14]. Thus, the choice of the rocuronium would increase the margin of safety for a resumption of spontaneous ventilation after a rapid sequence induction.

2.3.1. Desaturation in pediatrics

Desaturation attacks occur frequently in children, with 4–10% during induction and 20% during tracheal intubation [15]. Desaturation occurs faster if the child is younger [16, 17] and apnea duration in predesaturation has a linear relationship with the age of the patient. The low weight of the child increases the frequency of severe arterial desaturation. It is suggested that 95% SpO_2 may be the safe apnea limit during induction of pediatric anesthesia [18]. It was noted that upper respiratory tract infection increased desaturation risk during induction [15]. The number of important factors effect the time from the onset of apnea to the development of critical hypoxemia.

2.3.1.1. Functional residual capacity (FRC)

FRC is the most important oxygen storage in the body. The larger the FRC, the longer apnea times can be preceded before the critical hypoxia develops. Alveolar oxygen fraction (FAO_2) is around 13% in air breathing. For an adult with normal FRC and VO_2, the oxygen content of the lungs (290 mL) will be consumed within 1 minute. This explains why you can expect a critical hypoxia after 1-minute apnea. Reduced FRC patients (lung disease, kyphoscoliosis, pregnancy, and obesity) reach critical hypoxia much faster.

2.3.1.2. Preoxygenation

Preoxygenation using a high FiO_2 before anesthesia induction and tracheal intubation is particularly recommended in patients at risk for apneic arterial oxyhemoglobin desaturation. The success of preoxygenation to delay the onset of desaturation has been known for many years [19–21]. Preoxygenation during anesthesia induction is highly recommended in cases of desaturation prior to airway safety with endotracheal intubation. In situations where manual ventilation is not desired, such as patients with aspiration risk, preoxygenation has become

an integral component during rapid sequence induction/intubation [22–25]. It is also important when difficulties associated with preoxygenation, ventilation, or tracheal intubation are predicted and the patient's O_2 reserves are limited [26, 27].

Guidelines developed by the Difficult Airway Society in the United Kingdom for unforeseen difficult intubation management in 2015 suggest that all patients must undergo preoxygenation prior to induction of general anesthesia [28]. Residual effects of anesthetics or inadequate reversal of muscle relaxants can complicate emergence from anesthesia. These effects may result in decreased functional activity of the pharyngeal muscles, upper airway obstruction, effective cough insufficiency, a fivefold increase in aspiration risk, and hypoxic weakness controlled by peripheral chemoreceptors [29, 30]. Hypoventilation, hypoxemia and loss of airway may follow these changes. Preoxygenation can also minimize neostigmine-induced cardiac arrhythmias [31]. Considering the potential for airway and ventilation problems, "routine" preoxygenation is recommended before reversing neuromuscular blockage and before tracheal extubation [32]. The recommended guidelines for the management of tracheal extubation in 2012 by the Difficult Airway Society in the United Kingdom state that preoxygenation must be performed before extubation due to various perioperative anatomical and physiological changes that may put gas exchange in jeopardy [33]. Preoxygenation is also recommended before any ventilation interruption, such as open tracheobronchial aspiration.

3. Physiological basis, efficiency, and productivity

Preoxygenation increases the body O_2 stores, the main increase occurring in the functional residual capacity. Accurate quantification of the increases in the O_2 volume in various body tissues is difficult, but the estimated increases are notable when assuming that the partition coefficient for gases approximates the gas-water coefficients (**Table 1**, **Figure 1**) [2, 34].

The effectivity of preoxygenation is assessed by efficacy and efficiency. Efficacy indices include FAO_2 increase, decreases in alveolar nitrogen fraction (FAN_2), and increase in PaO_2 [35–42]. The efficiency of preoxygenation is assessed by the decrease in oxyhemoglobin desaturation (SpO_2) during apnea [10, 43, 44]. Preoxygenation increases FAO_2 and decreases FAN_2 (**Figure 2**) [45].

The key to achieve maximum preoxygenation is the excretion of alveolar nitrogen (N_2). The terms preoxygenation and denitrogenation have been used synonymously to describe the

Body store	Room air	100% O_2
Lungs	450	3000
Blood	850	950
Dissolved in tissue fluids	50	100
Combined with myoglobin	200	200
Total	1550	4250

Table 1. Body O_2 stores (in mL) during room air and 100% O_2 breathing [34].

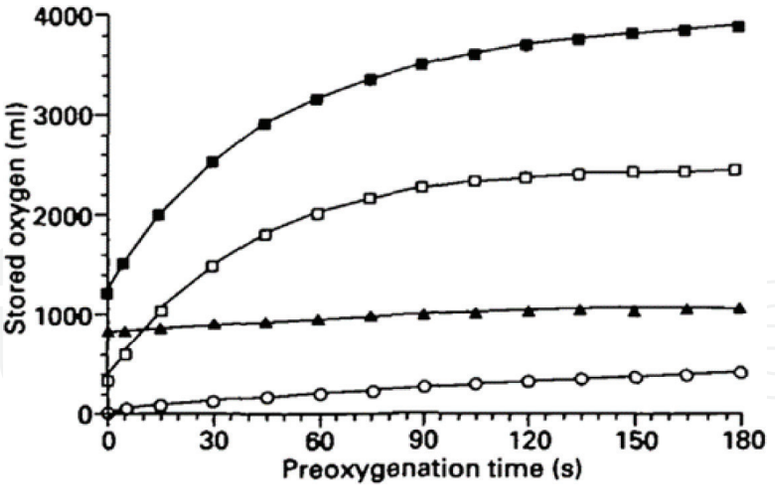

Figure 1. Variation in the volume of O_2 stored in the functional residual capacity (□), blood (▲), tissue (○), and whole body (■) with the duration of preoxygenation [2].

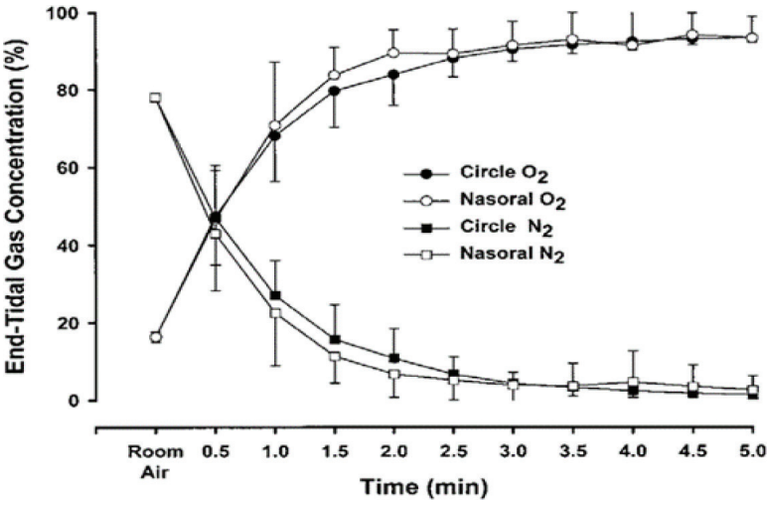

Figure 2. Comparison of mean end-tidal O_2 and N_2 concentration obtained at 30 second intervals during 5-minute period of spontaneous tidal volume oxygenation using the circle absorber and Nasoral systems in 20 volunteers. Data are mean ± SD [45].

same process. In a normal lung function case, filling with O_2 and discharging of N_2 are exponential functions and are controlled by the time constant (t) of the exponential curves. This constant is proportional to the ratio of alveolar ventilation to functional residual capacity. Since preoxygenation prior to anesthetic induction is typically carried out using a semiclosed circular absorber cycle, the washout of the circuit must also be considered using the time constant of the circuit, which is the time required for flow through a container (volume) to equal its capacity. Thus, there are two stages of preoxygenation (**Table 2**) [32]: washing the vessel with O_2 flow and washing FRC by alveolar ventilation.

After 1 t, O_2 at functional residual capacity is 63%; 2 t, then 86%; 3 t, then 95%; and after 4 t, an increase of about 98% is observed. The endpoints of maximum preoxygenation and denitrogenation were defined as an end-tidal O_2 concentration (EtO_2) of about 90% and an

Stage	Description	Determinant of *t*	Recommendation
1	Washout of anesthesia circuit by O_2 flow	Size of circuit/O_2 flow rate	Washout of circuit by high O_2 flow before placing face mask
2	Washout of FRC by VA	FRC/VA	Use of O_2 flow rate that eliminates rebreathing

FRC, functional residual capacity; t, time required for flow through a container (volume) to equal its capacity; and VA, alveolar ventilation [32].

Table 2. Stages of preoxygenation.

after-tidal N_2 concentration of 5% (EtN_2) [2, 35]. In an adult subject with a normal functional residual capacity and oxygen consumption (VO_2), an $EtO_2 > 90\%$ implies that the lungs contain >2000 mL of O_2, which is 8–10 times the VO_2 [26, 46]. Due to the presence of carbon dioxide (CO_2) and water vapor in the alveolar air, it is thought that $EtO_2 > 94\%$ cannot be obtained easily. Many factors affect efficacy and efficiency (**Table 3**).

Factors affecting the efficacy of preoxygenation are FiO_2, duration of preoxygenation, and alveolar ventilation/functional residual capacity ratio. Failure to achieve a FiO_2 of close to 1.0 depends on the height of the ozone beneath the face mask, the rebreathing of exhalation gases, and the high O_2 dispersion of resuscitation bubbles [45, 48, 49]. FiO_2 may also be affected by the duration of the aeration, the breathing technique, and the amount of fresh gas flow [50]. Bearded patients, toothless patients, elderly patients with sagging cheeks, facial mask use at the wrong size, and presence of gastric tubes (nasogastric) are common factors that cause air entrapment and a lower FiO_2. The lack of a normal capnography wave and expected lower end-tidal CO_2 concentration ($EtCO_2$) and EtO_2 should warn of the presence of leaks in the anesthetic cycle [26]. With a FiO_2 close to 1.0, most healthy adults with tidal volume respiration can achieve an $EtO_2 > 90\%$ target level within 3–5 minutes. The half-time for the exponential change in the FAO_2 fraction following each unit change in FiO_2 is given by the following equation:

$$FAO_2 = 0.693 \times \text{Functional residual capacity}/\text{Volume of alveolar ventilation.}$$

Efficacy
• Inspired oxygen concentration
• Presence of leak anesthetic system used level of FGF
• Type of breathing (tidal volume or deep breathing) and duration of breathing
• VA/FRC ratio
Efficiency
• Oxygen volume in lungs (alveolar oxygen tension, FRC)
• Systemic oxygen supply versus demand balance (arterial oxygen content, cardiac output, whole body oxygen consumption)

FGF, fresh gas flow; FRC, functional residual capacity; and VA, alveolar ventilation [32].

Table 3. Factors affecting the efficacy and efficiency of preoxygenation.

With a functional residual capacity of 2.5 L, the half-times are 26 seconds when alveolar ventilation = 4 L/minutes and 13 seconds when alveolar ventilation = 8 L/minutes [26]. These findings indicate that hyperventilation can reduce the time required to increase the O_2 stores in the lungs, which provides the basis for using deep breathing as an alternative to tidal volume breathing [41, 42, 51, 52].

3.1. Preoxygenation techniques

Equipment especially face mask should be adapted and it should fit the patient. Mask and stylistic mismatch between the patient's face (mask improper length, beards, or mustaches asset) can prevent the complete closure and lead to failure [35]. The mask must be applied securely on the face of the patient; 20% dilution of O_2 by ambient air occurs when the mask is not tightly applied and 40% dilution occurs when it is held close to the face. The mask should be applied firmly to the patient's face; when the mask is not fully seated, dilution of up to 20% with ambient air in O_2 and 40% dilution when held close to the face appear [53]. The circle system with fresh gas flow (5 L/minutes) is used as the standard for comparison in anesthesia studies evaluating the effectiveness of different circuits because it allows higher inspiratory flow rates. Some open circuit systems (Bain or Magill) have been shown to be much less efficient [54]. Before preoxygenation, the circuit and reservoir must be filled with O_2. Three preoxygenation techniques are used: spontaneous breathing at FiO_2 of 1 for 2–5 minutes, the "four vital capacities" method, and deep breaths.

3.1.1. Spontaneous breathing at FiO_2 of 1

This preoxygenation technique, first proposed by Hamilton in 1955, is still the reference standard: 3 -minute spontaneous breathing at FiO_2 of 1 level. In patients with normal lung function, this leads to denitrogenation with FAO_2 approaching 95%. Denitrogenation is effective from the first minute of preoxygenation; however, delay these effects with a rapid decline in the fugitive FiO_2 on the run [55]. Although pure O_2 breathing for longer than 1 minute seems it may have little SpO_2 or denitrogenation benefit, it has positive effect on apnea duration before desaturation [51]. In experiments with healthy subjects, the duration of the apnea can be as long as 10 minutes after the 3-minute classic preoxygenation. The apnea time can be increased by an additional 2 minutes by application of positive pressure during the preoxygenation and by ventilation to the mask after induction [56].

3.1.2. Vital capacity maneuvers

The four vital capacity method is used in cases where the patient cannot cooperate, and the duration of apnea without desaturation is shorter after four capacity maneuvers than with spontaneous breathing. Technical requirements are responsible for the limitations of this technic: bag capacity, inspiratory flow, and room gas inspiration. These problems are partially solved with an additional 2-liter bag and a non-rebreathing ambu valve. Vital capacity maneuver begins with forced expiration to optimize FeO_2 increase [57]. To be fully effective, the inspiratory O_2 flow should be greater than the peak inspiratory flow, which is attained by

activating the O_2 system "by-pass" during inspiration; 4 or 5 forced breaths of pure O_2 were found to be as efficient as conventional preoxygenation assessed on the FeO_2 [58]. However, these results were not verified when using PaO_2 for comparison. After four vital capacity maneuvers, it is observed that PaO_2 (293 ± 86 mmHg) is lower compared to after spontaneous ventilation in pure oxygen (397 ± 48 mmHg) [59].

3.1.3. Deep breathing method

Eight deep breaths at a constant oxygen flow of 10 mL/min in a 60-second period create a simple method for preoxygenation. This technique results in an average arterial oxygen pressure of 369 ± 69 mmHg, which is not significantly different from the value achieved by 3 minutes of tidal volume breathing at an oxygen flow of 5 L per minute [42]. It has been argued that the voluntary hyperventilation technique (1 minute in FiO_2 followed by voluntary hyperventilation for 2 minutes) prevents postapneic hypercapnia. Postintubation $PaCO_2$ was similar when preinduction hyperventilation was used as preoxygenation technique or normal respiration was used for 3 minutes [60].

3.1.4. Pressure-assisted ventilation (PSV)

In healthy volunteers, PSV has been shown to improve preoxygenation quality by two mechanisms: accelerate nitrogen excretion and provide better contact between mask and face. In a study of healthy volunteers, the mean expired fraction of O_2 (FeO_2) after 3 minutes of preoxygenation was higher ($p < 0.001$) with 4 cmH_2O (94 ± 3%) PSV/PEEP and 6 cmH_2O PSV/PEEP (94 ± 4%) [61]. Increasing fresh gas flow (FGF) between 5 and 10 L during deep breathing does not provide a significant increase in FiO_2 value during tidal volume breathing [50]. Due to the breathing properties of the circulator system, the minute ventilation during deep breathing can exceed the FGF, causing a reincrease in N_2 in the exhalation gases and therefore lower FiO_2. However, regeneration of N_2 in exhalation gases during tidal volume breathing is insignificant, and thus increasing FGF by 5–10 L has minimal effect on FiO_2 [50].

All investigations have demonstrated that preoxygenation markedly delays arterial oxyhemoglobin desaturation during apnea. [26, 36, 38, 43]. The extent of this delay in desaturation depends on the efficacy of preoxygenation, the capacity for O_2 loading, and the VO_2 [47]. Patients with a decreased capacity for O_2 transport (decreased functional residual capacity, PaO_2, arterial O_2 content, or cardiac output) or those with an increased VO_2 develop oxyhemoglobin desaturation more rapidly during apnea than healthy patients [26, 43].

Farmery and Roe developed and validated a computer model describing the rate of oxyhemoglobin desaturation during apnea [62]. The model is particularly useful for analyzing oxyhemoglobin desaturation values below 90%. These values are dangerous to allow in human subjects because below 90%, there will be a steep decline of PaO_2 due to the sigmoid shape of oxyhemoglobin dissociation curve. In a healthy 70 kg patient, when FaO_2 is progressively decreased from 0.87 (FiO_2 of 1.0) to 0.13 (air), the apnea time to 60% SaO_2 is decreased from 9.9 to 2.8 minutes (**Figure 3**) [43].

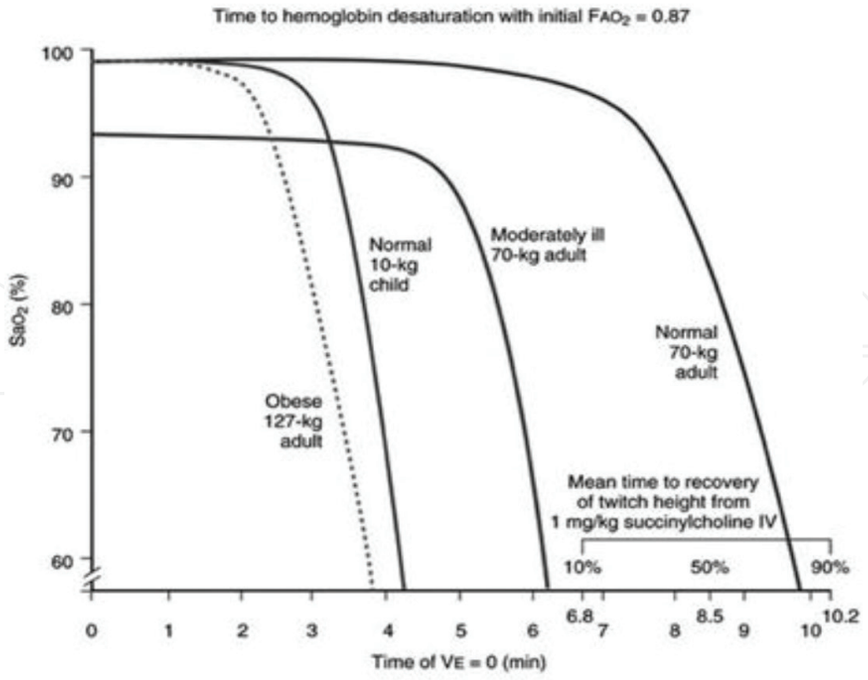

Figure 3. Arterial oxyhemoglobin saturation (SpO_2) versus time of apnea in an obese adult, a 10 kg child with low functional residual capacity and high ventilation, and a moderately ill adult compared with a healthy adult. FaO_2 indicates fractional alveolar oxygen concentration; VE, expired volume [43].

Regardless of the technique used, the goal is to reach the end of maximal preoxygenation, which can easily be measured by most anesthesia monitors.

3.2. Preoxygenation for high-risk patient population

3.2.1. Pregnant patients

Rapid sequence induction/intubation is often used in pregnancies given general anesthesia and preoxygenation is important in these patients. Maximum preoxygenation can be achieved faster in pregnant women than in nonpregnant women due to higher alveolar ventilation and lower functional residual capacity [37, 63]. However, oxyhemoglobin desaturation in pregnant women during apnea develops more rapidly because they are associated with a limited O_2 volume and increased VO_2 in their less functional residual capacities. During the apnea, the time required for SaO_2 to fall to 95% was 173 seconds for pregnant women and 243 seconds for women who were not pregnant in the supine position [64].

Using the 45° head up position causes an increase in the desaturation duration in nonpregnant women, but it is not seen in pregnant women. The size of the uterus may prevent the descent of the diaphragm and may not allow the expected increase in functional residual capacity in the head-up position [64]. Four deep breathing techniques in pregnant women are below the 3-minute tidal volume breathing technique and should not be used except in emergencies [65]. Increased minute ventilation in pregnant women requires the use of an O_2 flow of 10 L/minutes during preoxygenation [66].

3.2.2. Morbid obesity patients

Studies have demonstrated that following preoxygenation with tidal volume breathing for 3 minutes, the time required for SaO_2 to fall to 90% during apnea is markedly reduced in morbidly obese patients (BMI > 40 kg/m^2) compared with nonobese patients [67, 68]. During apnea after preoxygenation, the mean time to reach 90% of SaO_2 in normal body weight patients was 6 minutes, while in morbid obese patients it was 2.7 minutes [69]. Rapid oxyhemoglobin desaturation during apnea in morbidly obese patients was attributed to an increased VO_2 and a markedly reduced FRC.

Spontaneous respiration and effectiveness of eight deep breaths as preoxygenation method are similar in obese patients with previous apnea before reaching 95% of FeO_2 and SpO_2 [70]. Continuous positive airway pressure (CPAP) (7.5 cmH_2O versus Mapleson circuit) during spontaneous ventilation in pure O_2 was observed not to improve the duration of apnea (240 and 203 seconds CPAP versus zero end expiratory pressure, respectively) [71]. PaO_2 improved significantly after intubation when PEEP and PSV applied together after CPAP [72]. PSV improves preoxygenation quality, possibly by increasing alveolar circulation in obese patients [73]. Compared to 5 minutes of spontaneous ventilation with FiO_2 of 1, PSV results in increased FeO_2 (96.9 ± 1.3% versus 94.1 ± 2.0%) and acceleration of nitrogen elimination (185.3 ± 46.1 versus 221 ± 41.5 s) [74]. When combined with recruitment maneuvers, PSV activity has statistical significance in terms of arterial oxygenation [75]. In morbidly obese patients, preoxygenation resulted in better oxygenation compared to 5 cmH_2O CPAP neutral pressure breathing combined with 5 cmH_2O PSV and prevented desaturation episodes [76]. Postintubation PaO_2 was significantly higher in the CPAP/PSV group (32.2 ± 4.1 kPa) than in the control group (23.8 ± 8.8 kPa) ($p < 0.001$). Lower oxygen saturation was lower in the control group (median 98%, range, 83–99%) than the CPAP/PSV group.

The supine position reduces the functional residual capacity due to the upward displacement of the diaphragm. It has been shown that placement of severe obese patients in the 25° up position during preoxygenation prolongs the desaturation time [77]. Some anesthetists may prefer awake fiberoptic intubation instead of rapid sequence induction/intubation in morbid and super morbid obese patients (BMI > 50 kg/m^2), especially when they have associated problems [78].

3.2.3. Pediatric patients

Respiratory physiology of young children is age-specific. The inhibition of intercostal tone with general anesthesia is responsible for the reduction in FRC. Hypoxia occurs more rapidly in children due to higher VA/FRC ratio, higher O_2 consumption and lower O_2 reserves. Children exhibit a delay of approximately 80–90 seconds before reaching FeO_2 values close to 90% when breathing at FiO_2 of 1 level [79]. After a period of at least 2 minutes breathing at FiO_2 of 1 and after muscle paralysis, the duration of apnea before the SpO_2 reaches 90% is found to be 96.5 seconds in children less than 6 months of age, 160.4 seconds in 2–5 year olds, and 382.4 seconds in 11–18 year olds [80]. In children younger than 6 months, even shorter apnea time limits, on the order of 70–90 seconds have been reported [16]. The duration of apnea required to reach a SpO_2 of 98, 95, or 90% is significantly increased when the preoxygenation is extended for 1–2 minutes, but no benefit was found by extension past 3 minutes [18].

Studies have shown that maximal preoxygenation (EtO_2 = 90%) can be achieved in children faster than in adults [79, 81]. With tidal volume respiration, almost all children can reach 90% EtO_2 within 100 seconds, whereas it can be reached within 30 seconds by deep breathing [79, 81]. However, since children have a lower functional residual capacity and a higher VO_2 than adults, they may be at a greater risk of developing hypoxia when interruption of O_2 transport occurs, such as during apnea or airway obstruction [82–84]. In a comparison of three groups of children who breathed O_2 (FIO_2 = 1.0) with tidal volume breathing for 1, 2, and 3 minutes before apnea, the time needed for SaO_2 to decrease from 100 to 95% and then to 90% during apnea was least in those who breathed O_2 for 1 minute and there was no difference between those who breathed O_2 for 2 and 3 minutes [85]. Based on these findings, 2 minutes of preoxygenation with tidal volume respiration seems to be sufficient to provide a maximum benefit and a safe apnea period [85]. The advantage of preoxygenation is greater in a larger child than in a baby. For example, in an 8-year-old child, the duration of the apnea-safe period may be extended to 5 minutes or longer with preoxygenation, whereas the duration is 0.47 minutes without preoxygenation [86]. The smaller the child, the faster the start of desaturation [80, 83, 84]. After the onset of apnea, most infants reach 90% SpO_2 within 70–90 seconds (despite preoxygenation) and this time may be shorter in the presence of upper respiratory tract infection [16, 87]. Pediatric anesthesiologists expressed concern about the use of the "adult" version of the rapid sequence induction/intubation technique in children [88]. Concerns include the safe duration of apnea and the potential for airway obstruction induced by cricoid compression. A modified version of the rapid sequence induction/intubation technique appears to be more appropriate for children with emphasis on full muscle relaxation and gentle manual ventilation using high O_2 concentration with adequate anesthesia depth without cricoid pressure before intubation [89].

3.2.4. Elderly patients

Old age is associated with significant structural and physiological changes in the respiratory system [90, 91]. The changes also include a reduction in elastic recoil with weakened respiratory muscles and parenchymal changes in the lungs. Lung volumes are reduced by increased closure volume, which causes ventilation-perfusion mismatch, reduced pulmonary reserve, and impaired oxygen uptake in the lung. While basal VO_2 declines with aging, impaired O_2 intake creates a faster desaturation during apnea under anesthesia [91]. In elderly patients, tidal volume breathing of 3 minutes or longer has been shown to be more effective than four deep breathing techniques [92, 93].

3.2.5. Patients with lung diseases

Severe pulmonary disease is associated with decreased FRC, increased ventilation-perfusion incompatibility, and increased VO_2, which can reduce the safety margin. Anesthesia has been shown to cause further deterioration of gas exchange in patients with chronic obstructive pulmonary disease [94]. As well as in aspiration, even short ventilation interruptions can cause desaturation. Besides, atelectasis is not a consequence, presumably the chronic hyperinflation of the lungs resists volume decline and collapse [95]. For maximum preoxygenation in these patients, 5 minutes or more may be needed with tidal volume breathing [96].

3.2.6. Patients in high altitude

High altitude does not shift inhaled O_2 concentration but reduced barometric pressure causes in a decrease partial alveolar pressure and arterial PO_2 [97]. As altitude increases, PaO_2 decreases exponentially. Patients at high altitudes may need longer lasting preoxygenation.

3.3. Techniques to improve preoxygenation

3.3.1. Apneic diffusion oxygenation

Following preoxygenation, "apneic diffusion oxygenation" is an effective maneuver that prolongs the safe duration of apnea [32, 98–102]. The physiological basis of this maneuver is: In adults, VO_2 averages are 230 mL/min during apnea, whereas CO_2 delivery to alveoles is only 21 mL/min [32]. The remaining 90% (or more) of CO_2 is buffered in body tissues. As a result, O_2 enters the lung by diffusion, provided that the lung volume initially decreases by 209 mL/min and forms a pressure gradient between the upper airway and the alveoli, and the airway is not obstructed. If CO_2 cannot be excreted, $PaCO_2$ increases to 8–16 mmHg for the first minute of apnea followed by a linear increase of about 3 mmHg/min [103]. The advantage of apneic diffusion oxygenation depends on reaching the maximum preoxygenation before apnea, remaining open in the respiratory tract, and is on the presence of high FRC relative to body weight. Although the drop in PaO_2 is directly related to PaO_2, SpO_2 remains greater than 90% as long as the hemoglobin is oxygenated again in the lungs [46, 99, 100, 104]. SpO_2 decreases only after the O_2 stores in the lungs are exhausted, and PaO_2 falls below 60 mmHg. When SpO_2 becomes <80%, the saturation reduction rate is approximately 30%/min. In the presence of an airway obstruction, the volume of gas in the lungs decreases rapidly and the intrathoracic pressure decreases with respect to lung compliance and VO_2. When airway obstruction is relieved, a rapid O_2 flow begins in the lungs and preoxygenation with high FiO_2 improves [46]. Some studies have shown that through an open air pathway, apneic diffusion oxygenation can keep the SpO_2 value above 90% for up to 100 minutes [99, 100]. When FiO_2 is at a high level, a small increase can cause a fairly disproportionate delay in hemoglobin desaturation. The delay in hemoglobin desaturation obtained by FiO_2's raising from 0.9 to 1.0 was above that obtained by FiO_2's raising from 0.21 to 0.9 (**Figure 4**) [105].

Apneic diffusion oxygenation can be achieved with maximum face mask preoxygenation following O_2 insufflation to 15 L/minutes via a nasopharyngeal or an oropharyngeal cannula or a needle inserted into the cricothyroid membrane. In healthy patients with a healthy airway, this technique can provide adequate oxygenation for at least 10 minutes. Although oxygenation can be maintained for a longer period of time, a limiting factor of apneic oxygenation is the gradual rise of $PaCO_2$ during apnea [103].

3.3.2. Continuous positive airway pressure (CPAP) and positive expiratory pressure (PEEP)

The CPAP usage in the preoxygenation delayed the desaturation period by mechanical ventilation using positive end expiratory pressure (PEEP) for 5 minutes before removing the mask and securing the airway [106, 107].

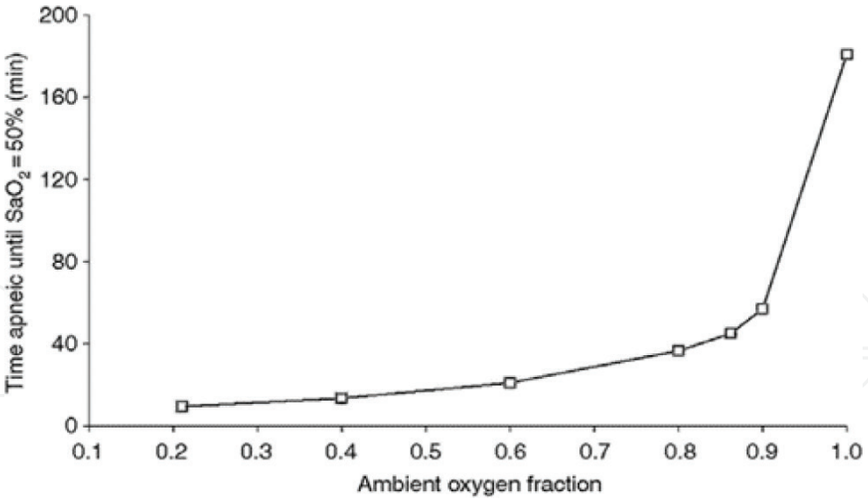

Figure 4. The time (duration of apnea) required to reach 50% SaO_2 with an open airway exposed to various ambient O_2 fractions [105].

3.3.3. Noninvasive bilevel positive airway pressure (BİPAP)

BiPAP combines pressure-assisted ventilation (PSV) and CPAP advantages and keeps the lungs open during the respiratory cycle. BiPAP has been used during preoxygenation to decrease intrapulmonary shunting and to increase the margin of safety during apnea in morbidly obese patients [108]. This technique is also used to reduce postoperative pulmonary dysfunction and to treat patients with respiratory insufficiency from various etiologies [109].

3.3.4. Transnasal humidified rapid insufflation ventilatory exchange (THRIVE)

THRIVE is a new technique that is available for use in critically ill patients and in patients with difficult airways. The technique combines the benefits of apneic oxygenation and CPAP with a reduction in CO_2 levels through gaseous mixing and flushing of the dead space [110]. THRIVE is used as standard with a nasal, high flow oxygen delivery system, as sold in the market. The THRIVE technique has been shown to significantly prolong the period of apnea safety while avoiding CO_2 increase [111].

3.4. Potential risks of the preoxygenation

- Delay in the diagnosis of the esophageal intubation.
- Absorption atelectasis.
- Production of reactive oxygen radicals.
- Cardio-cerebrovascular responses.

It causes a decrease in heart rate and cardiac output. Systemic vascular resistance and arterial blood pressure increase [112–114]. These changes are detected by chemoreceptors or baroreceptors. Direct coronary vasoconstrictor effect of hyperoxia is due to oxidative inactivation of nitric oxide and other vasodilators released by vasculature [115–117]; it reaches up to collapse

of the endothelin and K^+ channels sensitive to ATP [118, 119]. It is well known that high O_2 inhalation may reduce cerebral blood flow due to vasoconstriction [120–123]. It has been proposed that this effect may be because, at least in part, of the associated decrease in $PaCO_2$ that accompanies high O_2 breathing rather than to a direct effect of O_2 [121]. The decline mechanism in the $PaCO_2$ is that: When PaO_2 is increased by 100% O_2 inhalation, the CO_2 dissociation curve for blood changes (Christiansen-Douglas-Haldane effect), thus CO_2 affinity for blood is reduced. This causes an increase in the cerebral tissue PCO_2 and hydrogen ion concentration, which stimulate respiration that causes cerebral vasoconstriction with a decrease in $PaCO_2$ [122, 123]. Researchers assessed the effect of hyperoxia on cerebral oxygen consumption using a functional magnetic resonance technique and found that hyperoxia caused a reduction of about 20% in cerebral O_2 consumption and decreased neuronal activity [122]. The reduction in cerebral O_2 consumption is thought to be due to the fact that reactive oxygen radicals damage lipids and proteins and reduce enzyme activity in the oxidative metabolic pathways. Studies in animal models have shown that hyperoxia causes vasoconstriction and causes a decrease in blood circulation in the peripheral vascular beds, including the kidney and gastrointestinal tract [120, 124, 125]. However, it is doubtful that changes in peripheral vascular beds will have any significant clinical effect during preoxygenation. So far, cardiovascular findings do not provide any justification for limiting the use of preoxygenation.

4. Maintenance of a patent airway

There is a dynamical balance between O_2 and CO_2 during breathing. The volume of CO_2 passing from the pulmonary circulation to the alveolar space is 80% of the oxygen volume moving in the reverse direction. This changes radically at the onset of apnea. During apnea, the rate of oxygen extraction from the alveoli remains at 250 mL/min without being affected. The amount of CO_2 entering the alveoli is very low. The reason is that CO_2 is more water soluble than oxygen. For this reason, only 10% of the CO_2 produced per minute (about 20 mL) reaches the alveolar space. The remaining 90% remain molten in the textures. Therefore, the volume of gas in the lungs decreases rapidly during apnea, and if the airway becomes clogged, intrathoracic pressure decreases due to oxygen consumption and thoracic compliance. The closed airway apex begins with an intrathoracic pressure equal to or slightly greater than the ambient pressure. Oxygen uptake causes by an almost subatmospheric intrathoracic pressure. During long-standing apnea, the intrathoracic pressure may be much lower than the environmental pressure, and the alveolar partial pressure of oxygen is significantly dangerously reduced. An open airway will allow oxygen to spread to the apneic lung. Providing an open airway and exposing 100% oxygen creates "apneic mass movement oxygenation," which has been shown to provide oxygen saturation for up to 100 minutes in animal and simulated human studies. If the denitrogenesis of the alveolar space is as complete as possible and a tight compliance mask is used, this passive diffusion of oxygen is more effective. It is important to provide a very high oxygen fraction FiO_2 in order to extend the safety time of the apnea; increasing the oxygen fraction applied to the respiratory tract from 90 to 100% doubles critical hypoxia time with open air [126]. Increasing the FiO_2 applied to the airway from 21 to 90% has a much greater effect on the critical hypoxia time. In a patient with an apnea, 100% oxygen administration to the patent airway will delay the onset of critical hypoxia, but this approach will not reverse the

hypoxemia that is currently developing. Moreover, after a while, it does not prevent continuous development of hypercapnia, which is life threatening and acidosis related to hypercapnia.

5. Reoxygenation

When airway obstruction is relieved during apnea, there is a flow of gas through the pressureless thorax. Securing a high FiO_2 during this one passive inhalation saves time to save the airway. Securing a high FiO_2 during this one-time passive inhalation may lead to a significant prolongation of the duration of the apnea. If airway obstruction is relieved with 100% oxygen, the patient is likely to have a temporary improvement in hemoglobin oxygen desaturation, even though the tidal volume is not maintained and inspired oxygen volume is small.

6. Hemoglobin concentration

The prominence of hemoglobin is not that it is an oxygen storage but it is an efficient oxygen transport from the lungs to the tissues. Anemia causes a small decrease in the time of critical hypoxia; however, this effect will also be more pronounced in patients with reduced FRC.

7. Metabolic rate

Metabolic rate has a simple and predictable effect on the rate of oxygen uptake and hence the duration of critical hypoxia. Increasing the oxygen consumption from 250 to 400 mL/min reduces the time for SpO_2 to increase from 40 to 50% [126].

8. Physiological shunt and dead space

The venous shunt reduces the PaO_2 and SpO_2 foreseeably, but severe hypoxemia develops when the accessible oxygen stores are exhausted. However, many patients with venous shunts also have a reduced FRC (e.g., pulmonary edema), which will accelerate the onset of hypoxia.

8.1. Physiopathological responses to hypoxia

Heart attacks, stroke, and cancer have become the most common causes of death in the twenty-first century, as the average age in many countries around the world is constantly increasing. The causes of these diseases are many and varied; it indicates genetic predisposition and environmental effects. But limited oxygen is a common feature that is contributing to the development of these pathological conditions all around. However, cells and organisms can trigger adaptive responses aimed at helping them cope with these threats to hypoxic conditions. Under this heading, the role of hypoxin in three pathological conditions consisting of myocardial, cerebral ischemia, and tumorigenesis will be briefly explained. The ability to

sustain oxygen homeostasis is crucial for survival of all vertebrate species. For the O_2 presentation, correct forming of complex platform such as entry (lungs), transport vehicles (erythrocytes), motorways and secondary roads (vasculature), and repulsive force (heart) during development and regulations in organism entry form the basis for oxygen homeostasis.

8.2. Physiological responses to hypoxia

8.2.1. Systemic responses

Hypoxia and hyperoxia are detected by specialized chemoreceptor cells. In cases where the use of O_2 is impaired, chemoreceptor systems rapidly change blood circulation as well as pulmonary ventilation and perfusion to optimize O_2 delivery to tissues. This process is based on the direct response of the neuroepithelial bodies present in the airway to the specialized chemoreceptor cells, such as arterial circulation carotid bodies, and the hypoxia of vascular smooth muscle cells.

8.2.2. Vascular smooth muscle cells

While the peripheral vein are enlarged in response to low oxygen, the veins in the pulmonary vein narrows in order to achieve ventilation-perfusion matching by removing blood from areas where ventilation is worse [127]. Hypoxic pulmonary vasoconstriction is a rapid response in the pulmonary arteries and venules. It is abundant in small resistance arteries. Pulmonary vein is an intrinsic feature of the vein smooth muscles and begins with the inhibition of one or several of the various K^+ channels that regulate the membrane potential [128]. The resulting depolarization activates voltage-gated Ca^{+2} channels, and activation of the channels increases the systolic calcium level and leads to myocyte constriction (**Figure 5A**). While K^+ channels are the effects of hypoxic pulmonary vasoconstriction, it does not known that whether they are intrinsically O_2-sensitive or under the control of an actual O_2 receptor. Hypoxic vasodilatation is another rapid response that increases blood perfusion in O_2-deprived tissues. This is especially indicated in coronary and cerebral vessels. Hypoxic vasodilation is mediated in part by K-ATP channels opened in response to hypoxia-induced ATP reduction in vascular smooth muscle cells (**Figure 5B**) [129].

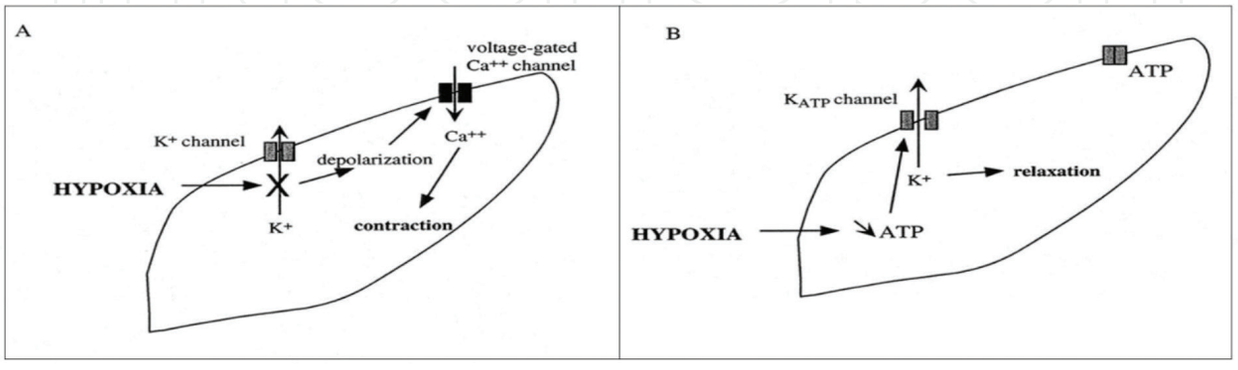

Figure 5. Schematic representation of the response of vascular smooth muscle cells to hypoxia. (A) Pulmonary smooth muscle cells and (B) peripheral smooth muscle cells [129].

However, there are other O_2-sensitive mechanisms that most likely function by regulating the entry of Ca^{+2} into the cell.

8.2.3. Carotid and neuroepithelial bodies

Airway neuroepithelial bodies perceive changes in oxygen inspired, while carotid objects perceive arterial oxygen levels. Both of them respond to low O_2 presentation by initiating activity in efferent chemosensory fibers to form cardiorespiratory regimens in the event of low O_2 [130, 131].

The induction activity of chemoreceptor cells by hypoxia/hypoxemia is dependent on the presence of membrane K^+ channels inhibited by low O_2. As a result, increased cytosolic calcium concentration causes activation of neurotransmitter release and efferent sensory fibers.

8.2.4. Regulation of the cellular metabolism

One of the most essential parameters that healthy cells have to maintain is high ATP content. Cell death occurs when the ATP production does not meet the energy required to sustain the ionic and osmotic balance. When ATP levels fall, ion-motivated ATPase regeneration occurs, leading to membrane depolarization, Ca^{+2} flow into the cell from voltage-gated Ca^{+2} channels, and subsequent activation of calcium-dependent phospholipases and proteases. These events result in uncontrolled cell swelling, hydrolysis of the major cell components, and eventual cell necrosis (**Figure 6**) [132].

8.2.5. Effects of hypoxia on mitochondria

Oxygen deprivation is generally considered mitochondrial respiratory failure in the case of hypoxia or ischemia. In fact, mitochondria are the main source of molecules with high-energy

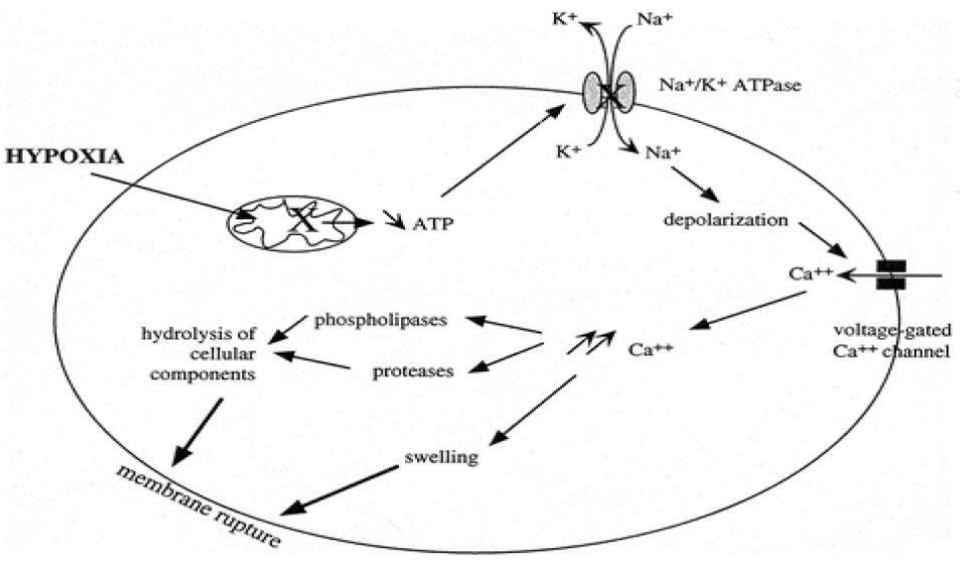

Figure 6. Schematic representation of the cascade leading to cell death when cells are exposed to severe hypoxia [132].

phosphate bonds in normal cells. Electron transport into O_2 in the oxidation of NADH and $FADH_2$ is tightly bound by ATP synthesis. Electron transport is carried out via protein-bound redox centers to complex III then (Co-enzyme Q-cytochrome c reductase) and complex IV from complex I (NADH-coenzyme Q reductase) or II (succinate-coenzyme Q reductase) and forms an electrochemical H + gradient in the inner membrane of the mitochondria. This gradient is used for ATP synthesis by complex V (ATP synthase) after electrochemical gradient: this process is known as oxidative phosphorylation.

Studies on isolated mitochondria have shown that the basic effect of decreasing O_2 on mitochondrial respiration is inhibition in the respiratory chain and increase in proton leakiness while phosphorylation is less affected [133, 134].

8.2.6. Adaptation to hypoxia

Hypoxia adaptation at the cellular level is accomplished by increasing the efficiency of the energy-producing pathways in a basically increased anaerobic glycolysis activity, while reducing energy consuming processes [135]. Ion-motive ATPase and protein synthesis are predominant processes in energy consumption in cells at standard metabolic rate, producing over 90% of ATP consumption in mouse skeleton and 66% in mouse thyocytes [136]. Hepatocyte studies have shown that protein synthesis is largely inhibited in response to hypoxia [137]. Buttgereit and Brand [138] have shown that ATP-consuming processes are in fact organized in a hierarchy, protein synthesis and RNA/DNA synthesis are the first inhibitory processes when energy becomes limited, and Na/K pump and Ca cycle have the highest priority. This phenomenon, also known as oxygen adaptation, involves very precise regulatory mechanisms at the level of translation initiation [139].

Hypoxic cells turn to glycolysis to meet energy needs. Oxygen-dependent mitochondrial respiration from two pathways of ATP production lowers oxygenation than oxidative phosphorylation in oxygen-independent glycolytic ATP production. In the presence of sufficient glucose, glycolysis may continue to produce ATP, depending on the increased activity of glycolytic enzymes. Phosphofructokinase is the major regulator that controls carbon flux by glycolysis. It is allosterically activated by ADP and AMP and inhibited by ATP; in this way, the rate of glycolysis is regulated according to the energy requirement. However, the most potent allosteric activator is fructose-2, 6-biphosphate [140]. The synthesis and degradation of the fructose-2, 6-biphosphatase are dependent on a single enzyme (6-phosphofluoro-2-kinase/fructose-2, 6-biphosphate [PFK-2]). This enzyme is regulated within minutes by phosphorylation via AMP-activated protein kinase (AMPK) [141], but the expression is also enhanced by transcriptional activation via hypoxia-induced factor-1 (HIF-1) [142]. AMPK phosphorylates PFK-2 in a single site resulting in an increase in the Vmax of kinase activity, thus the allosteric activation of phosphofructokinase enhances.

The active kinase opens the ATP-producing catabolic pathways and closes the ATP-consuming anabolic pathways [143, 144]. This acute direct phosphorylation is chronically provided by gene expression. Phosphorylation of PFK-2 is an example of this. AMPK activation has been reported to transport glucose-transporter Glut-4 to the plasma membrane, resulting in glucose uptake. Glut-4 increases the expression of mitochondrial enzymes that play a role in the

long-term hexokinase and tricarboxylic acid cycle and in the respiratory chain. On the other hand, AMPK directly inhibits the expression of fatty acid, triglyceride, and sterol synthase and the expression of fatty acid synthase and gluconeogenesis enzymes [145].

8.2.7. Regulation of the gene expression

When faced with hypoxic difficulties, various responses are developed by cells and tissues:

- Increased ventilation and heart rate
- Return from aerobic metabolism to anaerobic metabolism
- Promotion of increased vascularization
- Strengthening the O_2 transport capacity of blood.

Most of these processes take place very early with the onset of hypoxia and are caused by the activation of existing proteins; but in the long run, all of these responses are mediated by the upregulation of genes encoding key actors, for example:

- Tyrosine hydroxylase, which plays a role in dopamine synthesis in carotid body type I cells.
- Glycolytic enzymes phosphoglycerate kinase 1, pyruvate kinase m, phosphofructokinase, aldolase A, glyceraldehyde 3-phosphate dehydrogenase enolase 1, and glucose carriers Glut-1 and Glut-4.
- VEGF and PDGF to induce angiogenesis and NO synthase that increases vasodilatation
- Transferrin receptors supporting erythrocyte production [146]. The transcriptional side is largely mediated by the HIF-1 activity.

HIF-1 is a heterodimeric factor consisting of HIF-1α and HIF-1β/ARNT. Both subunits belong to the Per-ARNT/Ahr-Sim family of bHLH transcription factors. While the HLH and PAS motifs play a role in dimerization, the main coil is the DNA-binding site. The HIF-1 [alpha] protein contains two transactivation regions at the C-terminus. ARNT is structurally expressed and is located in the nucleus. On the other hand, hypoxia accumulates when HIF-1α mRNA levels are constant in normoxia and hypoxia, and normoxide protein is rapidly destroyed. Normoxide targets the HIF-1α polyubiquitin and destroys the protozoa. In addition to the reduction of hypoxic synthesis of all proteins, ARNT and HIF-1α proteins are translocated efficiently due to the presence of the internal ribosome entry in the mRNA corresponding to the normoxia and hypoxia and normoxside [147].

HIF-1α contains an oxygen-dependent degradation site in which a highly conserved binding site for the tumor suppressor von Hippel Lindau protein (pVHL) is present. The pVHL targets a HIF-1α degradation to form a complex that activates the E3 ubiquitin ligase that ubiquitinates HIF-1α. Inactivation of pVHL is associated with von Hippel Lindau cancer syndrome. It prevents the binding of pVHL mutations to HIF-1α, leading to structural expression of this transcription factor and target genes. Such mutations probably increase angiogenesis potential

by continuous VEGF synthesis. The interaction between HIF-1α and pVHL is regulated via the hydroxylation of two proline residues of HIF-1α with the prolyl hydroxylase enzyme. In the absence of oxygen, this enzyme is no longer active: unmodified prolyl-HIF-1α does not interact with pVHL and accumulates [148, 149]. The absolute oxygen requirement of this prolyl hydroxylase suggests that this enzyme may function as a direct oxygen sensor. Other pathways indicate that HIF-1α stabilization and/or synthesis is also dependent on the PI-3 kinase/Akt pathway in the case of hypoxia. The usage of PI-3 K inhibitors prevents accumulation of HIF-1 [150]. The increase in HIF-1α synthesis is also dependent on the PI-3 K/Akt pathway [151].

HIF-1α stabilization is the first step in HIF-1 activation: For complete transcriptional activity, sufficient redox conditions, separation from chaperone HSP90, phosphorylation as well as coactivators such as CBP/p300 or SRC-1 are required [152, 153]. Hypoxia directly regulates the association of HIF-1α with the coactivator CBP/p300. Similarly to prolyl hydroxylase, it hydroxylates the HIF-1α carboxy-terminal transactivation site on Asn 803 of asparagyl hydroxylase, whose activity is tightly bound to the oxygen. This modification prevents the association with CBP/p300 in the case of normoxia [154].

HIF-1α is not only essential for a variety of physiological responses in chronic hypoxia but also for embryonic survival and cardiac and vascular development. Hif1a$^{-/-}$ mice are not viable: development of Hif1a$^{-/-}$ embryos arrests by day E9.0 and mice die by E10.5 [155, 156]. There is a marked regression of blood vessels in the cephalic region and replacement by a smaller number of enlarged vascular structures. Loss of pericyte support of the endothelium leading to vascular regression is probably responsible for these defects. Massive cell death in cephalic mesothelium was observed concurrent with the deterioration of the vessel development. Heart development in HIF-1$\alpha^{-/-}$ embryos is also abnormal. In ARNT$^{-/-}$ mice, embryonic death probably occurs due to insufficiency of the embryonic component required for vascularization of placenta [157]. Observation of similar vascular abnormalities in HIF-1α and VGEF-deficient embryos suggests hypoxia-induced overexpression in VEGF for the development of the vascular system.

8.2.8. Pathological responses to hypoxia

Hypoxia due to deteriorated blood flow has detrimental effect on organ structure and function. This is especially true in prolapse (cerebral ischemia) and heart infarction (myocardial ischemia). Hypoxia also plays an important role in the regulation of tumor growth and metastasis. Here, we describe the role of hypoxin in these three pathological conditions.

8.2.9. Cerebral ischemia

High energy requirements compared to low energy reserves make the brain particularly susceptible to hypoxic conditions. Although the brain produces a small fraction of total body weight (2%), it proportionally accounts for a large percentage of O_2 consumption. The increased O_2 requirement in physiological conditions is met by a rapid and satisfactory increase in cerebral blood flow. However, hypoxemia and ischemia in children suffering from severe asphyxia and in prolapse sufferers result in brain damage. Longer periods of

hypoxia/ischemia lead to greater effects in the brain. The most sensitive areas appear to be the brain stem, hippocampus, and cerebral cortex. If the damage processes and eventually oxygenation is not restored, it becomes irreversible. Acute cell death is primarily caused by necrosis, but hypoxia also causes by late apoptosis. Although it is the only way to protect tissue, it should be noted that mainly reactive oxygen species reperfusion induces cell death through production and inflammatory cell infiltration. If the decrease in pO_2 is not too severe, it suppresses some of the cell functions; for example, proton synthesis and spontaneous electrical activity are suppressed and this condition is called penumbra, which is characterized with return when O_2 is provided [158, 159].

8.2.10. Myocardial ischemia

Acute coronary syndromes resulting from occlusion of one of the coronaries expose heart to ischemic conditions. If reperfusion is achieved after short ischemic periods (<20 minutes), it is reversible and not associated with necrosis development, but results in stunning phenomena. If the coronary occlusion duration goes beyond this point, a necrosis wave propagates from the subendocardium towards the subepicardium. After a few hours, reperfusion does not diminish the size of myocardial infarction.

Within seconds of cessation of blood flow energy metabolism shifts from mitochondrial respiration to anaerobic glycolysis. Concurrent active contractions are reduced and then terminated. Accumulation of lactate and protons in cardiomyocytes induces acidosis and osmotic load and subsequent cell edema. In addition, intracellular Ca^{+2} increases, probably due to the combined effect of Na^{+}/Ca^{+2} modulators activated by cellular acidosis. If this happens, it will lead to cell necrosis [160]. To restore aerobic metabolism and to protect ischemic myocytes, it is necessary to restore the arterial flow. However, this situation itself increases the damage. This process is called ischemia-reperfusion injury. In the first few minutes of reperfusion, a large amount of released reactive oxygen radicals is a possible cause of this contractile failure.

8.2.11. Tumor angiogenesis

The onset of new vascularization in many primary tumors is defined as the angiogenic switch. Several key signaling events have been identified that involve immune/inflammatory responses and genetic mutations, but metabolic stress (hypoxia) is probably the most important of these factors [161, 162]. Tumor cells survive in the fluctuations of HIF-1 activation in oxygen tension. Various studies using HIF-1 mutant cells have shown that HIF-1 has profound effects on tumor biology. For example, tumors arising from embryonic stem cells with HIF-1α defect show abnormal vascularity and low growth rate [39]. Furthermore, HIF-1 is upregulated in a wide range of tumors, and there are important links between tumor grade, vascularization, and HIF-1α overexpression [163, 164]. This expression pattern suggests that tumor cells respond to hypoxia caused by HIF-1–mediated angiogenic protein expression. The VEGF is the strongest of these and its expression is regulated by HIF-1. In addition to promoting VEGF secretion, HIF-1 is also important for hypoxia adaptation of tumor cells [165].

8.2.12. Determination of hypoxemia

Tumor hypoxia is the strongest prognostic factor in various cancers. Hypoxic cells contribute to intrinsic radiation resistance. Apoptosis resistance and increased metastasis capacity are other contributing factors to this negative outcome. Therefore, the factors that aim to determine tumor oxygenation have serious clinical safety. A number of studies aim to identify a good hypoxia marker that can be used in immunomicroscopy studies [166]. The use of 2-nitromidazole specifically binding to hypoxic cells has been suggested; pimonidazole and EF5 are the best known of these. Reduction enzymes metabolize these drugs in the presence of oxygen, but when there is no oxygen they are converted to highly reactive free radical molecules that are covalently bound to protein and DNA. Subsequently, drug-protein binding may be detected by specific antibodies. Studies similar to the work of Evans and his colleagues showed the suitability of this method. However, these drugs have the disadvantage that they need to be administered from a tissue sample.

The discovery that HIF-1α specifically undergoes hypoxic upregulation and is rapidly destroyed in the presence of oxygen suggests that this protein may be an endogenous marker of this kind. Several studies examining HIF-1α as an endogenous hypoxia marker have confirmed the spatial association of HIF-1α with EF5 and pimonidazole [167]. It should be noted that the use of HIF-1α as a hypoxia marker is not easy because the level of HIF-1α is also regulated by factors other than hypoxia, such as oncogenic mutations [168].

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