APNEIC OXYGENATION; PULMONARY AND CARDIOVASCULAR EFFECTS

[1]Kolettas A, [2]Grosomanidis V, [2]Fyntanidou B, [3]Kotzampassi K,
[5]Kolettas V, [4]Theodosiadis P, [2]Karakoulas K, [2]Mitos G, [2]Aidoni Z, [2]Vasilakos D

ABSTRACT

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Kolettas A, Grosomanidis V, Fyntanidou B, Kotzampassi K, Kolettas V, Theodosiadis P, Karakoulas K, Mitos G, Aidoni Z, Vasilakos D

Apneic oxygenation is an adjunct 'ventilation' technique that involves insufflation of oxygen at varying flows through a catheter that is inserted through the endotracheal tube and is positioned above the carina. Apneic oxygenation improves gas exchange efficiency and preserves the arterial oxygenation at an acceptable level. The understanding of the mechanism that is responsible for the sustained high alveolar and blood oxygenation levels requires the substantial knowledge of the physiology regarding the transport and exchange of alveolar gases. Application of apneic oxygenation may be necessary in some clinical situations, in which no movement of the chest or the lungs may be desirable, such as during cardiothoracic surgery or during some radiological procedures, in order to eliminate respiratory motion artifacts. Moreover, it is used during the apnea test for the diagnosis of brain death, to ensure an adequate arterial oxygenation. Under ideal conditions, apneic oxygenation could theoretically be sufficient to provide enough oxygen for survival for a longer time period. However, accumulation of carbon dioxide would remain the limiting factor. Hypercapnia and subsequent acidosis are responsible for most of the respiratory and cardiovascular effects of apneic oxygenation.

Apneic oxygenation is an alternative technique, which contributes to the maintenance of oxygenation during apnea by intratracheal insufflation of oxygen at different flow rates. Oxygen is insufflated through a catheter that is inserted through the endotracheal tube and is positioned just above the trachea bifurcation at a flow ranging between 2L/min and 10L/min. A modified apneic oxygenation technique is represented by the endobrochial apneic oxygenation. In this case oxygen is insufflated through a catheter that is inserted through a double lumen endotracheal tube and is placed in one of the two major bronchus. Besides oxygenation maintenance, carbon dioxide accumulation cannot be avoided. However, if high flow rates are used, carbon dioxide removal can be partly enhanced.

1: Thessaloniki Heart Institute, St. Luke's Hospital, Greece

2: Anesthesia and Intensive Care Clinic of Aristotle University of Thessaloniki, Greece

3: Surgical Clinic of Aristotle University of Thessaloniki, Greece

4: "Euromedica Central Clinic", Thessaloniki, Greece

5: Cardiological Clinic, General Hospital of Chalkidiki, Poligiros, Greece

Historic reference

The first report on apneic oxygenation was made in 1947 by Draper, Whitehead and Spencer, who studied the pulmonary gas exchange

and the ultimate survival of dogs subjected to a 45min period of diffusion respiration[1]. The head of the animals was placed in a chamber at which a low pressure valve was attached. Throughout the experiment 6-8L/min of oxygen was admitted into the chamber. Apnea was induced and maintained for a standard time period of 45min by infusion of 1% thiopental sodium and in order to ensure airway patency of the dogs, an artificial airway device was used. The data of this study show that during 45min diffusion respiration there is a marked accumulation of carbon dioxide in the pulmonary alveoli and a consistent decrease in the venous blood pH. However, all of the animals subjected to this ordeal, survived.

Frumin, Epstein and Cohen used in 1959 the term "apneic oxygenation" - which was first employed by Nahas in 1956 - instead of the older "diffusion oxygenation" to avoid the misconception regarding the mechanism that is responsible for the sustained high alveolar and blood oxygenation levels[2]. After induction of anesthesia, a cuffed endotracheal tube was inserted in eight healthy patients, who were scheduled for a variety of minor operations. Following denitrogenation, mechanical ventilation was stopped, whereas the patient remained connected to the circle apparatus, which was filled with oxygen 100% at a flow rate of 6-8L/min. SpO_2, pH, $PaCO_2$ and the epinephrine and norepinephrine concentrations in arterial plasma were determined at standard time intervals. During the whole study period, arterial pressure and the electrocardiogram were determined either continuously or at intervals no greater than 5min. They reported a linear rise in $PaCO_2$ and a decrease in arterial pH to about 6.72, while hemoglobin was fully saturated with oxygen throughout the apneic period (more than 30min). The arterial plasma epinephrine and norepinephrine concentrations increased as the apnea progressed. A limitation of this study might be that apnea was interrupted, since the criterion for administration of neuromuscular blocking agent was the detection of spontaneous respiration.

Two years later, in 1961, Millar and Morris studied the effects of 60min of apneic oxygenation in adrenalectomized dogs[3]. They attempted to determine the extent to which release of norepinephrine and epinephrine from areas outside the adrenal medulla contributes to the increased plasma catecholamine concentrations during apneic oxygenation, namely the extent of the compensatory sympatho-adrenal stimulation. From the results of this study it is concluded, that increases in plasma norepinephrine levels consistently accompany the rise in $PaCO_2$ and therefore it is reasonable to believe that release of norepinephrine during apneic oxygenation from extra-adrenal areas or organs is an early response to respiratory acidosis. In this study apneic oxygenation was induced by the connection of the endotracheal tube to a T-piece - with a loose expiratory valve - through which oxygen was delivered at a low flow rate. This technique resulted in larger carbon dioxide accumulation compared to that during endotracheal oxygen insufflation through a catheter that is positioned at the carina level.

Fraiolo, Sceffer and Steffenson studied apneic oxygenation in 13 patients undergoing microlaryngoscopy with a pharyngeal catheter for oxygen administration at a flow rate of 6L/min and 18 patients having minor surgical procedures with a cuffed endotracheal tube connected to an oxygen filled Collins spirometer for oxygen administration[4]. Any alteration of PaO_2, $PaCO_2$, P_AN_2, pH, FRC (Functional Residual Capacity) and the oxygen uptake was recorded, while ECG and the arterial pressure were continuously monitored. Fraiolo et al reported that PaO_2 decrease was faster and more profound in patients with a FRC/weight ratio <50ml/kg. Therefore, they suggested that the FRC/weight ratio could provide a useful guide for selecting patients that might be suitable for apneic oxygenation. The results of this study were attributed to the fact that patients with larger body mass index would have a greater amount of total body nitrogen as well as increased cardiac output and, therefore, a higher rate of nitrogen return to the lung. Nitrogen returning to the lung will replace alveolar oxygen causing a lower P_AO_2 and PaO_2. However, the oxygenation was preserved at an acceptable level for a time period of 15min and the worst PaO_2 value recorded during the study was 100mmHg.

In 1982 Pesenti et al studied a combination of apneic oxygenation and extracorporeal removal of carbon dioxide ($ECCO_2R$) in an experimental model of preterm lambs[5]. The aim of this study was to explore the possibility of hyaline membrane disease prevention. According to this study, apneic oxygenation in combination with extracorporeal removal of the carbon dioxide resulted in fewer ventilation related complications and better outcome, since there was time for the respiratory mechanics to stabilize before the onset of mechanical ventilation. The results of this study would be more impressive if oxygenation was restored only by apneic oxygenation.

In a similar study, Nielsen et al, combined apneic oxygenation with extracorproreal removal of the carbon dioxide in an experimental swine model, in which acute lung injury was conducted through recurring wash out of the surfactant[6]. Normal PaO_2 levels were restored by the combination of apneic oxygenation and the extracorporeal device membrane.

Finally, Cook et al studied in 1998 apneic oxygenation in infants and young children[7]. Their aim was to determine the time period, during which the application of apneic oxygenation could be considered as a safe technique. They reported that PaO_2 levels were acceptable during the whole time of the study (5min). Moreover, they concluded that, opposed to adults, in infants the most restrictive factor of the application of apneic oxygenation was the linear decrease in PaO_2 and not the increase in $PaCO_2$.

Transport of gases under apneic oxygenation conditions.

The movement of gases from one area to another depends on the pressure gradient between these two spaces. This pressure gradient may be a result of hydrostatic pressure gradient - and in this case the movement is more active (transport) - or a result of partial pressure gradient (the pressure that one component of a mixture of gases would exert if it were alone in a container) - and in this case the movement is less effective macroscopically (diffusion). The gas velocity depends on the airway resistance in the case of transport or on the resistance properties of the membrane across which the gas molecules are transferred in the case of diffusion.

Oxygen

In the alveoli, oxygen is continuously diffusing down its concentration gradient into the blood, and is replaced by diffusion of carbon dioxide in the opposite direction across the alveolar capillary membrane.

Oxygen passes into the pulmonary capillaries by passive diffusion across the alveolar-capillary membrane (oxygen diffusion from the air to the liquid state). The continuous oxygen diffusion is explained by the preservable alveolar-capillary partial pressure gradient due to the oxygen bound to hemoglobin[8,9].

The oxygen diffusing capacity depends on partial pressure gradient across the alveolar-capillary membrane, on the temperature, on the alveolar-capillary membrane surface area, on the distance until hemoglobin is reached and on the oxygen molecular weight[10,11]. The more soluble the gas, the bigger is the number of the molecules that are available for diffusion, under a given pressure gradient. Moreover, diffusion capacity is proportionally better when the alveolar membrane surface area is bigger. On the other hand, the diffusion capacity is decreased when the alveolar-capillary membrane is thickened. In addition to this, the gas diffusion capacity is proportional to the gas molecule velocity, which is inverse proportional to the square root of its molecular weight. Finally, the diffusion capacity will be increased when the temperature is high, since this will cause a greater molecular kinetic energy. However, the temperature level is not taken into consideration, since it is thought to remain constant. All of the above is included in the following equation:

$$D \propto \frac{\Delta P \times A \times S}{d \times \sqrt{MW}} \qquad (1\text{-}1)$$

where **D** is the diffusion velocity, **ΔP** is the pressure gradient between the alveoli and the capillary, **A** is the diffusion alveolar-capillary membrane surface area, **S** is the water solubility of oxygen, **d** is the diffusion distance (mem-

brane width) and **MW** is the oxygen molecular weight.

Two parameters that describe the physicochemical properties of the gas are included in this equation (1-1): the solubility (S) and the molecular weight (MB). The ratio $S/\sqrt{MW}$ is proportional to the gas diffusion coefficient. Therefore, the gas diffusion velocity is proportional to the gas diffusion coefficient for a given partial pressure gradient and a specific diffusion membrane. If oxygen diffusion coefficient is presumed to be 1, then the relative diffusion coefficients for the alveolar gases are shown in Table 1:

Table 1. Relative diffusion coefficients of various gases in body fluids.

Oxygen	1.0
Carbon dioxide	20.3
Carbon monoxide	0.81
Nitrogen	0.53
Helium	0.95

Alveolar gases are very soluble to lipid and therefore they can diffuse easily across the cell membranes[11]. Hence, the most important obstacle in the diffusion process is water, which is a standard tissue component. On the other hand diffusion across lipoid membranes does not present any difficulties.

The pulmonary capillary can be considered to have two different parts: the first one, which receives the mixed venous blood and the second part, which contains the enriched with oxygen blood after the oxygen diffusion process has been completed. The oxygen partial pressure in the beginning of the first part of pulmonary capillary is that of the mixed venous blood P_vO_2. Therefore the oxygen partial pressure in the first part of pulmonary capillary can be expressed as $P_{vc}O_2$.

The oxygen partial pressure in the second part of pulmonary capillary is that of the fully enriched with oxygen blood, namely P_cO_2. The partial pressure **gradient** responsible for the initiation of oxygen diffusion across the alveolar-capillary membrane is the difference between the alveolar partial pressure of oxygen and the oxygen partial pressure in the first part of pulmonary capillary and is described by the following equation (1-2):

$$\Delta P = P_AO_2 - P_{vc}O_2 \qquad (1\text{-}2)$$

where $\mathbf{P_AO_2}$ is the alveolar partial pressure of oxygen and $\mathbf{P_{vc}O_2}$ the oxygen partial pressure in the first part of pulmonary capillary.

As oxygen diffusion process evolves and the blood is passing from the capillary origination to its end, the pressure gradient ΔP gradually is decreasing and under normal conditions (normal thickness of alveolar-capillary membrane) becomes zero at the second part of the capillary, where the accommodated blood has become fully saturated.

P_AO_2 can be estimated by the following equation (1-3):

$$P_AO_2 = (P_B - P_{H_2O}) \times F_{iO_2} - \frac{P_{aCO_2}}{RQ} \qquad (1\text{-}3)$$

where $\mathbf{P_B}$ is the barometric pressure, $\mathbf{P_{H2O}}$ is the water vapour partial pressure, $\mathbf{F_iO_2}$ is the inspired oxygen fraction, $\mathbf{P_aCO_2}$ is the arterial partial pressure of carbon dioxide and **RQ** is the respiratory quotient (the $\dot{V}CO_2$ to $\dot{V}O_2$ ratio), which is considered to be 0.8.

After oxygen diffusion across the alveolar-capillary membrane is completed, oxygen is still separated from the hemoglobin by a thin plasma layer and the red blood cells membrane. After the oxygen molecule approaches hemoglobin, then it can be bound to heme. This diffusion procedure is described by equation (1-1).

The partial pressure gradient ΔP through alveolar-capillary membrane at the capillary beginning (equation 1-2) is preserved, due to the continuous return of mixed venous blood into the capillary vessels, which is poorly saturated with oxygen. Therefore, oxygen diffusion to the capillary is not interrupted. This continuous oxygen diffusion across the alveolar-capillary membrane causes a continuous oxygen uptake from the alveolus, resulting in the generation of a partial pressure gradient ΔP_1, which is responsible, under apnea conditions, for the air movement from the alveolar sacs, the 3 divisions of alveolar ducts, the 3 divisions of respiratory

bronchioles, the 13 divisions of terminal bronchioles, the 2 divisions of bronchioles, the main bronchus, the trachea and the pharyngeal cavity to the alveoli. In a setting of oxygen insufflation at a standard flow somewhere in the tracheobronchial tree (in case of a single insufflation catheter, the best place would be just above the carina), a second partial pressure gradient ΔP_2 is generated.

The pressure gradient ΔP_2 can be expressed generally by the following equation:

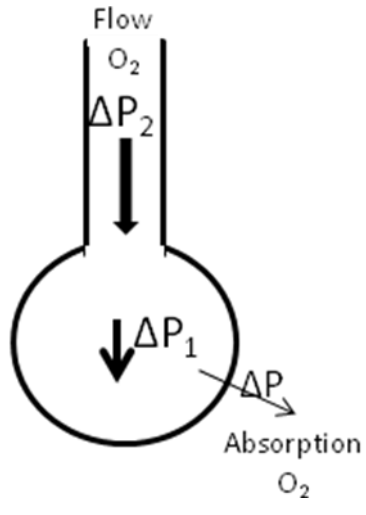
$$\Delta P_2 = \dot{V} \times R_{airways} \qquad (1\text{-}4)$$

The magnitude of ΔP_2 is not constant. ΔP_2 at the level of the tip of insufflation catheter is greater than at lower levels, since a part of ΔP_2 is always consumed to allow the oxygen to overcome the airway resistance during its downward motion to alveoli with the given flow ′V. ΔP_2 has the same direction as ΔP_1 and therefore is added to it. Thus, the total pressure gradient ΔP_{total} from the tip of insufflation catheter to the alveolar side of the alveolar-capillary membrane is the sum of ΔP_1 and ΔP_2 as described by the equation (1-5):

$$\Delta P_{total} = \Delta P_1 + \Delta P_2 \qquad (1\text{-}5)$$

The velocity of the air movement towards the alveoli is proportional to the total pressure gradient ΔP_{total} . ΔP_{total} depends on the diffusion rate across the alveolar-capillary membrane, on the oxygen insufflation flow rate, on the diameter of the insufflation catheter and on the location of its tip (Figure 1).

Figure 1. Oxygen movement from the major airway to the alveolus.



The above mentioned mechanism is responsible for the oxygen movement from the major airways to the alveoli and therefore, for the high levels of P_AO_2. Thereby, the continuous oxygen diffusion across the alveolar-capillary membrane is ensured.

When a single insufflation catheter is used, the best place for it is just above the carina, since from that point the distance to the alveoli is for both lungs the minimum possible. For a given oxygen flow, the oxygen ejection rate (velocity u) from the tip of the catheter depends on the oxygen flow and on the catheter diameter, which is determined by its cross-section A (equation 1-6):

$$\dot{V} = \frac{\Delta V}{\Delta t} = \frac{A \times \Delta S}{\Delta t} = A \times u \Leftrightarrow \dot{V} = A \times u \Leftrightarrow u = \frac{\dot{V}}{A} \qquad (1\text{-}6)$$

Therefore, the thinner the insufflation catheter, the higher the oxygen ejection rate u is, which results in better oxygen partial pressure gradient between the airways and the alveoli and in a more efficient oxygen transport[7]. However, the thinner the catheter, the bigger the resistance to the oxygen transport is. In order to maintain a standard oxygen flow, it is mandatory to apply a greater pressure at the upper tip of the catheter. The requisite pressure gradient is the limitation, which is designated by the characteristics of the external oxygen delivery system, whenever the oxygen flow reaches a maximum level or the catheter diameter a minimum diameter or both at the same time.

The role of Nitrogen.

When apnea is commenced, the alveolus volume (and the lung volume respectively) remains constant instead of becoming decreased due to the gas mixture movement from the major airways, that was described above. If the gas mixture consists of atmospheric air, the oxygen will be partly absorbed, whereas the nitrogen will remain in the alveolus and its concentration and partial pressure will increase. The partial

pressure of nitrogen depends on the total pressure in the alveolus (which depends on the atmospheric pressure) and on the nitrogen concentration in the gas mixture (equation 1-7).

$$P_A N_2 = (P_B - P_{H_2O}) \times F_{iN_2} \qquad (1\text{-}7)$$

This procedure results almost immediate (in 2min in humans) in a decrease of the alveolar partial pressure of oxygen (P_AO_2) and hypoxia[12].

If the gas mixture consists of pure oxygen, the oxygen that is absorbed is replaced by the same amount of oxygen and not by nitrogen. Therefore, P_AO_2 will decrease proportionally to the increase of P_ACO_2 (3-6mmHg/min after the first minutes). In this setting, hypoxia may occur after a longer time period.

In a setting, where before the apnea initiation, ventilation (mechanical or spontaneous) with pure oxygen is performed, there will be no nitrogen in the alveolus gas mixture and the initial P_AO_2 will be 660mmHg. Provided that oxygen is insufflated into the trachea and the patients have patent airway, hypoxia will occur in this case even later (theoretically after 100min).

Fraioli, Sheffer et al report another mechanism, which explains how nitrogen contributes to the P_AO_2 decrease[4]. Even when nitrogen has been entirely washed out of the alveoli by hyperventilation with pure oxygen, the nitrogen that is dissolved in blood diffuses across the alveolar-capillary membrane due to the partial pressure gradient between blood and alveolus. The nitrogen diffusion results in a P_AO_2 decline, which depends on the duration of the pure oxygen ventilation, on the total body nitrogen reservoir, on the cardiac output, on the FRC and on the body temperature.

The role of carbon dioxide.

Carbon dioxide (CO_2) is much more soluble than oxygen in water and undergoes a much more rapid (20 times more) tissue diffusion, despite the fact that its vapor density is bigger (table 1-1)[10]. Carbon dioxide is generated in the mitochondria and is then transported in the cytoplasm, in the interstitium, in the venous blood and in the pulmonary capillaries. During this transport its partial pressure is decreased. Then, carbon dioxide diffuses across the alveolar-capillary membrane and is then washed out of the alveolus by ventilation.

Carbon dioxide diffuses across the alveolar-capillary membrane and is converted from the liquid to the gas phase. Carbon dioxide diffusion depends on the parameters that are described in the equation 1-1. Due to the greater diffusion capacity of carbon dioxide, the requisite partial pressure gradient is much less (6mmHg) compared to the one required for the oxygen diffusion (60mmHg)[10]. In the pulmonary capillaries carbonic acid is dissociated to carbon dioxide and water under the action of carbonic anhydrase (equation 1-8).

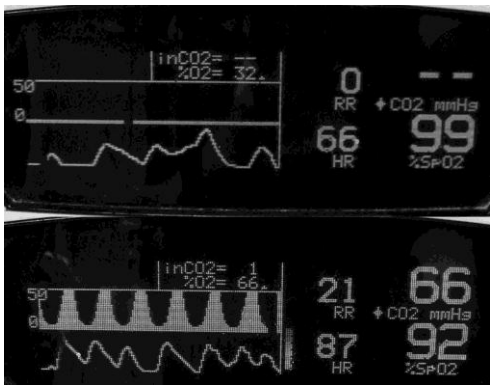
$$H_2CO_3 \rightarrow H_2O + CO_2 \qquad (1\text{-}8)$$

Then, carbon dioxide diffuses across the alveolar-capillary membrane and is washed out to the atmospheric air. Carbon dioxide elimination depends on its production rate and on the ventilation pattern. For a given carbon dioxide production rate, P_ACO_2 is inverse proportional to the lung ventilation[13]. During apnea there are no active respirations and therefore no active gas movement. This results in carbon dioxide accumulation in the alveolus, since carbon dioxide is not washed out. After the first minutes of apnea, the increase rate of P_ACO_2 is 3-6mmHg/min, whereas P_AO_2 decreases[12].

Oxygen insufflation during apnea at a flow bigger from the oxygen absorption rate is considered to contribute to a progressive alveolar gas mixture replacement. The replacement rate depends on all parameters that influence the oxygen ejection rate through the tip of the catheter. The partial alveolar gas mixture replacement contributes to the carbon dioxide wash out and therefore to a limited reduction of P_ACO_2 and P_aCO_2 increase rate.

During apneic oxygenation there is a gradual carbon dioxide increase (figure 2), causing hypercapnia and acidosis, despite the fact that carbon dioxide is partly washed out from the airways[14,15]. The incremental P_ACO_2 increase results in P_AO_2 decrease and consequently in partial pressure gradient reduction.

Figure 2. Capnography during apneic oxygenation and immediately after the onset of ventilation



PATHOPHYSIOLOGIC CHANGES DURING APNEIC OXYGENATION

Hypercapnia results in hydrogen ions $[H^+]$ blood concentration increase and consequently in acidosis. Buffers are substances that minimize the acid-base changes. One of the most important extracellular buffers in blood is the bicarbonate buffer system (H_2CO_3/HCO_3^-). Its action is described by the following equation (1-8):

$$H_2O+CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \quad (1\text{-}8)$$

The initial step is catalyzed by the enzyme carbonic anhydrase. Carbonic acid dissociates then immediately into $[H^+]$ and $[HCO_3^-]$. This reaction is accelerated by $[CO_2]$ rise. The relationship between pH and buffer pK_a may be calculated by the Henderson-Hasselbalch equation (equation 1-9), where 0.03 stands for the solubility coefficient of carbon dioxide in plasma:

$$pH = pK' + \log\left(\frac{[HCO_3^-]}{0.03 * P_{aCO_2}}\right) \quad (1\text{-}9)$$

The Henderson-Hasselbalch equation can be transformed into the Henderson equation, which has no logarithms (equation 1-10):

$$[H^+] = 24 * \frac{P_{aCO_2}}{[HCO_3^-]} \quad (1\text{-}10)$$

where $[H^+]$ is expressed as nEq/L, P_{aCO2} as mmHg and $[HCO_3^-]$ as mEq/L.

The extracellular $[H^+]$ and the corresponding pH can be calculated by this equation (Table 2).

Table 2 : Correlation between pH and $[H^+]$

pH	$[H^+]$ nEq/L
6.80	158
6.90	126
7.00	100
7.10	79
7.20	63
7.30	50
7.40	40
7.50	32
7.60	25
7.70	20

An acute increase in P_aCO_2 causes a minimum alteration in $[HCO_3^-]$. For example, a $PaCO_2$ increase from 40mmHg to 80mmHg results in an increase of the dissolved carbon dioxide from 1.3mEq/L just to 2.2mEq/l. In addition to that, the equilibrium coefficient of equation (1-8) ensures that carbon dioxide rise results only to minimum right shift of the equation.

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \quad (1\text{-}8)$$

Therefore, an acute P_aCO_2 increase and the minimum rise in dissolved carbon dioxide have no effect on the $[HCO_3^-]$ concentration.

The $[H^+]$ concentration for the given P_aCO_2 value (80mmHg) can be calculated by the equation (1-10): $[H^+]=(24*80)/24=80$ nEq/L, and the corresponding pH derives from Table 2 (pH=7.10).

Consequently, $[HCO_3^-]$ rises by 40nEq/L, since $[H^+]$ to $[HCO_3^-]$ production ratio is 1:1. Thereby, extracellular $[HCO_3^-]$ rises from 24mEq/L to 24.000040mEq/L, whereas pH decreases from 7.40 to 7.10 [16].

In acute P_aCO_2 alterations, it is possible to calculate the pH change as it was described above.

The P_aCO_2 value represents the equilibrium between carbon dioxide production and its elimination by ventilation. Under apneic oxygenation

carbon dioxide is no longer washed out of the lungs, since there is no ventilation, and this results in annihilation of the partial pressure gradient, which is the reason for the incremental P_aCO_2 increase. The P_aCO_2 increase rate depends on the body temperature, on the alertness or sedation of the patient, on the underlying pathology (fever, sepsis, trauma, operative stress, tremor), on the mechanical ventilation, on the use of muscle relaxants etc. The P_aCO_2 increase results in acidosis, which is the main mechanism through which apnea oxygenation affects the different systems.

The principal effects of hypercapnia and subsequent acidosis include the decreased myocardial contractility and the suppression of the smooth muscle fibers[17], which are compensated by the increased secretion of catecholamine, caused by hypercapnia. According to experimental studies in rats, hypercapnia induces an increase in coronary circulation. This seems to be the result of the release of nitric oxid (NO) and the simultaneous activation of ATP channels[18]. Moreover, hypercapnia and acidosis are responsible for an increased tendency to fibrillation and other arrhythmias. Increased carbon dioxide levels have an indirect effect on the vasomotor center in brain, which induces a huge sympathetic action, causing vasoconstriction of blood vessels and increase of systemic vascular resistance and blood pressure[19]. However, as acidosis becomes more excessive and concentration of [H+] and [K+] increase, the main effect is dilatation of blood vessels and decrease of systemic vascular resistance [19]. When apneic oxygenation is applied for a prolonged time period (>30min), there is a big possibility that it will be necessary to support the circulation with vasoconstrictors (such as phenylephrine or norepinephrine).

In an unpublished experimental study in pigs (doctorate thesis of Kolettas A with the title "Actions of Apneic Oxygenation on the Circulatory and Respiratory Systems under General Anesthesia"), the systemic vascular resistance (SVR) increased during the first 20min after the initiation of apneic oxygenation. Then the SVR decreased and reached lower levels than before apneic oxygenation was commenced. SVR remained low even after the piglets were reconnected to the ventilator (after 40min). After 10min of mechanical ventilation and restoration of the acid-base homeostasis, SVR returned to the initial values.

Hypoxic pulmonary vasoconstriction (HPV) is a physiologic response of resistance pulmonary arteries to alveolar hypoxia. HPV regulates ventilation-perfusion matching, aiming to the reduction of shunt fraction and the optimization of systemic P_aO_2. The core mechanism of HPV is the smooth muscle cell of the resistance pulmonary arteries. The mechanism of HPV is very complex. The Redox theory proposes the coordinated action of a redox sensor (the proximal mitochondrial electron transport chain) that generates a diffusible mediator (a reactive oxygen species (ROS)) that regulates an effector protein (voltage gated potassium (K_v) and calcium channels). Inhibition of oxygen-sensitive Kv channels depolarizes pulmonary artery smooth muscle cells, resulting in activation of Ca^{+2} channels and in Ca^{+2} influx and vasoconstriction [23]. Hypoxia and hypercapnia induced acidosis triggers the above cascade causing an increase of pulmonary vascular resistance (PVR).

The above mentioned experimental study of unpublished doctorate thesis of Kolettas A demonstrated a statistical significant increase of PVR after the initiation of apneic oxygenation, which returned to normal values after the piglets were reconnected to the ventilator.

In the study of Lynch et al, hypercapnia caused constriction of the isolated pulmonary arteries of rats. However, this response was not present when the endothelium of the vessels was removed. Furthermore, the non specific inhibition of the nitric oxide synthase (NOS) by 10^{-3}M L-NAME (L-nitro-arginine mehthyl ester) also diminished this response. In conclusion, the data of this study suggest that hypercapnia causes constriction of the pulmonary vessels, which is related to the endothelium and the reduced production of NO [24].

Hypercapnia causes alterations in the cerebral blood flow and in the consciousness level. Pa-

rallel to the P_aCO_2 rise, the cerebral blood flow increases in a rate of 1-2ml/100g/min for every 1mmHg [17]. Hypercapnic induced acidosis activates the endothelial NOS, via prostaglandin PGE_2. This process depends on K^+ and Ca^{2+} channels. This results in vasodilatation of the cerebral circulation and cerebral blood flow increase [25].

When P_aCO_2 reaches 60-75mmHg, the non-anaesthetized patient starts to experience dyspnea. This results in stimulation of the respiratory center and in increase of the frequency and the depth of the respiratory efforts.

P_aCO_2 values that exceed 90-120mmHg, induce carbon dioxide anesthesia[26]. Moreover, the inhalation of a gas mixture with more than 30% carbon dioxide induces anesthesia, which is complicated by convulsions[27]. At carbon dioxide levels greater than 150mmHg, the respiratory center is suppressed and a vicious cycle is evoked, which may lead to death[28].

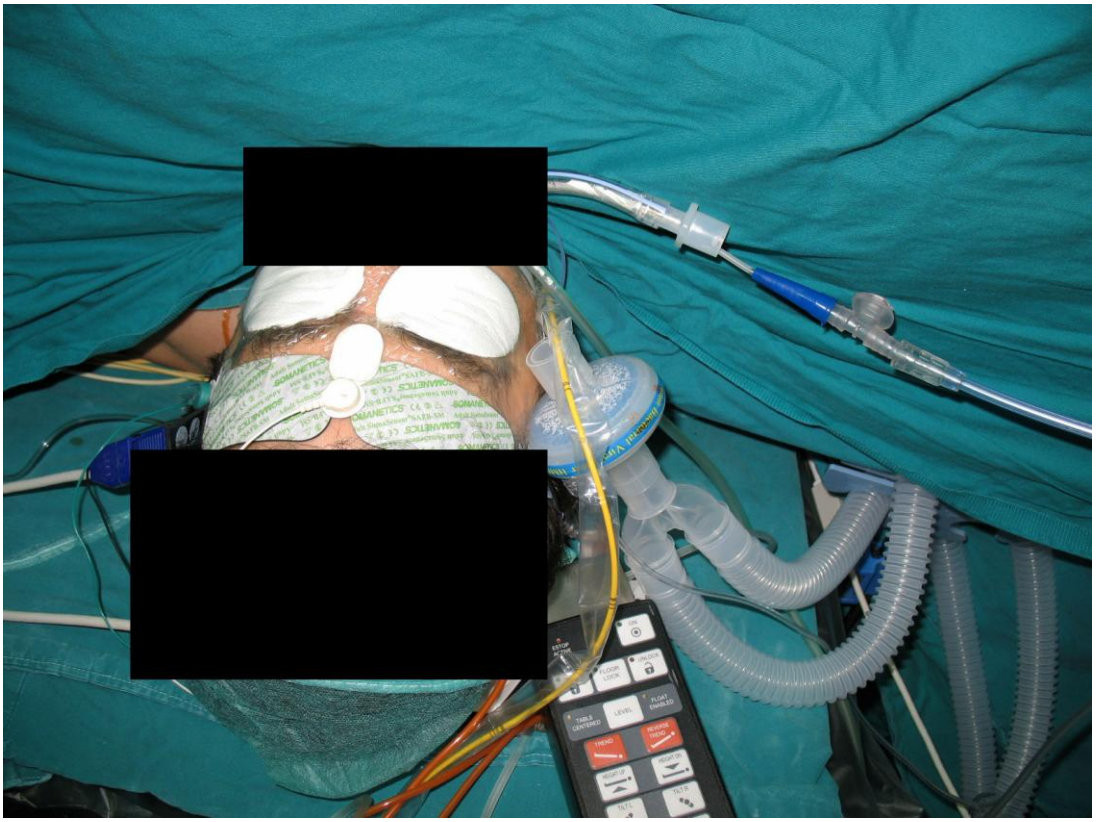
In the literature there is a report of one patient who recovered after hypercapnia. He underwent a cosmetic surgery of 4-6 hours duration under manual ventilation with a face mask. His oxygenation was preserved at acceptable levels (S_aO_2>90%). The initial blood gases analysis revealed a severe respiratory acidosis (pH=6.60 and $PaCO_2$=375 mmHg). The patient was then intubated and after a period of mechanical ventilation and a return of plasma pH towards normal, he woke up without any neurological deficit[20].

CLINICAL APPLICATION OF APNEIC OXYGENATION

Since apneic oxygenation can maintain P_aO_2 above normal levels for a short but important time period, this technique can be applied in a **cannot intubate- cannot ventilate** (CICV) situation (jet ventilation is an alternative technique of apneic oxygenation). In fact, this method provides us with time, until a more effective and permanent way of ventilation is ensured or until muscle relaxants action is reversed and spontaneous ventilation starts again.

Apneic oxygenation by endotracheal oxygen

Figure 3: Apneic oxygenation during a cardio surgery procedure by endotracheal insufflation of oxygen

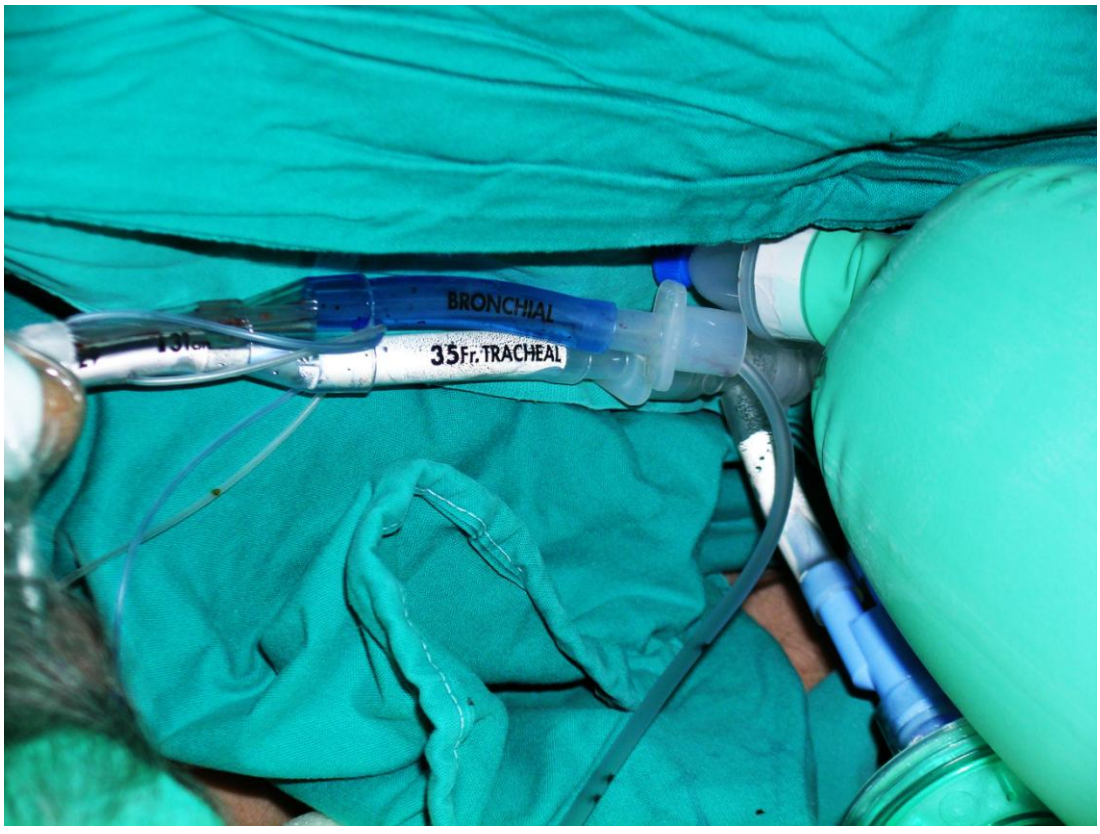


insufflation is applied during **apnea test for the diagnosis of brain death**. Thereby, a sufficient oxygenation is ensured for an acceptable time period (for at least 10min). In the mean while we observe for any respiratory efforts due to the carbon dioxide increase. The application of other ventilation techniques is not recommended, since they interfere in a more intense way in the carbon dioxide removal and they cause some kind of respiratory efforts, which deteriorate the value of the test.

Apneic oxygenation can be applied during some surgical **or radiological procedures**, where it is mandatory to have absolutely no movement of the lungs, the thoracic cage, the diaphragm and the abdomen for a short time period. Such procedures are conducted in cardio and thoracic surgery and in surgery of the trachea, bronchus and larynx.

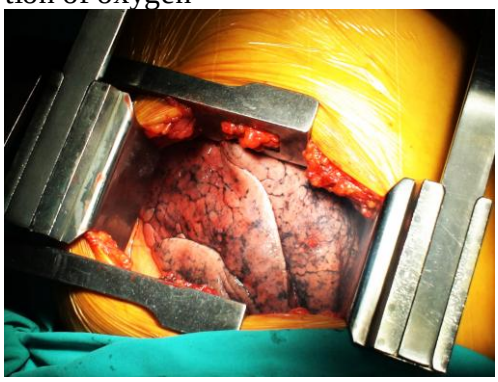
In **coronary surgery** the use of the internal mammary artery graft has been proven to be superior to the venous graft in regard to the long term patency. Moreover, there is no need for central anastomosis, when the mammary artery graft is used, which results in minimizing the risk of an atheromatic plug to be detached from the inner wall of the aorta leading to embolism of the cerebral circulation. However, during the internal mammary artery harvest, the cognate lung might be expanded in the surgical field, causing difficulties in the harvest and increasing the risk of possible injury of the graft, especially when PEEP is applied. One strategy that may help us to deal with this situation is the application of ventilation with small tidal volumes, high respiratory rates and a low level of PEEP or ZEEP. However, even this ventilation pattern may induce an increase in the lung volumes in emphysematic patients, whose lung compliance is above normal levels. Another alternative might be the one-lung ventilation technique, which requires the insertion and positioning of a double lumen endotracheal tube, a method that is associated with some risks. A third alternative would be the application of apneic oxygenation, which provides the best condition for the internal mammary harvest (figure 3).

Figure 4: Apneic oxygenation during a thoracic surgery procedure by endobrochial insufflation of oxygen through a catheter positioned into a double lumen tube.



Watson et al assessed endobrochial insufflation of oxygen for 20-30min at a flow of 45L/min in 11 patients with an open chest during internal mammary artery harvest[29]. In all patients, clinically acceptable gas exchange was achieved and surgical access for internal mammary artery harvesting was improved. The efficient carbon dioxide wash out could be attributed to the high oxygen flow rate.

Figure 5. Overdilatation of the nondepended lung during endobrochial insufflation of oxygen

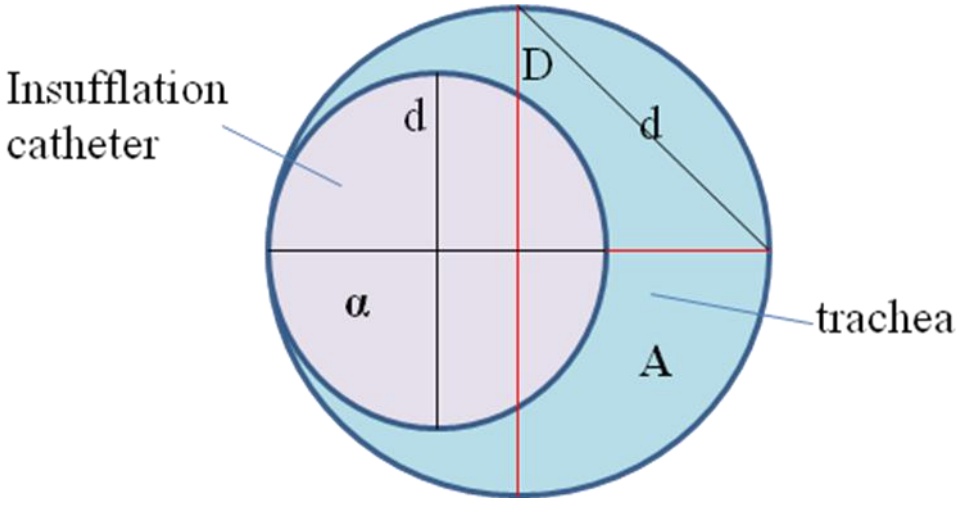


During **thoracic surgery** one lung ventilation is a very commonly used technique, during which only the depended lung is ventilated. Thereby, the operative conditions are enhanced. This technique is applied also in some cardiosurgical procedures, where lateral thoracotomy is required. An absolute requirement for that technique is the positioning of a double lumen endotracheal tube. After the initiation of the depended lung ventilation, the non-depended upper lung is open to the atmospheric air, which results in its collapse. The fact that the collapsed lung continues to be perfused without being ventilated sometimes causes a great right to left intrapulmonary shunt (20-30%) and subsequently leads to hypoxemia, which is resistant to the PEEP application in the depended lung, since this method increases the right to left shunt by diverting more blood to the non-ventilated upper lung.

The application of apneic oxygenation in the non-ventilated upper lung (figure 4), could improve P_aO_2 levels, since it diminishes ventilation disorders by allowing the oxygenation of the blood that perfuses this lung. Moreover**,** the positive pressures that are achieved by the oxygen flow contribute to the decrease of the shunt, allowing the PEEP application to the depended lung. Finally, arterial oxygenation will benefit even more by the application of continuous positive airway pressure [CPAP] to the non-depended lung via a relief valve.

Whenever apneic oxygenation is applied, the tip of the oxygen insufflation catheter should be placed as close as possible to the alveolar-capillary membrane. In case that both lung oxygenations are needed, the catheter should be positioned just above the carina. In case that left lung oxygenation is needed, the best place is

Figure 6: Relation of cross-sections of trachea and insufflation catheter. The remaining free space has cross section A-a. d=.707*D. **A**: trachea cross-section, **α**: insufflation catheter cross-section, **D**: trachea diameter, **d**: insufflation catheter diameter.



just above the bifurcation of left major bronchus. In case that right lung oxygenation is needed, the best place is inside the major right bronchus just after the carina, since the bronchus of the upper lobe branches just after the trachea bifurcation.

UNDESIRABLE EFFECTS FROM APNEIC OXYGENATION APPLICATION

The application of apneic oxygenation, like any other medical intervention, can result in some undesirable (side) effects, which fortunately are very seldom and are of no significant clinical relevance.

First of all, the continuous endotracheal or endobronchial oxygen insufflation may cause lung hyperinflation (figure 5). The endobronchal insufflation is more probable to have this effect [30]. The reason for this is that during apneic oxygenation the intrapulmonary pressures remain increased during the whole respiratory circle, slightly opposing to the expiration phase [30]. The degree of hyperinflation depends on the lung compliance, on the insufflation flow rate and on the place that the catheter is positioned. When the tip of the catheter is just above the carina, both lungs inflate at the same degree. On the contrary, when the tip of the catheter is inside the one of the two major bronchus, the inflation is greater in the cognate lung.

The gap between the wall of the trachea or the bronchus and the catheter determines the leakage rate of the oxygen that has been insufflated and of the alveolar carbon dioxide. The bigger this gap is, the larger the leakage is and therefore the smaller the increase of the intrapulmonary pressures and of the lung inflation is. According to the mass preservation principle, the quantity of gases that enters the lung in a standard time period should be equal with the gas quantity that comes out, taking into account the amount of gases that is absorbed in the alveolus. The amount of gases that is absorbed can be ignored, since it is of minor importance, when high insufflation flow rates are used. Thus, the insufflation catheter cross-section should be smaller or maximum equal to the cross-section of the remaining for the gas leakage free space. The ideal condition is when the cross sections of catheter insufflation and of the remaining free space are equal.

We presume that the trachea, the bronchus and the endotracheal tubus have a circular cross-section (figure 6).

D is the diameter of the endotracheal tube, the trachea or the bronchus and **d** the diameter of the insufflation catheter. The respective cross-sections are $A=\pi*(D/2)^2$ and $\alpha=\pi*(d/2)^2$. In order for the catheter cross-section **α** to be smaller or maximum equal to the cross-section of the remaining space **A-α**, the following equation should be valid:

$$a \le A-a \Rightarrow 2a \le A \Rightarrow 2\left(\pi\left(\frac{d}{2}\right)^2\right) \le \pi\left(\frac{D}{2}\right)^2 \Rightarrow 2d^2 \le D^2 \Rightarrow d \le \frac{D}{\sqrt{2}} \Rightarrow d \le \frac{\sqrt{2}}{2} D$$

Namely: $d \le .707 \times D$ (1-9)

Therefore, according to this equation, we can easily calculate the diameter of the insufflation catheter that should be used, if we know the internal diameter of the endotracheal tube. It is obvious that the presence of secretions anywhere in the remaining free space between the endotracheal tube and the insufflation catheter, reduces the cross-section area of the free space, and has a negative effect on the leakage rate and on the lung inflation degree[30]. Especially, during cardiothoracic surgery the lung inflation can be directly estimated by a direct inspection of the operative field (figure 5).

If the insufflation catheter has been placed blindly or in a traumatic way, then there is a possibility of the development of subcutaneous emphysema, due to the high oxygen flow rate that is used. This subcutaneous emphysema is usually small without any symptoms. It is very easy to recognize it and it recedes gradually after the termination of apneic oxygenation. Finally, as it was previously mentioned, when there is a time period of ventilation before the initiation of apneic oxygenation, the oxygen reservoir becomes bigger, since all of the nitrogen is washed out. Thereby, a longer time period of acceptable oxygenation is accomplished. However, the absence of nitrogen in the alveolus may result in the development of atelectasis, due to the complete alveolar oxygen absorption. In this case, PEEP application, achieved by the

use of a specific release valve, can partially inhibit the development of atelectatic lung regions, due to denitrogenation.

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CORRESPONDENCE:

Alexandros Kolettas: Anaesthesiologist, Thessaloniki Heart Institute, St. Luke's Hospital

Address: Kardia, 57500 Thessaloniki, p.o.box 087, Greece

tel: (0030) 2310430197

e-mail: akolettas@hotmail.com

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