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Research Article

Experimental Rat Model: Is Preoxygenation with 100% O_2 Before Anesthesia Induction Appropriate or Not?

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Abstract

Preoxygenation is recommended method for prolonging safe time due to airway concerns before induction of anesthesia. However, debates about the damages of hyperoxemia in intensive care patients and chest diseases have been made for a long time and the issues related to oxygen management have taken place in the guidelines. Our aim was to determine the pathological and biochemical results of preoxygenation with 100% O_2, based on the hypothesis that some damagescan be seen, even in the short duration of hyperoxia. Firstly, a container for rat model of preoxygenation was designed. Four and six month old healthy 16 male rats were randomly divided into two groups [Group21 (n=8): 21% O_2 and Group100 (n=8): 100% O_2]. Groups were sacrificed under the ketamine and xylazine (50 and 5 mg/kg, respectively) at the end of 5 min. Blood, lung, heart, liver, and kidney samples were taken for biochemical tests and histopathological grades of tissue damage. The data were analyzed statistically by Mann-Whitney-U test. This study is significant in terms of the direct toxic effects of preoxygenation with 100% O_2 before anesthesia induction. However, there is a need for further studies on the determination of the ideal O_2 concentration for preoxygenation in patients.

Keywords: *Preoxygenation, Oxygen, Oxidative stress, Anesthesia, Oxygen radicals*

Deneysel Rat Modeli: Anestezi İndüksiyonu Öncesi %100 O_2 İle Preoksijenizasyon Uygun mu Değil mi?

Öz

Preoksijenizasyon anestezide indüksiyon öncesi havayolu endişeleri nedeniyle güvenli zamanı uzatmak adına hala önerilen ve uygulanan bir yöntemdir. Ancak yoğun bakım hastaları ve göğüs hastalıkları açısından hiperokseminin zararları ile ilgili tartışmalar çok uzun zamandır yapılmış ve klavuzlarda oksijen yönetimi ile ilgili hususlar yerini almıştır. Hiperokseminin indüksiyon sırasındaki kısa süreli uygulamasında bile bazı hasarların olacağı hipotezinden yola çıkarak %100 O_2 ile preoksijenizasyonun patolojik ve biyokimyasal sonuçlarını saptamak üzere bu çalışmayı planladık. Öncelikle, preoksijenizasyonun hayvan modeli için bir konteyner tasarlandı. Dört-altı aylık sağlıklı 16 erkek rat rastgele iki gruba ayrıldı [Grup 21 (n=8): %21 O_2 ve Grup 100 (n=8): %100 O_2]. Gruplar 5 dk. istenilen konsantrasyonda kaldıktan sonra ketamin ve xylazin (sırasıyla 50 ve 5 mg/kg) ile uyutularak sakrifiye edildi. Histopatolojik olarak doku hasarı derecelendirmesi ve biyokimyasal testler için kan, akciğer, kalp, karaciğer, böbrek doku örnekleri alındı. Veriler Mann-Whitney-U testi ile istatistiksel olarak değerlendirildi. Bu çalışma anestezi indüksiyonunda %100 O_2 ile preoksijenizasyonun akciğerdeki direkt toksik etkilerini göstermesi açısından anlamlıdır. Ancak hastalarda preoksijenizasyon için ideal olan O_2 konsantrasyonunun belirlenmesiyle ilgili olarak daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar sözcükler: *Preoksijenizasyon, Oksijen, Oksidatif stres, Anestezi, Oksijen radikalleri*

INTRODUCTION

Prior to induction of general anesthesia, preoxygenation and 100% oxygen (O_2) is strongly recommended as a standard procedure against potential prolonged apnea [1]. The functional residual capacity, defined as the volume

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of gas remaining after passive expiration, is the most important source of oxygen for preoxygenization [2]. However, because of the fear of hypoxia, 100% oxygen that is easily used is not so innocent [3]. The oxygen has been defined as the doubled-edge sword by Hafner [3]. Oxygen plays a crucial role during adenosine triphosphate (ATP) synthesis in Krebs cycles, besides it has strong oxidizing properties and the capacity of damaging any biological molecule due to its chemical characteristics [4]. The status is defined as oxygen toxicity [3], which directly correlates with the oxygen level, and is believed to be caused by reactive oxygen species (ROS) affecting the defense and signal cascade significantly [5]. However catalase (CAT), nitric oxide (NO), glutathione (GSH), superoxide dismutase (SOD) and malondialdehyde (MDA) levels are directly related with severity of oxygen toxicity. CAT, GSH and SOD scavenge free oxygen radicals and thus are protective for cells in the body; on the other hand NO and MDA are markers of oxidant injury.

The human body reduces oxygen 1-3% in the mitochondrial plane despite taken 21% oxygen from air [6]. This feature shows how toxic oxygen is and it also raises the question whether human beings are facultative anaerobes [7]. The use of O_2 at high concentrations has been restricted in guidelines primarily involving lung protective ventilation strategies for intensive care and chest diseases. The damages of hyperoxia are well known in intensive care units and there are a number of related studies [3]. Sensitivity and interest to hyperoxia is not satisfactory in anesthesia induction and perioperative period, although anesthesia is so closely related with intensive care. Preoxygenation with 100% before induction is still recommended in anesthesia textbooks [7,8]. These may be due to habits related to past airway concerns and healthy patients being able to eliminate the damage caused by the operation-induced hyperoxia. As there are no studies regarding the preoxygenation in the experimental model, we aimed to determine the pathological and biochemical consequences of preoxygenation with 100% O_2 before induction of anesthesia.

MATERIAL and METHODS

Animals

Four to six month-old male rats were obtained from Experimental Animal Center of Adnan Menderes University and all experiments were performed in accordance with the principles and guidelines of Adnan Menderes University Animal Ethical Committee's approval (HADYEK: 64583101/2016/56).

Experimental Design

The rats were firstly examined, then randomly assigned into two groups with eight rats per group and they were measured on the beginning of study. No medication was administered to any rats in the groups. The experimental groups were as follows:

Group21: Exposured to the room air in container (21% oxygen) served as healthy rats

Group100: 100% oxygenated healthy rats for 5 min in container

Firstly, A container for rat model of preoxygenation was designed *(Fig. 1)*. Therefore, the rat cage has been put in a bigger size of container without restricting food and water consumption and sealed. Oxygen and air were given by two separate small pipes from the one side of the container and monitored. The container has also included two small electrical fans to mix the air inside and some soda lime to absorb the CO_2. The oxygen and carbon dioxide ratios in the container were continuously measured with the aid of a monitor (GE Datex Ohmeda Engstrom, Helsinki, Finland) which performed infrared absorption analysis. A gas outlet line and oxygen and carbon dioxide measuring pipelines

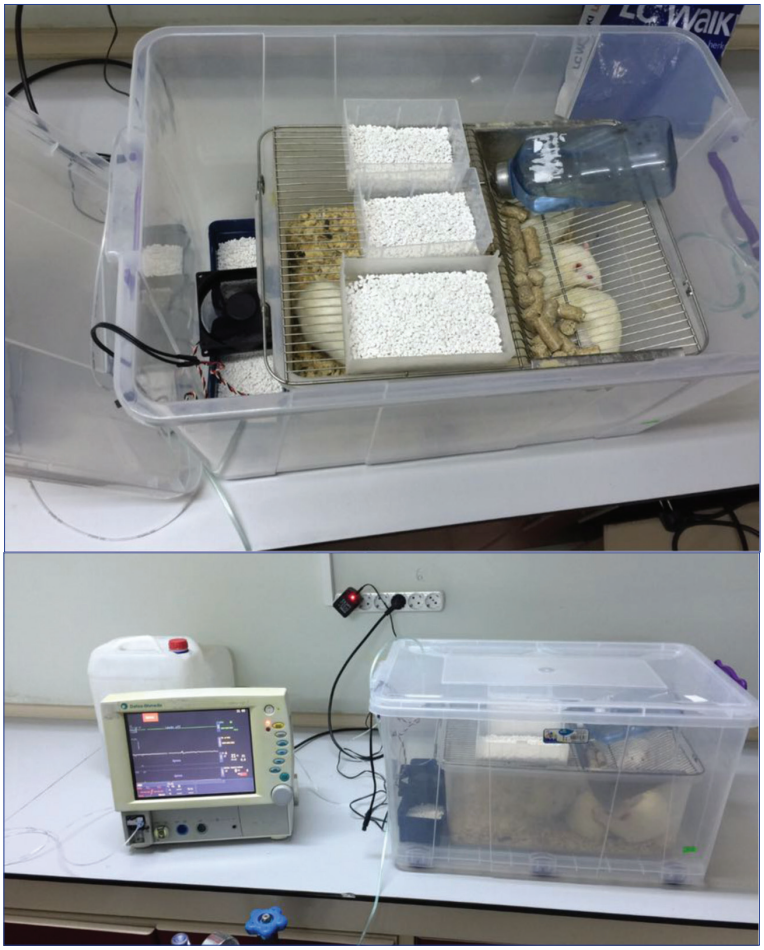

Fig 1. Container for experimental rat model of preoxygenation

were placed to another corner of container. When the oxygen concentration in the monitor reached the 100% concentration determined for Group100, the rats were placed into the container from a small inlet without changing the concentration in the container.

At the end of 5 min, the rats of two groupswere sacrificed immediatelyunder the anesthesia of Ketamine and Xylazine (50 mg/kg and 5 mg/kg, respectively). The blood samples were obtained by cardiac puncture. While some parts of liver, kidney, lung, heart tissues kept on -80ºC, the other parts of the tissues were fixed in to 10% neutral buffered formalin solution.

Histopathological Examination in Tissue

Samples of lung, liver and kidney tissues were fixed with 10% formalin solution and it was embedded in paraffin after routine tissue follow-up with fixation. Then, 4 µm thick sections were taken from the tissue specimens and stained with hematoxylin-eosin. After staining, sections were examined under 40, 100, 200 and 400's with magnification lenses under light microscope (Carl Zeiss Axio Lab A1, Germany).It was scored by an experienced observer who was blinded of the grade of inflammation and neutrophil infiltration. It was scored by an experienced observer who was blinded of the grade of inflammation, neutrophil infiltration and tissue damage. The severity of tissue damage was assessed as follows as shown in Zolali et al.[9] study: regular structure of tissue; normal (grade: 1), only mild inflammatory cell infiltration; mild (grade: 2), moderate inflammatory cell infiltration and mild tissue damage; moderate (grade: 3), intense inflammatory cell infiltration and marked tissue damage; severe (grade: 4).

Oxidant and Antioxidant Parameters in Blood and Tissues

Blood Analyses: Blood was taken from the rat's heart via without anticoagulant and EDTA tube.Without anti-coagulant tube centrifuged at 1000 g for 10 min. The supernatant was collected and kept at -80°C for analysis. Glutathione, superoxide dismutase, catalase tests were run immediately without delay. Tubes containing EDTA as anticoagulants were used for these tests.

The MDA production and lipid peroxidation were assessed in the serum by the method of Ohkowa [10]. Nitric oxide (NO; nitrite + nitrate) was assayed by a modification of the cadmium-reduction method of Navarro-Gonzalves et al.[11]. For determination of cellular total glutathione (GSH), the colorimetric Beutler method [12] was used. Catalase (CAT) activity was measured by the method of Aebi [13]. The reduction rate of H_2O_2 was measured at a wavelength of 240 nm for 30 sec at room temperature. SOD content in tissue supernatants was measured according to the method of Sun et al.[14].

Tissue Analyses

Preparation of Tissue Homogenates: Specimens from the liver, kidney and lungs were weighted and homogenized separately with tissue homogenizer (PRO 250 Scientology Inc. Monreo, CT USA). Tissues were homogenized for to detect of tissue GSH, MDA, NO (nitrite + nitrate) levels and the activities of CAT in 50 mM phosphate buffer saline at pH 7.4. The crude tissue homogenate was centrifuged at 20.000 g, for 15 min in ice-cold centrifuge, and the resultant supernatant was collected and stored at –85°C.

Malondialdehyde: The MDA production and lipid peroxidation were assessed in the tissues by the method of Ohkowa [10]. MDA forms a colored complex in the presence of thiobarbituric acid, which is detectable by measurement of absorbance at 532 nm. Absorbance was measured with Shimadzu UV-160 spectrophotometer. 1,1′, 3, 3′Tetraethoxypropane used as Standard.

Nitric Oxide: Nitric oxide (nitrite+nitrate) was assayed by a modification of the cadmium-reduction method of Navarro-Gonzalves et al.[11]. The nitrite produce was determined by diazotization of sulfanilamide and coupling to naphthylethylenediamine. The samples were analyzed spectrophotometrically using a microplate reader (ELX800, BioTek Instruments, Inc. Winooski, Vermont, USA) and quantified automatically against KNO_3 standard curve.

Glutathione: GSH content in tissue supernatants was measured according to the method of Beutler et al.[12]. The absorbance was measured at 412 nm using a Shimadzu UV-160 spectrophotometer. The GSH concentration was determined using Standard aqueous solutions of GSH.

Catalase: Catalase (CAT) activity in tissue was measured by the method of Aebi [13]. The reduction rate of H_20_2 was followed at 240 nm for 30 sec at room temperature.

Superoxide Dismutase: SOD content in tissue supernatants was measured according to the method of Sun et al.[14]. The absorbance was determined at 560 nm using Shimadzu UV160 spectrophotometer. The Percent inhibition (% inhibition) is calculated.

Data Presentation and Statistics

Microscopically grades of tissue damage and biochemical data were assessed by using Mann Whitney-U. Data were presented as mean±SEM, P values below 0.05 were considered as significant.

RESULTS

Rat Clinical Findings

While control mean weight of the group's was 342±11.3 g, oxygen treated group's weight was 335±9.3 g (P>0.05). The rats did not show any respiratory distress or agitations allthroughout the study.

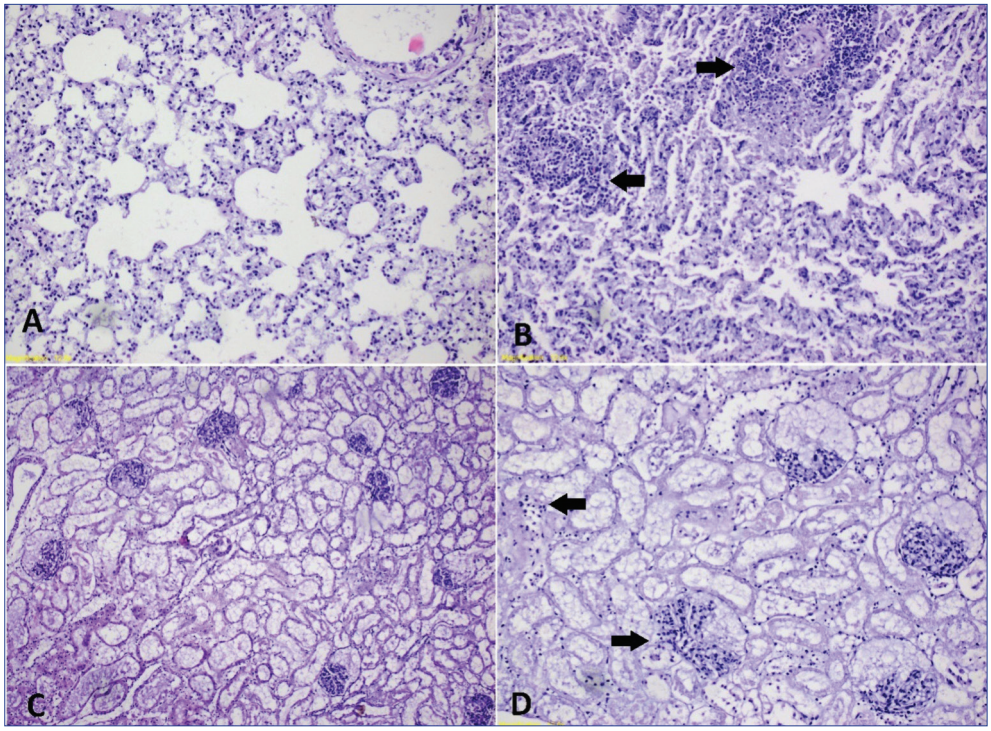

Fig 2. The histopathological view of lung and kidney section

A: Normal lung tissue without inflammation grade 1 (H&E, x200); B: Lung tissue with moderate inflammation grade 3 (H&E, x200), *arrows:* moderate inflammatory cell infiltration; C: Normal kidney tissue without inflammation grade 1 (H&E, x100); D: Kidney tissue with mild inflammation grade 2 (H&E, x200), *arrows:* mild inflammatory cell infiltration

Table 1. *Blood oxidant and antioxidant status*

In Blood	Group21 (n=8)	Group100 (n=8)
Catalase (U/mL)	35.33±0.3	36.11±0.7*
MDA (nmol/mL)	22.38±0.5	24.53±1.2*
GSH (umol/L)	6.63±0.2	7.03±0.4*
SOD (ng/mL)	81.85±6.7	103.88±8.1*
NO (umol/L)	445.62±16.1	457.00±13.3*

** P>0.05*

Blood Oxidant and Antioxidant Status

Although blood CAT; MDA, GSH, NO and levels were high in Group100 than Group21, there were no statistical significance in between (P>0.05) *(Table 1)*.

Tissue Oxidant and Antioxidant Status

CAT, NO, GSH SOD levels in the lung tissue (P<0.05), SOD (P<0.05) and catalase (P=0.05) levels in the kidney tissue, MDA levels in liver and heart tissues were found to be significantly higher in Group100 statistically (P<0.05). All other parameters in all tissues were higher in Group100 than Group21 *(Table 2)*. But these were not statistically significant (P>0.05). SOD in liver and catalase in kidney levels were statistically determined as P=0.05 when compared to both groups *(Table 2)*.

Table 2. *Tissue oxidant and antioxidant status*

In Tissue	Group21 (n=8) Lung	Group100 (n=8) Lung	Group21 (n=8) Kidney	Group100 (n=8) Kidney	Group21 (n=8) Liver	Group100 (n=8) Liver	Group21 (n=8) Heart	Group100 (n=8) Heart
Catalase U/g	34.3±4.0	48.1±8*	26.38±6	31.6±3†	43.8±4	48±7	4.33± 0.4	4.78±0.7
MDA µmol/g	1.55±0.1	1.69±0.1	156.25±12	170.5±14	0.18±0.03	0.22±0.02*	1.18±0.02	1.22±0.02*
GSH µM/g	3.22±0.7	4.05±0.6*	5.4±0,6	5.64±0.8	0.24±0.08	0.29±0.13	0.24±0.07	0.28±0.01
SOD (ng/g)	721±36	766±23*	521.7±36	561.5±23*	517.5±43	577.5±56†	465.1±42	525.8±60
NO µmol/g	1.74±0.1	2.13±0.1	0.72±0.1	0.79±0.1	2.07±0.3	2.19±0.3	2.73±0.6	2.29±0.3

** P<0.05, † P=0.05*

Histopathological Findings

The degree of inflammation and tissue damage in the lung, kidney, liver, and heart tissue of the rats in Group21 was evaluated as grade 1 (normal) in all tissues. Lung tissues in Group100 were detected for tissue damage of grade 2 in two rats, grade 3 in four rats and grade 4 in two rats. Tissue grading in the kidney in Group100 was found to be grade 2 infive rats and 1 (normal) in three rats. Heart and liver tissues were evaluated as grade 1 (normal) all rats in Group100 *(Fig. 2)*.

DISCUSSION

In this study, although oxygen is indispensable for us, it has been revealed how dangerous concentration increase

is. It has also been observed how accurate the definition of Hafner (double-edge sword) for oxygen was, in our study [3]. It is clear that hyperoxia has potency to be detrimental even in a wide variety of clinical conditions in intensive care units [15]. In 2008, the British Thoracic Society published a guide for emergency oxygenation in adult patients [16]. While these developments are experienced in terms of the internal medicine, 100% preoxygenation still performs its position in the anesthesia, although anesthesia is a part of intensive care. We assume that the reasons for not changing 100% preoxygenation in routine anesthesia practice are as follows:

- Initially, these effects (most likely caused by 5 min of 100% O_2) return when O_2 is reduced to low concentrations.

- Secondly, we do not think preoxygenization as cause of developing postoperative complications,

- Thirdly, we may not use 100% preoxygenation despite textbook suggestions.

Pedersen et al.[17] reviewed five randomized controlled trials with 22.992 patients, and found that hypoxemia was defined 1.5-3 times earlier preoperatively with the use of pulse oximetry. However, despite the early recognition and correction of hypoxemia in this study, there was no difference in postoperative cognitive function between hospitalization and mortality in complications.

Although some researchers show the risks of 100% O_2 in their work, they have not completely rejected the standard preoxygenization. In a study conducted by Edmark et al.[18], they showed a significant increase in atelectasis with preoxygenation with 100% O_2, they still recommended continuing preoxygenation with 100% O_2, until more extensive studies indicate that it affects morbidity.

In this study, biochemical and pathologic data were found to be compatible in terms of tissue damage in only lung tissue. This may be due tooxygen's toxic effect directly to the lung. None of the tissues were found to be significant in terms of NO. We think that intracellular Ca does not increase at a level that would increase NO synthetase, because of NO has very short half-life in tissues and fluids. This issue was also emphasized by Kiechle and Malinski [19]. However, one of the most interesting points in our study is that high degree of pathological lung and renal damage were not reflected in blood results. We think that this damage to the lungs and kidneys may be due to the direct toxic effect of hyperoxemia, and not reflected on the blood results may be due to short-term 100% O_2 application.

At high concentrations, the use of oxygen has been shown to inhibit direct hypoxic pulmonary vasoconstriction (HPV) [20,21]. Firstly, Antoine Lavoisier described the impairment of gas exchange caused by acute hyperoxia, which was later defined as the Lorrain-Smith effect [22]. Some investigators have emphasized the need to distinguish between acute pulmonary O_2 toxicity and the Lorrain-Smith effect [23]. Actually, there are two sequent processes: decrease in HPV leads to deterioration of pulmonary gas exchange and increase in right-left shunting and concomitant inflammation with reduced atelectasis and vascular perfusion [3]. In our study, the occurrence of severe lung injury, even at short-term 100% O_2, indicates the importance of the rate of action and direct toxic effect. The second interesting finding in our study was that there were different results in different organs at tissue level. Although these results may seem unexpected, it is also an indication of why every patient who has been given preoxygenation with 100% O_2 does not have serious problems. Our normal body physiology protects the body from oxygen toxicity by reducing oxygen up to 21% to 1-3% [6] with direct and indirect protection mechanisms until reaching the mitochondria from the lung. This is probably valid for 100% O_2, too. We interpret results depending on both an effect of this protection mechanism and the short time 100% O_2.

Our study showed that 100% preoxygenation does not seriously affect other organs except the direct toxic effect in the lung. We interpret the results depending on both effect of this protection mechanism and the short time 100% O_2. It is important to know that in terms of awareness of the event direct lung toxicity has been detected even in such a short period of preoxygenation.

Although we did not directly correlate the height of all parameters in the lungs to direct toxicity, the finding of a significant result in the liver and heart MDA levels only. SOD and catalase levels in the kidney suggests different mechanisms in different organs. In addition to the need for further work, the most damage in site of first contact with 100% O_2 is an indicator of the harm in the lung rather than protecting it. For this reason, perhaps it will be more accurate with new guidelines to be developed through extensive studies to determine the O_2 concentration to be applied in preoxygenation, not according to our airway concerns.

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Declaration of Interest

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