

Effects of short-term hyperoxic ventilation on lung, kidney, heart, and liver in a rat model: A biochemical evaluation *

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ABSTRACT

BACKGROUND: Despite studies on the adverse effects of hyperoxia, its use is still recommended by the World Health Organization. The aim of this study was to test the possible harmful effects of hyperoxia on the lung, kidney, heart, and liver in a rat mechanical ventilation model.

METHODS: Male Wistar rats were randomly assigned into two groups (n=6/group): Normoxic (FiO₂: 0.3) or hyperoxic (FiO₂: 1.0) ventilation for 4 h. The injury was evaluated in bronchoalveolar lavage (BAL), blood, lung, liver, kidney, and heart was evaluated in terms of cell surface integrity, extracellular matrix (sialic acid, syndecan-1), osmotic stress (free hemoglobin), and redox homeostasis-lipid peroxidation (malondialdehyde). BAL and wet/dry weight ratio were also evaluated for cellular permeability.

RESULTS: Four hours of hyperoxic ventilation did not lead to significant changes in (1) sialic acid, syndecan-1, (2) malondialdehyde levels and wet/dry weight ratio in liver, kidney, heart, and lung compared to normoxic ventilation.

CONCLUSION: Mechanical ventilation with hyperoxia seems to have almost similar effects compared to ventilation with normoxia. However, the long term effect of hyperoxia should be evaluated.

Keywords: Hyperoxia; hyperoxic ventilation; mechanical ventilation; organ injury.

INTRODUCTION

There is an ongoing discussion about the advantages and disadvantages of the administration of hyperoxia in different clinical settings. Hyperoxic ventilation therapy is thought to be effective at suppressing surgical site infections following colorectal resection and ameliorating ischemic brain injury,^[1-3] that recently, its use is recommended by World Health Organization (WHO) for surgical site infection prevention.^[4]

On the other hand, the supposedly positive effects of hyperoxia are challenged in a number of articles. Hyperoxia is known to affect the human lung negatively.^[5] Histopatho-

logical alterations of hyperoxic lung injury include early and late phase as characterized by inflammation, atelectasis, edema formation, and irreversible loss of respiratory function, respectively.^[6] Hyperoxia has been shown to be detrimental also in brain injury,^[7] acute myocardial infarction,^[8] and post-resuscitation.^[9,10]

Hyperoxia could trigger an inflammatory response by activating microvascular endothelial cells and circulatory neutrophils,^[11] and generating reactive oxygen species.^[12] It induces also vasoconstriction; and can cause a redistribution of cardiac output in favor of the kidney and hepato-splanchnic system and a decrease in the cerebral and coronary circulation. In

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any case, it can be assumed that hyperoxia shows its effects (whether beneficial or deleterious) via the vascular system.

Glycocalyx, a complex layer of membrane-bound proteins on the luminal surface of the vascular endothelium, is a primary component of the vascular system. Numerous studies have shown a relationship between various stress conditions and glycocalyx integrity in organs and in vitro systems.^[13] However, whether glycocalyx is affected by changes in oxygen tension has not been examined yet. It is also not known, whether hyperoxia affects the systems directly, or with the interaction of other factors/stimulants (so-called “multiple-hit-phenomenon.”).

We aimed to examine the effects of hyperoxia on cellular injury products and on different organs as lung, kidney, heart, and liver in a rat model of mechanical ventilation. To examine the effects of “only” hyperoxia, we tried to avoid the effects of other possible “hits.”

MATERIALS AND METHODS

Animals

All animal experiments comply with the ARRIVE guidelines and were carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978). All experimental protocols were approved by the animal experimentation committee of Acibadem Mehmet Ali Aydinlar University (2017/33). Care and handling of the animals were in accordance with the guidelines for Institutional and Animal Care and Use Committees. Experiments were conducted on 12 male adult Wistar rats with the body weight of 370–400 g.

Surgical Protocol

The rats were anesthetized with an intraperitoneal injection of a mixture ketamine (50 mg/kg i.p.) and xylazine (5mg/kg i.p.) and the depth of anesthesia was assessed by tail reflexes. After tracheotomy, the animals were mechanically ventilated with a FiO_2 of 0.4 and an peak inspiratory pressure to obtain a tidal volume of 6–8 mL/kg and a positive end expiratory pressure of 3 mmHg was applied for ventilation in pressure controlled mode. Ventilation frequency was adjusted to maintain an arterial carbon dioxide partial pressure of 35–40 mmHg. pressure-controlled mode. Body temperature was maintained at $37\pm 0.5^\circ\text{C}$ throughout the whole procedure by external warming. For hemodynamic monitoring, blood sampling and fluid management, femoral artery and femoral vein were cannulated with polyethylene catheters with outer diameters of 0.9 mm. After the surgical protocol, the surgical fields (neck and perineum) were covered with a warm gauze pad moistened throughout the experiment to prevent the exposed tissues from drying out.

Experimentation

Following a stabilization period of 20 min, blood samplings were performed for the baseline measurement (t_0) and the animals were subsequently randomized into 2 groups: (1) Normoxia ($n=6$) with an FiO_2 of 0.3 and (2) Hyperoxia ($n=6$) with an FiO_2 of 1.0 for the following 4 h of ventilation. Anesthesia was maintained with isoflurane in oxygen/air or oxygen according to group randomization.

After experimentation, saline (2 mL) was administered to the main bronchus and then withdrawn slowly 2 times to achieve the bronchoalveolar lavage (BAL) samples. The obtained fluid was centrifuged (2000 rpm 5 min at $\pm 4^\circ\text{C}$). The supernatant was stored at -80°C until the day of measurements. The experiments were terminated following the BAL sampling by inducing hypovolemia with cardiac puncture (t_1). After sacrifice, the kidneys, lung, heart, and liver were removed and weighed. All biochemical evaluations in blood were performed with serum samples obtained by centrifugation ($\pm 4^\circ\text{C}$, 5000 rpm, 10 min). Serum and tissue samples were stored at -80°C until the day of measurements.

Biochemical Measurements

All tissue samples were mechanically homogenized in 10% (w/v) homogenizing buffer (100 mM KH_2PO_4 : K_2HPO_4 , pH 7.4). Protein contents in tissue and serum samples were determined spectrophotometrically using a Folin kit (Sigma Diagnostics, St. Louis, MO, USA).

Pulmonary Permeability Index (PPI) Determination

PPI was ascertained with the ratio of serum protein levels to BAL protein levels.

Free Hemoglobin (fHb) Determination

fHb levels in serum were determined according to Harboe's methods.^[14,15] All serum samples were diluted 11-fold in Na_2CO_3 , 0.942 mol/L. The diluted serum samples were measured at 450, 415, and 380 nm. After the measurements, the formula at below was used to calculate the fHb concentration as g/L: $\text{cHb (g/L)} = 1.65 \times \text{A415} - 0.93 \times \text{A380} - 0.73 \times \text{A450}$

Sialic Acid (SA) Determination

Tissue SA levels in kidneys, lung, liver, heart, serum, and BAL were measured according to Sydow's method.^[16] Tissue homogenate, serum, and BAL samples were mixed with perchloric acid. Subsequently, the mixture was incubated at 100°C for 5 min, were then centrifuged at 3,000 g for 4 min. The supernatants as upper fraction were mixed with the Ehrlich reagent and then incubated at 100°C for 5 min. Distilled water was added to the mixtures and the absorbance was measured at 525 nm.

Thiobarbituric Acid Reactive Substances Levels:

Malondialdehyde (MDA) Determination

Lipid peroxidation in kidneys, lung, liver, heart, serum, and

BAL were determined via the formation of MDA, which was estimated by the modified thiobarbituric acid method, described by Buege and Aust.^[17]

Serum Syndecan-I Level Determination

Syndecan-I level was measured using a commercial ELISA kit.

Ratio of Wet/Dry Weight Analysis

The kidney, lung, liver, and heart tissues were weighed and dried in an oven at 80°C for 48 h. Following this procedure, the dried tissues were re-weighed to calculate the wet/dry ratio. The edema was denoted by an increase in this ratio.

Statistical Analysis

The mean ± SE values of data sets were presented in graphics. Statistical analysis was performed with GraphPad Prism version 6.0 for Windows (GraphPad Software v5.0, San Diego, CA, USA). One-way ANOVA and Tukey as *post hoc* tests were performed for the statistical comparison. A $p < 0.05$ value was considered as significant.

RESULTS

Measurements in Blood Samples

At baseline, the serum fHb (0.04 ± 0.01 and 0.05 ± 0.01 g/dL), MDA (0.21 ± 0.03 and 0.09 ± 0.05 $\mu\text{mol/g}$ protein), and SA (0.15 ± 0.02 and 0.14 ± 0.02 nmol/mg protein) levels were found similarly in both groups. The fHb level was increased in hyperoxia compared to normoxia group but not significantly (0.96 ± 0.53 and 0.18 ± 0.05 g/dL; respectively). The serum MDA levels were increased in both groups but not significantly at the end of experimentation (0.58 ± 0.26 and 0.34 ± 0.15 $\mu\text{mol/g}$ protein). SA levels were similar at baseline and at the end of experimentation (0.15 ± 0.01 and 0.13 ± 0.01 nmol/mg protein). Serum syndecan-I levels were also similar at the end

of experimentation compared to both groups (0.50 ± 0.12 and 0.43 ± 0.03 nmol/mg protein) (Fig. 1).

Measurements in BAL and Lung Tissue Samples

SA levels (0.34 ± 0.04 vs. 0.31 ± 0.07 nmol/mg protein) of BAL samples and PPI (0.36 ± 0.04 vs. 0.42 ± 0.07) in hyperoxia were found to be similar in normoxia compared to hyperoxia. At the end of experiment, MDA (0.04 ± 0.01 $\mu\text{mol/g}$ protein) and SA (0.15 ± 0.01 nmol/mg protein) levels of lung tissues were insignificantly increased in hyperoxia (MDA: 0.06 ± 0.03 $\mu\text{mol/g}$ protein; SA: 0.63 ± 0.46 nmol/mg protein) compared to normoxia. Wet dry tissue ratio of lung tissues in both group were found to be similar (6.58 ± 0.21 vs. 6.06 ± 0.57) (Fig. 2).

Measurements in Liver Tissues

At the end of experiment, SA levels (0.09 ± 0.00 vs. 0.11 ± 0.02 nmol/mg protein) and wet dry tissue ratio (3.32 ± 0.33 vs. 4.05 ± 0.55) of liver tissues were insignificantly increased in hyperoxia compared to normoxia. The MDA levels of liver tissues in hyperoxia (0.15 ± 0.12 $\mu\text{mol/g}$ protein) were found to be similar compared to normoxia (0.19 ± 0.09 $\mu\text{mol/g}$ protein) (Fig. 3).

Measurements in Kidney Tissues

At the end of experiment, MDA levels of kidney tissues were insignificantly increased in hyperoxia compared to normoxia (0.02 ± 0.01 vs. 0.09 ± 0.07 $\mu\text{mol/g}$ protein). Wet dry tissue ratio (4.20 ± 0.14 vs. 4.30 ± 0.14) and SA levels (0.09 ± 0.00 vs. 0.092 ± 0.00 nmol/mg protein) of kidney tissues in hyperoxia were found to be similar compared to normoxia (Fig. 4).

Measurements in Heart Tissues

At the end of experiment, MDA levels of heart tissues were insignificantly increased in hyperoxia compared to normoxia

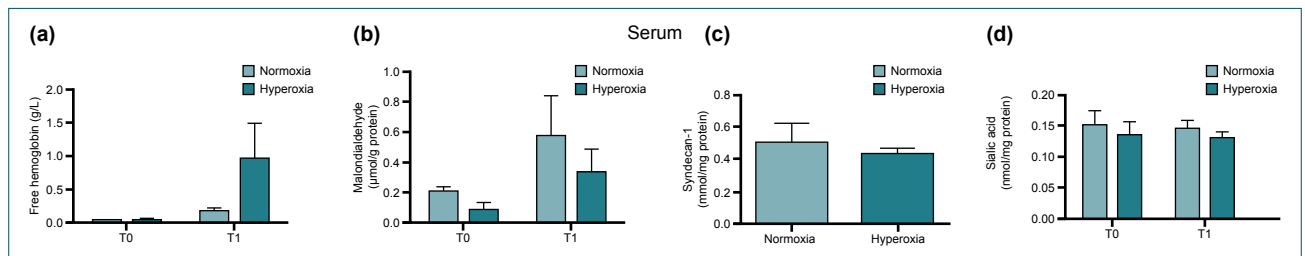


Figure 1. Measurements in serum: Free hemoglobin (a), malondialdehyde (b), syndecan-1 (c), sialic acid (d) levels

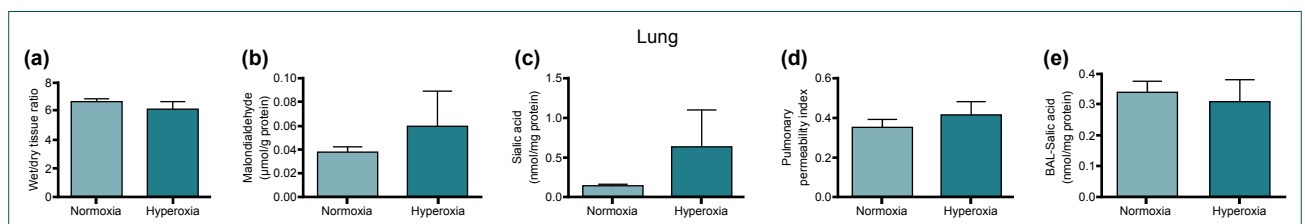


Figure 2. Measurements in bronchoalveolar lavage and lung tissue: Sialic acid (a), malondialdehyde (b), sialic acid (c), pulmonary permeability index (d), wet/dry tissue ratio (e).

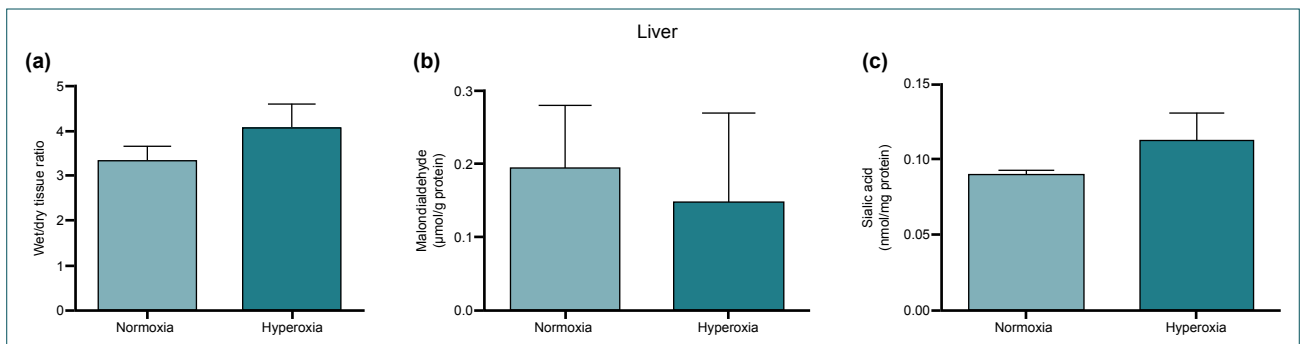


Figure 3. Measurements in liver tissue: Wet/dry tissue ratio (a), malondialdehyde (b), sialic acid (c).

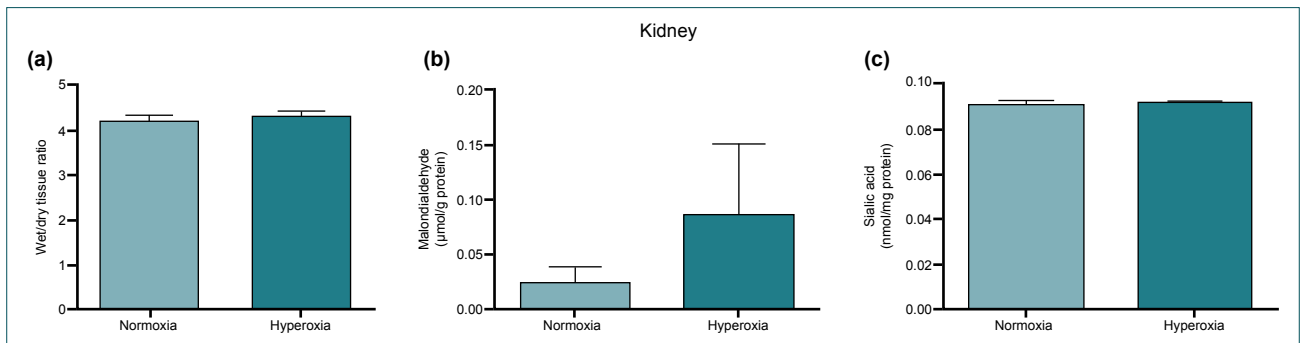


Figure 4. Measurements in kidney tissue: wet/dry tissue ratio (a), sialic acid (b), malondialdehyde (c).

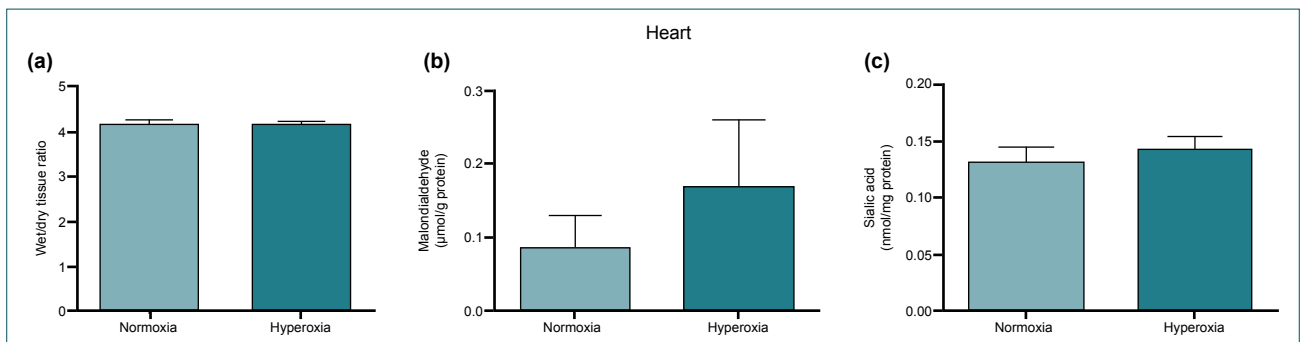


Figure 5. Measurements in heart tissue: Sialic acid (a), malondialdehyde (b), wet/dry tissue ratio (c).

(0.08 ± 0.05 vs. 0.17 ± 0.10 $\mu\text{mol/g}$ protein). Wet dry tissue ratio (4.51 ± 0.12 vs. 4.15 ± 0.08) and SA (0.13 ± 0.01 vs. 0.14 ± 0.01 nmol/mg protein) levels of heart tissues in hyperoxia were found to be similar compared to normoxia (Fig. 5).

DISCUSSION

To our best knowledge, this is the first study aiming to examine the effects of “sole” hyperoxia on the cell surface, extracellular matrix, and redox homeostasis during mechanical ventilation in a rat model. In this experimental study, we have shown that a 4-h exposure to hyperoxic ventilation with protective strategy, did not lead to significantly (1) changes in cell surface and extracellular matrix, (2) imbalance in redox homeostasis via oxidative stress, (3) increases in cellular permeability in the liver, kidney, heart, and lung compared to normoxic ventilation.

During the surgical process, the inspired oxygen concentration used in mechanical ventilation continues to be a matter of discussion. This debate was further provoked after WHO’s recommendation on hyperoxia concerning its benefits.^[4] However, the use of excessive oxygen can lead to oxidative stress which can cause multiorgan failure and promote direct wreckage to DNA oxidation and indirect injury by cytotoxic products and mutagenic effects.^[18] Additionally, hyperoxia increases the release of endogenous damage-associated molecular pattern molecules that stimulate an inflammatory response.^[19] Moreover, Cortés et al.^[20] revealed the common effects of hyperoxia in healthy volunteers. Considering all these, it is clear that hyperoxia can affect all organ systems. Hence, in this present study to explain hyperoxia-induced wide-spread damage, we have focused on both blood environment and specific organs including lung, liver, kidney, and heart during short-term hyperoxic ventilation.

Regarding blood environment, we measured the cellular residues including SA, syndecan-1 and MDA, that have been poured out of the cells into the blood. SA as a member of the inner glycocalyx layer of the vessel is one of the terminal carbohydrate residues in the glycan moiety on glycoproteins and contributes to a variety of cellular functions.^[21] Syndecan is also a member of glycocalyx components. Glycocalyx is responsible for the negative cell surface charge preventing the passage of water into the cell, thereby inhibiting the formation of edema.^[22,23] SA is also located in cells which is the part of non-vascular tissue compartments and mediates to extracellular matrix change signaling.^[24] Any hit (injury) causing redox imbalance can lead to desialylation, i.e., the disintegration of SA from the glycoproteins increasing its levels in blood and tissue samples.^[25] Same insults can also cause oxidation of lipid membranes as evidenced by increased MDA levels in the same samples.^[26] Furthermore, the oxidation process can modify the three-dimensional structure of proteins. In the present study, we could not find any significant differences in serum SA levels obtained from hyperoxic ventilated rats compared to normoxic ones and although serum MDA levels tended to be higher in the hyperoxic group than normoxic, the results were also similar for MDA levels. This denotes that insignificant increased oxidative stress caused by hyperoxia did not produce desialylation. However, this is not guaranteed for further hyperoxic exposure.^[27]

Erythrocyte membrane is highly sensitive to oxidant mediators and it can easily lose its integrity against oxidant attacks. Henceforth, the determination of liberated hemoglobin can be a follow-up marker for oxidative stress.^[28] Loomis et al.^[29] have recently shown that fHb-induced lipid peroxidation can initiate an inflammatory response through toll-like receptor 9 in pulmonary smooth muscle cell proliferation. Additionally, fHb could be an important predictor of mortality.^[30] Our results indicate that hyperoxia does not cause a significant increase in free hemoglobin, hence membrane integrity can be maintained during short-term hyperoxic environment.

In a very recent study, although short term hyperoxia was not associated with peripheral microcirculatory derangements,^[31] some studies have previously shown the hazardous effects of hyperoxia in various groups of critically ill patients, including post-cardiac arrest,^[32] after cardiac surgery,^[33] traumatic brain injury or stroke.^[34] Excessive use of O₂ can cause oxidative stress and exceeding the detoxifying capacity of the mitochondria may lead to cellular necrosis and apoptosis.^[35] From a logical point of view, the lung is the first organ that is exposed to excessive O₂ by mechanical ventilation thus pro-inflammatory cytokines and histological damage should occur early at the cellular level. In the present study, we evaluated the lung tissue extracellular matrix changes and lipid peroxidation. We found similar results albeit an insignificant increase in SA and MDA levels in hyperoxic lung tissues. This points out that 4 h of protective mechanical ventilation (which mimics the routine practice of operational period) with FiO₂ of 1.00 did not

cause any extracellular matrix changes and lipid peroxidation in the lung. Moreover, we did not find any increase in cellular permeability evidenced by similar results in PPI.

Overall, our findings may suggest an optimistic approach to the use of short-term hyperoxia. Nevertheless, it must be remembered that lung injury has been shown to be a result of “multiple hit” phenomenon, and we have tried our best to be protective against other insults. That is, we used restrictive fluid management, a protective ventilation strategy as well as isoflurane inhalational anesthesia which has been shown to be even protective against lung injury (compared to IV propofol-anesthetics). Moreover, no other possible “hit” such as ischemia-reperfusion, surgical trauma, or pain has been applied during the study period. From this point of view, this study can be considered as a root experiment for further derivative studies looking at the combination of hyperoxia and other insults. Last but not the least, we can not speculate on prolonged effects of hyperoxia as opposed to 4 h of mechanical ventilation. Bailey et al.^[36] concluded that a physiological strategy could contribute to the inflammatory response and cause alterations to the pulmonary surfactant with prolonged mechanical ventilation of healthy rat lungs. In another study, Helmerhorst et al.^[27] have also demonstrated that 12 h can cause damage while 8 h ventilation did not. These researches also confirm our hypothesis that short-term period of hyperoxia does not affect the cellular physiological balance. We have chosen on purpose a mechanical ventilation period of 4 h to mimic the average duration of a surgical procedure.

An injury focus in any organ can also trigger to remote organ dysfunction and remote organ injury was shown in both animal experiments and human trials.^[37,38] In our study, remote organs other than the lungs were evaluated for possible damage, assuming that the first damage had started in the lung. For this purpose; SA (for ECM change determination), MDA (for lipid peroxidation levels), and wet/dry weights (for permeability changes) were measured in the liver, kidney, and heart tissues. Although there was no significant difference in any of these measured parameters, increase in SA and wet/dry weight averages were observed in the liver of hyperoxic rats, but not other organs. This finding is surprising showing that in our experimental set-up, the most sensitive organ against hyperoxia in terms of extracellular matrix changes may be the liver. This change in SA could be attributed to changes in hepatocyte glycoproteins synthesis during hyperoxia. In this sense, if the duration of hyperoxia persists, we would expect refer to the liver as the first remote organ which reacts to hyperoxia.

When the lipid peroxidation levels of the tissues were evaluated, parallel increase in MDA levels was observed with SA findings. In this sense; while the SA levels are increased, the level of MDA in the liver is not altered in hyperoxic rats. Moreover, while the level of MDA in the kidney and heart is slightly increased this increase has not been observed in SA

levels. This contrast between SA and MDA indicates that SAs (or glycoproteins on cell surface) act as a protection against possible hyperoxic tissue damage as a result of extracellular matrix changes.

Ultimately, this animal study inherits basic limitations of experimental studies i.e. extrapolation to human physiology. One cannot assume that the effects of the duration of mechanical ventilation would be similar in animals and humans, regarding that even different animal strains can show varying responses to duration of mechanical ventilation.^[39] Yet, the same drawback would also be valid for our definition of “short-term” mechanical ventilation. A further study of a longer duration of mechanical ventilation with otherwise same setting should be performed and is on the run.

Conclusion

In this experimental study, the hyperoxic mechanical ventilation of rats seems to have similar effects with normoxic ventilation. However, if prolonged exposure to hyperoxia, remote organs could have different tolerances and the liver can be the most adaptive organ against to prolong hyperoxic challenge. As a conclusion; hyperoxia can be a sneaky trigger for organ dysfunction and the effect of hyperoxia may be different in each organ. Further researches are needed to clarify this phenomenon.

Ethics Committee Approval: This study was approved by the Acibadem University Animal Experiments Local Ethics Committee (Date: 07.09.2017, Decision No: 2017/34).

Peer-review: Internally peer-reviewed.

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DENEYSSEL ÇALIŞMA - ÖZET

Kısa süreli hiperoksik ventilasyonun bir sıçan modelinde akciğer, böbrek, kalp ve karaciğer üzerine etkileri: Biyokimyasal değerlendirme

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AMAÇ: Hiperoksinin olumsuz etkileri üzerine yapılan çalışmalara rağmen, Dünya Sağlık Örgütü (WHO) hiperoksinin kullanımını önermektedir. Bu çalışmanın amacı sıçan mekanik ventilasyon modelinde hiperoksinin akciğer, böbrek, kalp ve karaciğer üzerindeki olası olumsuz etkilerini test etmektedir.

GEREÇ VE YÖNTEM: Erkek Wistar sıçanlar dört saat boyunca normoksik (FiO₂: 0.3) veya hiperoksik (FiO₂: 1.0) ventile edilerek iki gruba (n=6/grup) ayrıldı. Hasar hücre yüzey bütünlüğü, ekstraselüler matriks (sialik asit, sindekan-1), ozmotik stres (serbest hemoglobin) ve redoks homeostazi-lipit peroksidasyonu (malondialdehit) açısından bronkoalveolar lavaj, kan, akciğer, böbrek, kalp ve karaciğer örneklerinde değerlendirildi. Ayrıca bronkoalveolar lavaj ve ıslak/kuru ağırlık oranı ile hücre geçirgenliği değerlendirildi.

BULGULAR: Dört saatlik hiperoksik ventilasyon sialik asit, sindekan-1, malondialdehit düzeylerinde ve organların ıslak kuru ağırlıklarında anlamlı bir değişikliğe neden olmadı.

TARTIŞMA: Hiperoksik ventilasyonun normoksik ventilasyona benzer bir etki gösterdiği görülmektedir. Ancak, hiperoksinin uzun vadeli etkileri değerlendirilmelidir.

Anahtar sözcükler: Hiperoksi; hiperoksik ventilasyon; mekanik ventilasyon; organ hasarı.

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