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Research Article

Desflurane 6% Inhalation Inhibits Erythrocyte Deformability and Alters Oxidative Stress in Rat Lung and Kidney in a Time-Dependent Manner

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Abstract: Time-dependent effects of 6% desflurane applied for 6 h on erythrocyte deformability and tissue oxidative stress levels within 24 h period are unknown. This study aimed to investigate the influences of 6% desflurane, on erythrocyte deformability and serum, heart, lung, kidney oxidative stress in a time-dependent manner (6 h intervals) following exposure. 10-12 week-old Wistar-albino male rats were divided into five groups (n=6 per group). Rats of the 0h group were not exposed desflurane. The other rats were named in terms of time (6 h, 12 h, 18 h, 24 h) passed following anesthesia. Desflurane was administered at concentration of 6% in 6L min−1 flow-rate of 100% oxygen for 6 h in an anesthetic chamber. Erythrocyte deformability was determined using an ectacytometer. Total oxidant status (TOS), total antioxidant status (TAS) were determined using commercial kits, while oxidative stress index (OSI) was calculated. Desflurane inhalation caused a general decrement in erythrocyte deformability, the effect being more prominent at 18th h following anesthesia. Oxidative stress was not altered in serum, heart. TOS was increased at 6th and 18th h following desflurane exposure in lung. TOS and OSI in kidney were decreased at 18th and 24th h compared to 6th. Our results suggest that the oxidative potential and adverse effect of deflurane on tissue oxygenation by inhibiting RBC deformability in the first 24 h should be kept in mind especially in the presence of comorbidities.

Keywords: *Desflurane, Erythrocyte deformability, Oxidative stress, Lung, Kidney*

%6 Desfluran İnhalasyonu Eritrosit Deformabilitesini İnhibe Eder ve Sıçan Akciğeri İle Böbreğindeki Oksidatif Stresi Zamana Bağlı Olarak Değiştirir

Öz: Altı saat boyunca uygulanan %6'lık desfluranın, 24 saatlik periyotta zamana bağlı olarak eritrosit deformabilitesi ve doku oksidatif stres seviyeleri üzerindeki etkileri bilinmemektedir. Bu çalışma, %6'lık desfluranın eritrosit deformabilitesi ve serum, kalp, akciğer, böbrek oksidatif stres indeksleri üzerindeki etkilerini, desfluran inhalasyonunu takiben 24 saatlik sürede zamana bağlı bir şekilde (6 saat aralıklarla) araştırmayı amaçladı. 10-12 haftalık Wistar-albino erkek ratlar beş gruba ayrıldı (her grupta n=6). 0.saat grubundaki sıçanlar desflurana maruz bırakılmadı. Diğer sıçanlar anestezi inhalasyonundan sonra geçen süreye (6. saat, 12. saat, 18. saat ve 24. saat) göre isimlendirildi. Anestezi odasında altı saat boyunca 6 L dk-1 akım hızında %100 oksijen içinde %6 desfluran uygulandı. Eritrosit deformabilitesi, bir ektasitometre kullanılarak belirlendi. Toplam oksidan kapasitesi (TOK) ile toplam antioksidan kapasitesi (TAK) ticari kitler kullanılarak belirlendi ve oksidatif stres indeksi (OSI) hesaplandı. Desfluran inhalasyonu eritrosit deformabilitesinde genel bir azalmaya neden oldu ve bu etki anesteziden sonraki 18. saatte daha belirgin hale geldi. Oksidatif stres serum ve kalpte değişmedi. Akciğerde desfluran maruziyetini takiben 6. ve 18. saatlerde TOS arttı. Böbrekte TOS ve OSİ 18. ve 24. saatlerde 6. saate göre azaldı. Sonuçlarımız, desfluranın oksidatif hasara neden olma potansiyelinin ve ilk 24 saatte eritrosit deformabilitesini inhibe ederek doku oksijenasyonu üzerindeki olumsuz etkisinin özellikle komorbidite varlığında önemini düşündürmektedir.

Anahtar sözcükler: *Desfluran, Eritrosit deformabilitesi, Oksidatif stres, Akciğer, Böbrek*

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Introduction

Desflurane, one of the third generation inhaled anesthetic drugs, is frequently preferred in clinical use for providing safe and effective anesthesia. Recovery and extubation are also rapid following desflurane anesthesia [1]. Desflurane is minimally metabolized but it is known to affect various systems such as the central nervous, respiratory, neuromuscular and cardiovascular systems. Desflurane generally depresses these systems in a dose-dependent manner [2]. Like other anesthetics, desflurane can cause a decrease in cardiac and urinary output, and glomerular filtration. Although there was a significant decrease in perfusion pressure following desflurane anesthesia; based on the mixed venous oxyhemoglobin saturation, oxygen consumption, oxygen transport and oxygen transport/consumption ratio, it has been suggested that tissue perfusion may be sufficient [3].

Microcirculation is essential for adequate tissue oxygenation and therefore organ function. Red blood cell (RBC) deformability is an important determinant of resistance to flow since erythrocytes need to change their shape (deformability) in order to pass through narrow capillaries [4]. Thus, erythrocyte deformability is not only a very important feature for the cell to perform its gas transport function, but also for the cell's circulating half-life [5]. Although a few studies in the literature report alterations in RBC deformability after desflurane inhalation [6,7], it is not clear yet how long these changes persist following anesthesia.

Oxidative stress is one of the determinants of erythrocyte deformability. Membrane proteins forming cross-bridges with each other and/or with hemoglobin due to oxidative stress adversely affect erythrocyte deformability [8]. It is known that the effects of desflurane on oxidative stress occur depending on the concentration and duration of anesthesia [9-13]. 6% desflurane is commonly used in clinics, and the amount of anesthetic substance exposed in long-term surgeries also increases proportionally with time. Time-dependent oxidative status of different organs following anesthesia may be an important factor for post-op recovery.

In this study, we aimed to investigate the time-dependant effects of desflurane at 6% concentration in 100% oxygen 6 L min-1 for 6 h on erythrocyte deformability and oxidative stress in serum, heart, lung and kidney tissues. Tissues were selected considering the organs and systems that may be affected by desflurane as mentioned above. Samples were obtained at 6-h intervals (0, 6, 12, 18 and 24 h) within 24 h following anaesthesia. Blood flow affected by anesthetics at various parts of the body may lead to organ dysfunction in the postoperative period. It is anticipated that our data may provide contribution to this clinical issue.

Material and Methods

Ethical Approval

All experimental procedures were carried out according to Pamukkale University animal care guidelines and Animal Experiments Ethics Committee of the same University (PAUHADYEK-2022/20, 08.08.2022-06) approved the study.

Animals

200-250 g, 10-12 week-old Wistar albino male rats (n=30, Pamukkale University Animal Laboratory, Denizli, Türkiye) were used in the experiments. Rats were housed in a temperature and humidity controlled (22-23°C, 50±5%) room under a 12 h light-dark cycle. Standard diet food and water were available ad libitum. The animals were divided into five groups (n=6 per group).

Anesthesia Protocol

Rats of the 0 h group were not exposed to desflurane but were placed in the anesthetic chamber to minimaze the stress and then were sacrified at 07.00 am. The other rats were administered desflurane at 6% concentration in 6 L min-1 flow rate of 100% oxygen and divided in terms of time passed following anesthesia inhalation as; 6 h group (Rats were exposed to desflurane at 07:00-13:00 am and sacrified 6 h after anesthesia), 12 h group (Rats were exposed to desflurane at 07:00-13:00 am and sacrified 12 h after anesthesia), 18 h group (Rats were exposed to desflurane at 07:00-13:00 am and sacrified 18 h after anesthesia) and 24 h group (Rats were exposed to desflurane at 07:00-13:00 am and sacrified 24 h after anesthesia).

Rats were placed in the anesthetic chamber approximately for 1 h, 4 days before beginning the experimental procedure for adaptation. Desflurane at a concentration of 6% in 6 L min-1% 100% oxygen for 6 h was applied to anesthesia groups in a transparent anesthesia box between 07:00-13:00 am. After anesthesia, the fresh gas flow was decreased to 1 L/min. These procedures were performed under dark conditions, and under a dim red light that did not affect the circadian rhythm. The rats were sacrified every 6 h following anesthesia within a 24-h period and blood, heart, lung, kidney tissues were immediately obtained. Blood samples from the tail vein of the animals were collected into standard tubes containing EDTA (3.5 mg/mL) for the determination RBC deformability. Serum obtained by centrifugation (6450 g, 5 min) was used for measuring oxidative stress indices. RBC deformability was determined within 4 h; while serum, heart, lung and kidney were stored at –80°C until use.

Determination of RBC Deformability

The deformability of erythrocytes was determined at nine

shear stresses between 0.3 and 30 Pa using an ectacytometer (LORCA; RR Mechatronics, Hoorn, The Netherlands) at 37°C, and similar patterns of RBC deformability alterations were obtained between groups at all stress levels [14]. A suspension of low hematocrit (Hct) RBC in an isotonic viscous medium (4% polyvinylpyrrolidone 360 solution; MW 360 kD; Sigma P 5288; St. Louis, MI) was sheared in a Couette system consisting of a glass beaker and a close-fitting flask with a gap of 0.3 mm between the cylinders. Through the sheared sample, a laser beam was directed and the diffraction pattern produced by the deformed RBC was examined by a computer. Based on the geometry of the elliptical diffraction pattern, an elongation index (EI) was calculated as EI = (L−W)/(L+W), where L and W are the length and width of the diffraction pattern, respectively.

Measurement of TOS, TAS and Calculation of OSI

Serum, heart, lung and kidney TOS and TAS were determined using novel automated colorimetric measurement method (Thermo Scientific, Multiskan Go) using commercial kits (Rel Assay Diagnostics, Turkey). Results were expressed in micromolar hydrogen peroxide equivalents per liter (mol H_2O_2 Eq/L) for TOS and mmol Trolox/L for TAS. OSI was calculated according to the following formula; OSI (arbitrary unit)=TOS (mol H_2O_2 Eq/L)/TAS (mmol Trolox Equiv./L) X 100 [15,16].

Statistical Analysis

As a result of the power analysis we performed, it was calculated that a power of 80% at a confidence level of 95% could be obtained if at least 6 rats (at least totally 30 rats for all groups) were included in the study and the effect size was d=0.69. All calculations and power analysis were performed by the G-power program (version 3.1.9.2. Heinrich-Heine-Universitat. Duesseldorf. Germany). All statistical analyses were performed using SPSS 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.). Continuous variables were defined by the mean ± standard deviation. Shapiro Wilk tests were used for determination of normal distribution. For independent groups comparisons, we used One Way Analysis of Variance (post hoc: Tukey method) when parametric test assumptions were provided, Kruskal Wallis Variance Analysis (post hoc: Mann Whitney U test with Bonferroni Correction) were used when parametric test assumptions were not provided. The level of statistical significance was set at P≤0.05.

Results

Table 1 demonstrates time-dependant alterations in RBC deformability at 9 different shear stresses between 0.30 and 30 Pa following desflurane anesthesia. When all shear stresses are evaluated together, the effect of desflurane anesthesia on reducing erythrocyte deformability was most evident at the 18th h. Namely; RBC deformability measured at 0.3-3 Pa at the 18th h was lower than both 0 and 6 h groups (P<0.05). On the other hand, erythrocyte deformability determined under at 5.33-16.87 Pa shear stresses at the 18th h following anesthesia was decreased compared to the group which did not receive desflurane (P<0.05). The desflurane anesthesia applied, resulted in a decrement in RBC deformability under 0.95 and 1.69 Pa

Table 1. *Time-dependant effects of desflurane anesthesia on RBC deformability under different physiological shear stresses*

EI Shear Stress (Pa)	0 h	6 h	12 h	18 h	24 h
0.30	0.186±0.022	0.157±0.032	0.126±0.035	0.096±0.007*,#	0.113±0.008
0.53	0.252±0.021	0.227±0.031	0.188±0.039	0.158±0.008*,#	0.178±0.006
0.95	0.337±0.007	0.314±0.025	0.2765±0.037*	0.248±0.007*,#	0.268±0.004
1.69	0.420±0.006	0.397±0.017	0.365±0.031*	0.342±0.004*,#	0.361±0.003
3.00	0.483±0.009	0.469±0.010	0.4445±0.026	0.426±0.002*,#	0.441±0.005
5.33	0.532±0.008	0.520±0.016	0.5055±0.02	0.492±0.006*	0.502±0.007
9.49	0.566±0.004	0.554±0.023	0.549±0.015	0.54±0.006*	0.548±0.008
16.87	0.597±0.002	0.578±0.029	0.582±0.011	0.577±0.007*	0.582±0.007
30.00	0.622±0.001	0.597±0.034	0.608±0.011	0.610±0.007	0.608±0.007*

*Values are expressed as mean ± SD. *P<0.05, difference from 0 h group; # P<0.05, difference from 6 h group*

shear stress at 12 h post-anesthesia and under 30 Pa at 24 h following desflurane compared to the 0 h group (P<0.05) *(Table 1)*.

Fig. 1 demonstrate that serum oxidative stress was not altered within a 24 h period after desflurane anesthesia. When the oxidative stress states of different organs were exemined, it was observed that, desflurane anesthesia applied herein, did not affect oxidant-antioxidant levels in the heart, as well *(Fig. 2)*.

Lung TOS, TAS and OSI levels following desflurane inhalation are shown in *Fig. 3*. Although desfluare inhalation resulted in increment of lung TOS the alteration being statistically significant at 6 and 18 h groups compared to 0 h group (P<0.05), no statistically significant alteration was observed in lung TAS and OSI. Desflurane at 6% concentration resulted in a decrement in kidney TOS and OSI at 18 and 24 h following anesthesia compared to 6 h group. Additionally, OSI of 24 h group was less than 12 h group (P<0.05). TAS of kidney was not affected by desflurane *(Fig. 4)*.

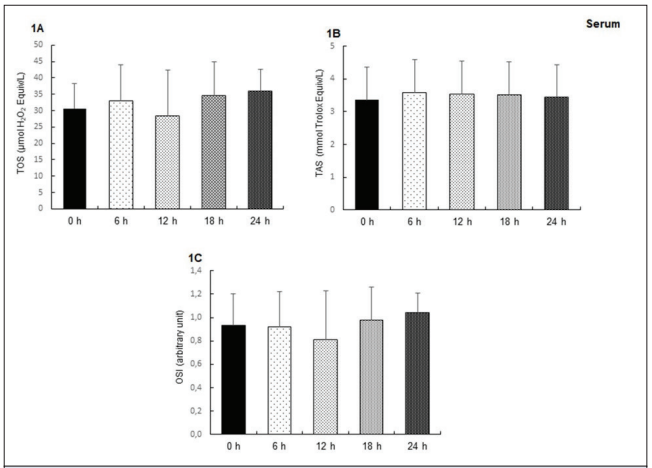

Fig 1. Serum TOS, TAS and OSI of the groups. **A.** Total oxidant status (TOS) levels of serum in the control and experimental groups. **B.** Total antioxidant status (TAS) levels of serum in the control and experimental groups. **C.** Oxidative stress index (OSI) levels of serum in the control and experimental groups. Values are expressed as mean ± SD

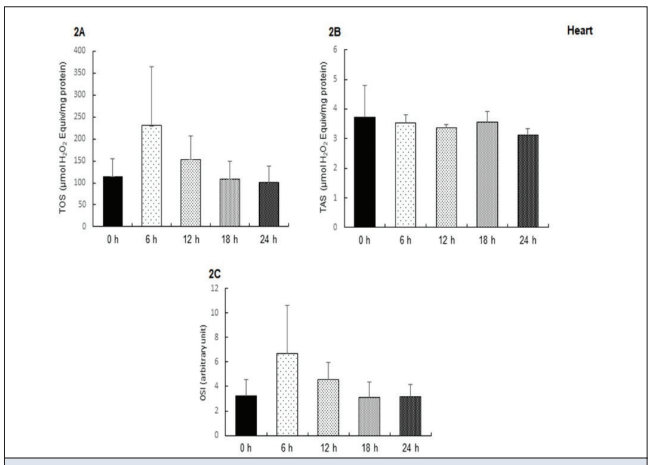

Fig 2. Heart TOS, TAS and OSI of the groups. **A.** Heart total oxidant status (TOS) levels following desflurane anesthesia. **B.** Heart total antioxidant status (TAS) levels following desflurane anesthesia. **C.** Heart oxidative stress index (OSI) levels following desflurane anesthesia. Values are expressed as mean ± SD

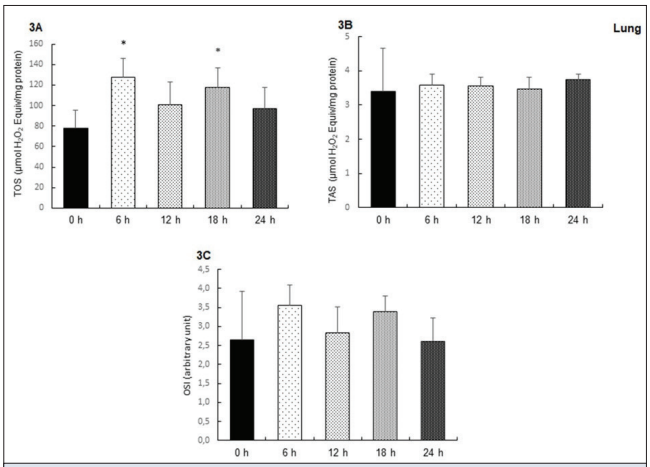

Fig 3. Lung TOS, TAS and OSI of the groups. **A.** Lung total oxidant status (TOS) levels of the groups. **B.** Lung total antioxidant status (TAS) levels of the groups. **C.** Lung total oxidative stress index (OSI) levels of the groups. Values are expressed as mean ± SD. :P<0.05, difference from 0 h group

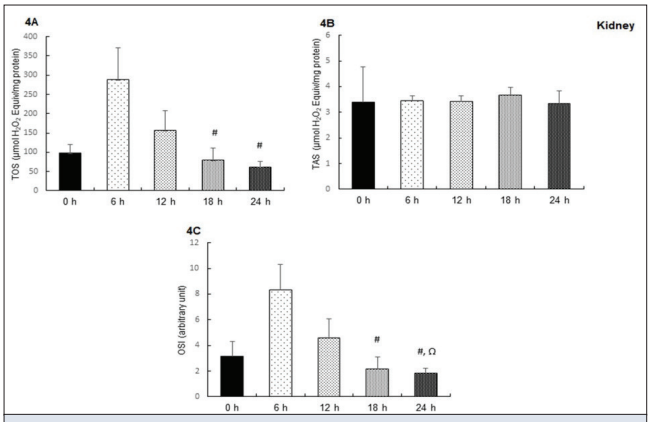

Fig 4. Kidney TOS, TAS and OSI of the groups. **A.** Kidney total oxidant status (TOS) levels of the groups. **B.** Kidney total antioxidant status (TAS) levels of the groups. **C.** Kidney oxidative stress index (OSI) levels of the groups. Values are expressed as mean ± SD. Values are expressed as mean ± SD. # :P<0.05, difference from 6 h group: Ω: P<0.05 difference from 12 h group

Discussion

Sevoflurane, isoflurane and desflurane are the most commonly used inhalation anesthetics in clinical practice [17,18]. Lungs, kidney and vessel rich group of organs are especially important to find out the time constants for wash-out of an anesthetic drug [19]. Renal and hepatic toxicity of halogenated ethers result from biotransformation to toxic

metabolites [20]. Although desflurane has lower solubility in blood and tissues compared to other halogenated agents [1], it was also suggested that, the estimated tissue distribution of desflurane may not differ significantly from that of isoflurane [20]. On the other hand, the low fat solubility of desflurane provides benefits in long surgeries. Studies have shown that midazolam, sufentanil, propofol, desflurane and sevoflurane may result in alterations in sublingual microcirculation [21,22]. In the present study, the effects of 6% desflurane applied for 6 h were investigated on RBC deformability and oxidative stress in serum, heart, lung and kidney tissues of rats within a 24-h period. The dose of desflurane was selected in accordance with the dose commonly used in surgeries in our hospital, and the duration of anesthesia was chosen as 6 h in order to observe the alterations in cases requiring long-term anesthesia such as some cancer and bypass surgeries. It was observed that, desflurane inhalation resulted in a general decrement in RBC deformability, the effect being more prominent at the 18th h (12-24 h) following anesthesia. Although oxidative stress was not altered in serum and heart, TOS was increased at 6th and 18th h following exposure to desflurane in lung. Kidney TOS was also increased at the 6th h but this alteration was not statistically significant. On the other hand, TOS in kidney tissue was decreased at the 18th and 24th h measurements compared to the 6th h value. OSI in kidney was also decreased at 18th and 24th.

Circulatory disorders caused by anesthetic agents may cause organ failure by disrupting tissue oxygenation due to their systemic cardiovascular and direct hemorheological influences [23]. On the other hand, although desflurane has dose-dependent depressive effects on cardiovascular functions and myocardial contractility, it was demonstrated that hemodynamic stability may be maintained after desflurane inhalation [20]. RBC deformability affects both the microcirculation and the macrocirculation. At the microcirculatory scale, RBC deformability is essential for perfusion of small vessels, in which capillary diameters are smaller than that of the eryrtrocyte [24]. In larger vessels, the ability to change its shape aids in the orientation of the erythrocyte to the streamlines as well as their migration towards the central regions of the vessel. These factors contribute to improvement of blood fluidity [25]. Yerer et al.[7] observed an increment in erythrocyte deformability using a laser diffractometer (Myrenne Rheodyne SSD) in male and female rats in response to 6% desflurane anesthesia administered for 1 h. In another study, it was observed that erythrocyte deformability increased in young rats, while it decreased in aged rats following the administration of 6% desflurane for 1 h [6]. Authors have commented that this anesthetic agent may reduce erythrocyte deformability due to changes in membrane structure with age and inhalation of desflurane may cause more serious problems during surgery by affecting hemorheological parameters in the elderly [6]. In the current study, we used 10-12 week-old adult male rats and showed for the first time that, 6% desflurane anesthesia applied for 6 h causes decrement in RBC deformability, the alteration being more prominent at all shear stresses 18 h after the inhalation. RBC deformability was measured at nine shear stresses between 0.3 and 30 Pa using an ectacytometer (LORCA) in our study. 9 different shear stresses are selected to mimic the different flow conditions encountered by RBC in different parts of the body. We observed that, at smaller shear stresses (0.95 and 1.69 Pa) desflurane anesthesia resulted in a decrement in RBC deformability earlier (12 and 18 h), while at higher shear stresses (30 Pa) at 24 h. The instrument (LORCA) we used to measure erythrocyte deformability is accepted as a trustworthy device with a good repetition of consecutive measurements. Our results recommend that the patient should be followed closely in terms of circulatory disorders for at least 24 h after exposure to desflurane and emphasize once again the importance of dose and time dependent effects of anesthesia.

Both erythrocyte deformability and osmotic fragility are physical features applied to diagnostics of RBC. Deformability determines the extensibility of a RBC upon mechanical stress, while osmotic fragility shows membrane extensibility upon hypotonic stress [26]. Therefore, erythrocyte osmotic fragility would be a good parameter to support the results of deformability. We did not investigate osmotic fragility in this study, and to the best of our knowledge, there is no study measuring this parameter following desflurane anesthesia. On the other hand, halothane or its metabolites, at concentrations occurring during anaesthesia, were demonstrated not to alter erythrocyte fragility in malignant hyperthermia-susceptible and resistant pigs [27].

Determinants of RBC deformability may be listed as "passive" properties in response to external forces, RBC morphology, internal viscosity and membrane flexibility [5]. Oxidative stress impairs RBC deformability through disruption of the biconcave disc structure by affecting the erythrocyte membrane lipids and especially proteins such as hemoglobin [8]. Studies examining the alterations in oxidative stress parameters following desflurane anesthesia in the literature have obtained contradictory results depending on the species and tissue studied, the measured oxidant/antioxidant levels, the duration and dose of desflurane, the sampling period following anesthesia, and the method used [9,11-13]. The measurement of TOS and TAS used in our study practically represents the cumulative action of oxidant and antioxidants and their synergistic interaction, which reflects the total oxidant-antioxidant status as well as OSI of the organism. We observed that,

serum TOS, TAS and OSI were not altered significantly in response to 6% desflurane anesthesia for 6 h. It may be concluded that, the decrement in RBC deformability is far from beeing explained by blood oxidative stress levels. Nogueira et al.[12] investigated blood oxidative stress markers in humans undergoing septoplasty surgery based on protein carbonyls, lipid peroxidation and antioxidant defense following 6% desflurane anesthesia, and similar to our results found no alteration within 18 h after the induction of anesthesia. On the other hand, measurement of oxidative indices directly on erythrocyte membrane would be a more suitable way to discuss effects of desflurane-induced oxidative stress on RBC deformability compared to measuring serum oxidative status. Unfortunately, we did not determine oxidative stress on erythrocyte membrane directly; but Turkan et al. examined erythrocyte malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) up to 3 days following desflurane anesthesia and observed no change, supporting our comment above that the change in RBC deformability is not related to oxidative stress [10].

There is a growing interest in the field of anesthesiology on the cardioprotective effects of myocardial preconditioning provoked by halogenated anesthetics especially in cases of ischemic myocardial damage. Preconditioning with desflurane was demonstrated to reduce oxidative stress-induced cardiomyocyte death [9]. We have observed that, desflurane administered at a dose of 6%, for 6 h does not alter TOS, TAS and OSI at heart. The tissue directly exposed to anesthetic gases is the lung. Lung MDA levels were shown to be increased in response to desflurane (4%) inhalation [10]. Additionally, desflurane inhalation for 2 h was demonstrated not only to decrease GSH, but also cause neutrophil and macrophage infiltration, hemorrhage, alveolar damage, and edema in the rat lung [13]. Another study suggested that isoflurane and sevoflurane prevent ventilator-induced lung injury, while desflurane does not [11]. Here, we have demonstrated that 6% desflurane applied for 6 h causes oxidative stress by increasing TOS in lung until at least the 18th h post exposure. Blood and urine fluoride metabolites are considered as markers of fluorinated ether anaesthetic metabolism. Exposure to desflurane was demonstrated to cause slight rises in urine and serum trifluoroacetic acid levels [28]. When we examined the effects of desflurane on the kidneys, we observed that the main effect was again on total oxidants and OSI, causing a non-significant increase at the 6th h and a time-dependent decrease afterwards, the decrements being most pronounced at the 18th and 24th h. Post-exposure first 24 h seems remarkable in terms of desflurane's effects on oxidative status as well as erythrocyte deformability. Türkan et al.[29] evaluated liver, brain, kidney, and lung oxidative stress in rats exposed to 4%. desflurane. They demonstrated that lung MDA levels increased (in line with our results), while liver decreased after four h of exposure. Liver SOD level decreased and brain increased in response to desflurane exposure. Brain is one of the organs that will be mostly affected by the alteration of erythrocyte deformability. Unfortunately, liver and brain oxidative status following desflurane anesthesia were not assessed in the current study due to technical reasons.

Findings of the current study are important in terms of giving information to anesthetists about a few issues they should pay attention to when choosing the anesthetic agent they will use. First one is that, while preferring desflurane they should be aware that, RBC deformability may be inhibited and thus tissue oxygenation may be adversely affected for at least 24 h. Other points to be considered are that desflurane may cause oxidative damage, especially in the lungs, in the first 18 h following exposure, and may increase oxidants in the kidneys in the early period while decreasing them over time within 24 h. These data may be particularly important in the presence of additional cardiovascular, respiratory and/or renal disorders. The physiological mechanisms of these effects are not fully clarified yet. This study was conducted in adult, male, healthy rats. The time-dependent influences of different desflurane concentrations on hemorheological parameters and oxidative stress indices in humans of different ages especially in the presence of some comorbidities may also be examined. Another limitation of the study is that; erythrocyte osmotic fragility was not examined herein. Investigation of oxidative stress indices in brain and other tissues expected to be affected by desflurane anesthesia as well as erythrocyte osmotic fragility in future studies may contribute to the clarification of the subject. Determination of oxidative stress directly on RBC membrane may also be a more suitable approach to interpret the alteration in erythrocyte rheological properties in future studies.

Availability of Data and Materials

The authors declare that data supporting the study findings are also available from the corresponding author (İ. H. Akbudak) on reasonable request.

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Conflict of Interest

The authors declare that there is no conflict of interest in publishing this article.

Author Contribution

I.H.A, O.K.E.: Conceptualization, methodology, data curation, investigation, resources, project administration; M.B.K.: Methodology, writing, review, and editing. All authors read and approved the final manuscript.

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