The effects of mechanical ventilation on oxidative stress

Os efeitos da ventilação mecânica no estresse oxidativo

João Batista Raposo Mazullo Filho[1], Silvia Bona[2], Darlan Pase da Rosa[2], Fabiano Gomes da Silva[3], Luiz Alberto Forgiarini Junior[4], Alexandre Simões Dias[5], Norma Possa Marroni[6]

1. Postgraduate Program (MSc level) in Genetics and Applied Toxicology, Universidade Luterana do Brasil - ULBRA - Canoas (RS), Brazil.
2. Postgraduate Program (PhD level) in Medicine: Medical College, Universidade Federal do Rio Grande do Sul - UFRS - Porto Alegre (RS), Brazil.
3. Graduation Biomedicine Course, NOVAFAPI College, Teresina (PI), Brazil.
4. Methodist University Center - IPA - Porto Alegre (RS), Brazil.
5. Physical Therapy Course, Universidade Federal do Rio Grande do Sul - UFRS - Porto Alegre (RS), Brazil; Postgraduate Program in Movement Sciences and Pulmonology Sciences, Universidade Federal do Rio Grande do Sul - UFRGS - Porto Alegre (RS), Brazil.
6. Postgraduate Program in Genetics and Applied Toxicology, Universidade Luterana do Brasil - ULBRA - Canoas (RS), Brazil, and Postgraduate Medical Program: Medical College and Physiological Sciences, Universidade Federal do Rio Grande do Sul - UFRS - Porto Alegre (RS), Brazil.

Study conducted at Hospital São Marcos - Teresina (PI), Brazil and Hospital de Clínicas de Porto Alegre – HCPA – Porto alegre (RS), Brazil.

Conflicts of interest: None.

Submitted on January 23, 2012
Accepted on March 14, 2012

Corresponding author:
Norma Possa Marroni
Hospital de Clinicas de Porto Alegre (HCPA) – Laboratório Experimental de Hepatologia e Gastroenterologia
Rua Ramiro Barcelos, 2350
Zip Code: 90035-903 - Porto Alegre (RS), Brazil.
Phone: + 55 51 3359-8847
E-mail: nmarroni@terra.com.br

ABSTRACT

Objective: Mechanical ventilation is a mainstay of therapy in intensive care units; however, its deleterious effects need to be assessed. Therefore, we aimed to assess oxidative stress in patients admitted to an intensive care unit undergoing invasive mechanical ventilation.

Methods: This cross-sectional study included 12 invasive mechanical ventilation patients. Blood samples (3 mL) were collected on the first and last days on invasive mechanical ventilation. Thiobarbituric acid-reacting substances (TBARS) were assessed in plasma, and superoxide dismutase (SOD) and catalase (CAT) were assessed in erythrocytes.

Results: The mean age was 64.8 ± 17.6 years, the tidal volume (VT) 382 ± 44.5 mL, and the APACHE II score 15 ± 7. When initial and final TBARS were compared, a significant difference was identified (3.54 ± 0.74 vs. 4.96 ± 1.47, p = 0.04). Antioxidant enzymes showed no significant differences. Correlations between PaO_2/FiO_2 and TBARS (r = 0.4), SOD and PaO_2/FiO_2 (r = 0.51) and APACHE II and SOD (r = 0.56) were identified. Six patients died.

Conclusion: Patients undergoing invasive mechanical ventilation can develop redox state changes, showing increased TBARS and reduced antioxidant enzymes.

Keywords: Oxidative stress; Intensive care units; Respiration, artificial; Thiobarbituric acid reactive substances

INTRODUCTION

Invasive mechanical ventilation (IMV) consists of a positive pressure device connected to a tracheal tube. IMV is used for the treatment of patients with acute respiratory failure or in acute worsening of chronic respiratory failure. The purposes of IMV are to maintain gas exchange, to reduce respiratory muscle workload (increased in acute conditions with increased metabolic requirements), to reduce oxygen consumption, thereby reducing respiratory distress, and to allow for the use of specific therapies.[1]

Maintaining gas exchange with IMV has consequences to organ systems. Both higher positive pressures and inspired oxygen fractions greater than 21% are believed to cause oxidative stress levels so high that antioxidant methods are ineffective.[2]

The inspired oxygen fraction (FiO_2) is a mechanical ventilation parameter used to optimize tissue oxygenation. However, an

inappropriately adjusted FiO_2 can lead to the harmful effects of hypoxia or hyperoxia. Some tissue hypoxia consequences are cell changes and increased anaerobic metabolism. Toxic oxygen effects are not well established in humans; however, high or prolonged oxygen doses can cause both pulmonary and systemic injuries. In hyperoxia, most of the damage is caused by oxidative stress, which can cause organ molecule degeneration and consequent cell failure and death. Many intensive care unit (ICU) patients are on prolonged mechanical ventilation and therefore on prolonged oxygen use. These patients should receive FiO_2 levels sufficient to fit their metabolic requirements but not high enough to change their respiratory patterns and vital signs.[3-5]

The severity and prognosis of ICU patients must be assessed.[6] The Acute Physiology and Chronic Health Evaluation II (APACHE II) is a useful and affordable prognostic score that was validated by Kruse and that is widely used in ICUs. This score is used for a range of diagnoses and is based on physiological parameters and clinical information that are available in most hospitals.[7]

Growing evidence shows that oxidative stress has a relevant role in several clinical conditions, such as neoplasms, diabetes, atherosclerosis, neurovegetative diseases, chronic inflammatory diseases and ischemia/reperfusion injuries, among other common conditions in critically ill patients.[8]

This article reports on a study aimed to assess and correlate oxidative stress in the plasma and erythrocytes of ICU patients undergoing IMV.

METHODS

This study was approved by the ethics committee of Faculdade NOVAFAPI - Teresina - Piauí, Brazil, and is considered to be in compliance with the Brazilian National Health Council's Law 196/96 on research involving human subjects.

This was an observational, quantitative study assessing oxidative stress in patients admitted to the ICU of Hospital São Marcos, in Teresina, Piaui, Brazil.

Male and female patients between 18 and 80 years of age, admitted between September and October 2011 and signing a written informed consent form (ICF), were included during their first day on IMV. No exclusion criteria were applied.

Data and sample collections

After inclusion and completion of the subjects' identification sheets, initial and final IMV respiratory monitoring data were collected. The data were collected daily, therefore allowing for the assessment until the day of mechanical ventilation discontinuation or death. The case report form included identification (name, age, weight, height, gender, APACHE II score, date of admission, underlying disease and comorbidities), date of each blood collection and ventilator parameters (ventilation mode, peak pressure [Ppeak], tidal volume [TV], inspiratory time [Ti], positive end-expiratory pressure [PEEP] and FiO_2), arterial blood gases (pH, PaO_2, $PaCO_2$, HCO_3), hemodynamic status (heart rate [HR] and mean blood pressure [MBP]) and peripheral oxygen saturation (SpO_2).

On the first and last days of IMV, 3-mL arterial blood samples were collected from the radial artery to analyze blood gases, and venous blood samples were collected for oxidative stress assessment. A GEM Premier 3000 blood gas meter was used for all blood gas measurements.

Oxidative stress was measured from 3-mL venous blood samples collected and stored in heparin and EDTA bottles. The blood was centrifuged to separate the plasma and erythrocytes. Plasma was stored and later analyzed for lipid peroxidation using the thiobarbituric acid-reacting substances (TBARS) technique. Erythrocytes were washed and centrifuged three times with saline 0.9%, discharging the supernatant. Following the last washing, erythrocyte precipitates were stored in acetic acid and magnesium sulfate solution for anti-oxidant enzyme analysis.

For lipid peroxidation and anti-oxidant enzyme assessment, the protein concentration in pulmonary tissue homogenate was calculated using the Bradford method, using bovine albumin as the standard. The samples were measured spectrophotometrically and the values expressed as mg/mL. Plasma lipid peroxidation was determined with the TBARS method. This technique consists of heating the material with thiobarbituric acid until the formation of a pink material, which is subsequently measured at 355 nm using a spectrophotometer. The results are expressed as nmol/mL TBARS.[9] Superoxide dismutase (SOD) anti-oxidant enzyme activity was measured on a plate reader, assessing epinephrine degradation and adenochrome formation; the data

are expressed as SOD units per mg of protein (U-SOD/mg prot.)[10] Catalase (CAT) activity was measured with hydrogen peroxide in a plate reader at 240 nm, and the results are expressed as nmol/mg protein.[11]

Statistical analysis

A data bank was prepared using Microsoft Excel software. The data were analyzed using the SPSS statistical package, version 17.0, and the results are expressed as the mean ± standard deviation. A significance level of 5% was adopted, with $p < 0.05$ considered statistically significant. Before/after comparisons were made using a pairwise t test, and correlations were tested with Pearson's correlation test. The sample's normality was assessed with the Kolmogorov-Smirnov test.

RESULTS

Table 1 displays the patients' overall characteristics. Most of the patients were female — 75% of the sample. The mean age was 64.8 ± 17.6 years. The mean height was 155 ± 0.05 centimeters. The predicted weight was 47.7 ± 5.5 kilograms, and the predicted tidal volume (TV) was 382 ± 44.5 mL. The median APACHE II score was 15 ± 7. The mean IMV time was 5.5 ± 3.5 days. The following comorbidities were recorded: three patients (25%) with systemic hypertension (SH), two patients (17%) with diabetes mellitus (DM) and two patients with acute renal failure (ARF) (17%). Six patients (50%) died during their hospitalizations.

Analyzing initial and final oxidative stress data, the TBARS levels were significantly higher after IMV ($p < 0.05$). No statistically significant differences were found for SOD or CAT; however, enzyme activity was identified as decreasing after IMV (Table 2).

No arterial blood gas parameters were shown to change significantly (Table 3). Similarly, as shown in table 4, the initial and final ventilation parameters were not different.

A statistically significant correlation was observed between FiO_2 and TBARS before ($r = 0.4$) and after ($r = 0.4$) IMV, suggesting that the higher FiO_2 was, the more oxidative stress there was (Figure 1). Analyzing the correlation between the final PaO_2/FiO_2 and final SOD, $r = 0.51$ ($p < 0.05$) was found, suggesting that patients with higher PaO_2/FiO_2

Table 1 - Anthropometric and clinical sample characteristics

Characteristics	
Gender	
Male	3 (25)
Female	9 (75)
Age (years)	64.8 ± 17.6
Height (m)	1.55 ± 0.05
Predicted weight (Kg)	47.7 ± 5.5
Predicted TV (mL)	382 ± 44.5
APACHE II	15 ± 7
IMV time (days)	5.5 ± 3.5
Comorbidities	
SH	3 (25)
DM	2 (17)
ARF	2 (17)
Outcome	
Death	6 (50)
Discharge	6 (50)

TV - tidal volume; APACHE II - Acute Physiology and Chronic Health Disease scoring system II; SH - systemic hypertension; DM - diabetes mellitus; ARF - acute renal failure. The results are expressed as the mean ± standard deviation or as number (%).

Table 2 - Initial and final invasive mechanical ventilation oxidative stress assessments

Variable	Initial	Final	p value
TBARS (nmol/mg protein)	3.54 ± 0.74	4.96 ± 1.47	0.04*
SOD (U-SOD/mg protein)	18.02 ± 7.78	16.85 ± 7.30	0.7
CAT (pmol/mg protein)	0.977 ± 1.05	0.935 ± 0.57	0.9

The results are expressed as the mean ± standard deviation. *Statistically significant difference between initial and final data ($p < 0.05$). TBARS - thiobarbituric acid reactive substances; SOD - superoxide dismutase; CAT - catalase.

Table 3 - Initial and final invasive mechanical ventilation arterial blood gas assessments

Variable	Initial	Final	p value
pH	7.39 ± 0.07	7.38 ± 0.14	0.82
PaO_2 (mm Hg)	125 ± 45	109 ± 33	0.33
$PaCO_2$ (mm Hg)	35.3 ± 12.8	42.4 ± 16.9	0.25
HCO_3(mEq/L)	21.6 ± 5	25.4 ± 7.4	0.15
SpO_2	98.4 ± 2.6	96.6 ± 3.6	0.17
PaO_2/FiO_2	336.1 ± 157.9	307.2 ± 149.6	0.75

The results are expressed as the mean ± standard deviation or percent. PaO_2 - arterial oxygen pressure; $PaCO_2$ - arterial carbonic gas pressure; HCO_3 - bicarbonate; SpO_2 - peripheral oxygen saturation; FiO_2 - inspired oxygen fraction.

Table 4 - Ventilation parameters

Parameter	Initial	Final	p value
Ppeak (mbar)	22.3 ± 3.3	21.5 ± 3.8	0.58
TV (mL)	517.2 ± 118	519 ± 196.1	0.97
Ti (s)	1.01 ± 0.05	1.03 ± 0.06	0.38
PEEP (mbar)	6 ± 1.5	6.75 ± 2.1	0.32
FiO_2	46.2 ± 10.2	38.7 ± 11.6	0.1
Cest (mL/mbar)	41.5 ± 12.2	46.6 ± 19.4	0.44
R (mbar/mL/s)	13.9 ± 7	13 ± 3.5	0.69

The results are expressed as the mean ± standard deviation or percent. Ppeak - peak pressure; TV - tidal volume; Ti - inspiratory time; PEEP - positive end-expiratory pressure; FiO_2 - inspired oxygen fraction; Cest - static compliance; R - resistance.

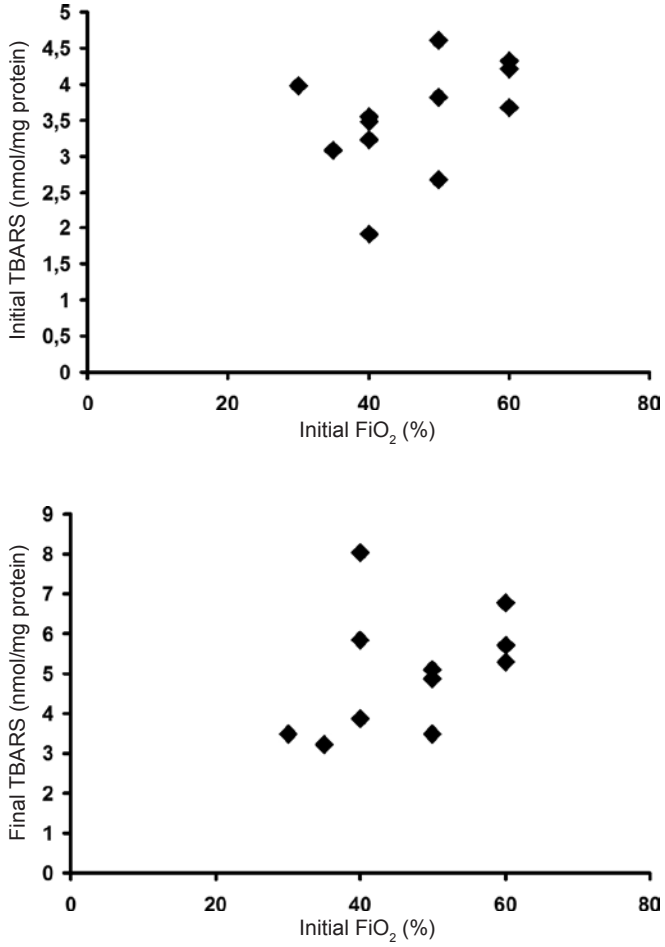

Figure 1 - Analysis of the correlation between FiO_2 and thiobarbituric acid-reactive substances before and after invasive mechanical ventilation. A significant positive correlation was identified at the beginning (r = 0.4; p < 0.05) and end (r = 0.4; p < 0.05) of invasive mechanical ventilation.

TBARS - thiobarbituric acid reactive substances.

ratios have more active SOD following IMV (Figure 2). Analysis of the correlation between the IMV time and final CAT showed r = -0.30 (p < 0.5), i.e., patients with shorter mechanical ventilation time had larger CAT values after IMV (Figure 3).

Figure 4 shows the correlations between the APACHE II score and initial SOD (r = 0.56; p < 0.05) and between the APACHE II and final SOD (r = 0.59; p < 0.05).

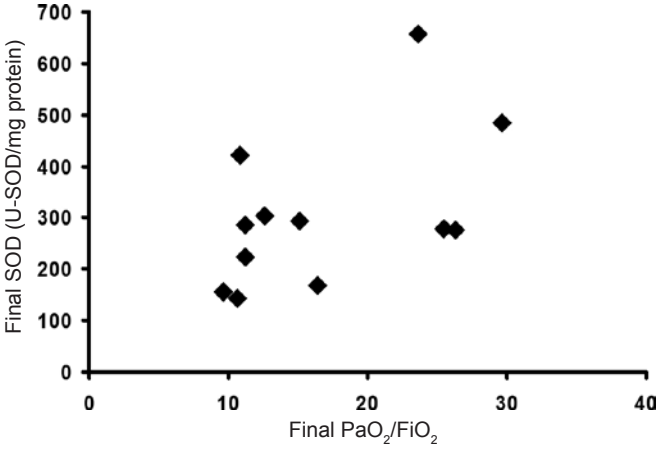

Figure 2 - Correlation between PaO_2/FiO_2 and the antioxidant enzyme superoxide dismutase by the end of invasive mechanical ventilation. A significant positive correlation was observed (r = 0.51; p < 0.05).

SOD - superoxide dismutase.

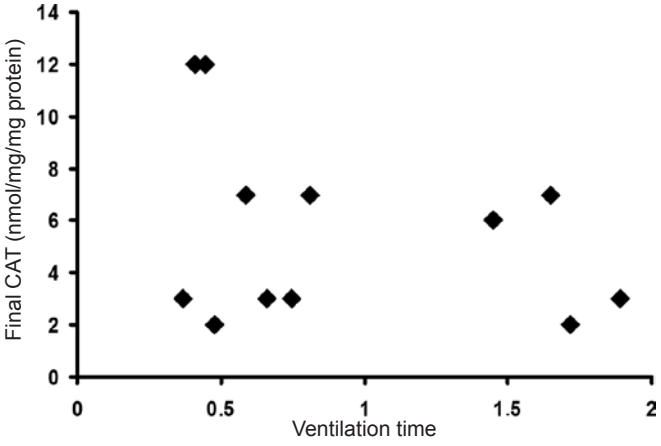

Figure 3 - Correlation between hospital length of stay and the antioxidant enzyme catalase by the end of invasive mechanical ventilation. A negative correlation was observed (r = -0.30; p < 0.05).

CAT – catalase.

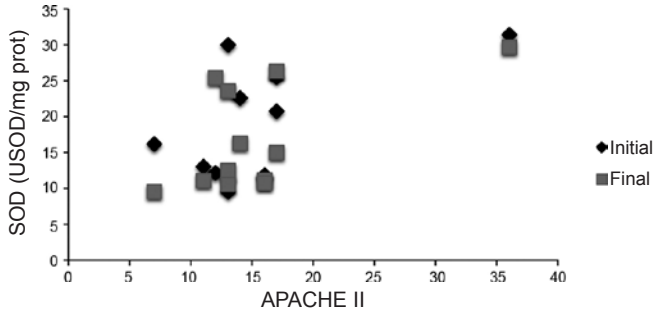

Figure 4 - Correlation between the APACHE II prognostic score and the antioxidant enzyme superoxide dismutase before and after invasive mechanical ventilation. A significant positive correlation was identified at the beginning ($r = 0.56$; $p < 0.05$) and end ($r = 0.59$; $p < 0.05$) of invasive mechanical ventilation.

APACHE II - Acute Physiology and Chronic Health Evaluation scoring system; SOD - superoxide dismutase.

DISCUSSION

This study assessed the correlation between oxidative stress and IMV in ICU patients; our findings suggest that IMV might influence the redox state.

Analyzing oxidative stress after IMV, significantly increased TBARS levels were identified. Although the medical literature lacks reports from clinical trials assessing oxidative stress and IMV, our data agree with the findings of other authors who assessed biological models.[13] Experimental animal and human oxidative stress studies have shown that increased metabolic activity favors oxidative molecular injuries.[14] Oxidative stress, shown by increased TBARS, could be associated with endothelial dysfunction and prolonged IMV due to an increased production of oxygen-derived free radicals and also reactive oxygen species, such as hydrogen peroxide, causing both pulmonary and systemic injuries.[15] Oxidative stress markers are remarkable tools for the assessment of possible effects on and implications for several metabolic processes, and they might be markers of pathologic and inflammatory processes. These substances can be measured in the blood, thus making them suitable for bedside care.[13,16] Respiratory muscle contractions, either active or passive due to IMV, promote transient ischemia, while relaxation leads to reperfusion. This process characterizes the oxygen paradox in which a lack of oxygen followed by reperfusion leads to increased reactive oxygen species and can cause an unbalanced condition, characterizing oxidative stress.[17] Additionally, significant reductions of CAT and SOD anti-oxidant enzymes were observed after IMV. These serum enzyme decreases could be explained by the body's reduced self-defense mechanisms, as the subjects were prolonged IMV patients with associated comorbidities.[18]

The initial and final arterial blood gas and ventilation parameters demonstrated no statistically significant differences. However, the patients had increased oxidative stress and reduced levels of anti-oxidant enzymes.[19,20]

A significant correlation was observed between the initial FiO_2 and initial TBARS ($r = 0.4$), as well as a correlation between the initial FiO_2 and final TBARS ($r = 0.4$; $p < 0.05$). This correlation shows that a higher FiO_2 leads to higher oxidative stress, as a high FiO_2, with the consequence of more circulating oxygen, causes oxidative injury. However, PaO_2 conditions that are too low can also cause oxidative stress.[17]

Additionally, a correlation between the final PaO_2/FiO_2 ratio and final SOD was identified ($r = 0.51$; $p < 0.05$). Patients with higher PaO_2/FiO_2 ratios showed higher final SOD values, therefore showing that more oxygen from circulating FiO_2 might stimulate the production of SOD, increasing anti-oxidant defenses, as SOD acts by transforming superoxide radical anions (produced from oxygen) into hydrogen peroxide.[21]

Analysis of the correlation between the IMV time and final CAT showed $r = 0.3$ ($p < 0.05$), demonstrating that patients with prolonged ventilation had higher CAT values by the end of IMV. This finding suggests that patients with less IMV time have more effective anti-oxidant systems and thus higher CAT concentrations. CAT's anti-oxidant action takes place when free radicals reach the bloodstream via erythrocyte catalase. Catalase prevents meta-hemoglobin accumulation and also degrades hydrogen peroxide — a toxic metabolism byproduct — into water and molecular oxygen.[22] Excessive H_2O_2 causes hemoglobin oxidation, consequently leading to a reduced oxygen concentration; this process can lead to infections, ulcers or even necrosis.[23]

The predictive APACHE II score had a correlation with SOD anti-oxidant enzyme levels at the initial ($r = 0.56$; $p < 0.05$) and final assessments ($r = 0.59$; $p < 0.05$), suggesting that more severely ill patients had lower SOD values, both on the first and last days of IMV. This finding shows that, in general, ICU

oxidative parameters are associated with severity and outcome.[24]

This study had some limitations: a) the small sample size; b) the lack of control patients, which would have allowed for the assessment of whether oxidative stress changes are secondary to underlying disease progression; and c) the use of TBARS as a single oxidative stress marker. Most analytes are generated during heating, which is part of the TBARS technique. Not adding butylated hydroxytoluene (BHT) can increase endogenous production of analytes, thus changing TBARS assessments.

Additional longitudinal studies and larger sample sizes are required to assess the predictive value of the selected variables, as well as the possibility of stratifying oxidative stress, anti-oxidant enzymes and patients' outcomes.

CONCLUSION

This study's results suggest that patients with invasive mechanical ventilation have increased oxidative stress by the end of IMV, with increased TBARS and reduced superoxide dismutase and catalase serum levels.

RESUMO

Objetivo: A ventilação mecânica constitui um dos pilares terapêuticos da unidade de terapia intensiva, entretanto, deve-se avaliar os efeitos deletérios por ela ocasionados, logo objetivamos avaliar o estresse oxidativo de pacientes internados em unidade de terapia intensiva submetidos à ventilação mecânica invasiva.

Métodos: Estudo transversal onde foram incluídos 12 pacientes que estavam em ventilação mecânica invasiva. As coletas sanguíneas (3 mL) foram realizadas no primeiro e último dia em que o paciente estava submetido a ventilação mecânica invasiva e utilizou-se o plasma para avaliação das substâncias que reagem ao ácido tiobarbitúrico (TBARS) e os glóbulos vermelhos para dosagem de superóxido dismutase (SOD) e da catalase.

Resultados: Os pacientes apresentaram média de idade de 64,8±17,6 anos; volume corrente de 382±44,5 mL e APACHE II de 15±7. Quando comparado o TBARS inicial e ao final da ventilação houve diferença significativa (3,54±0,74 *vs.* 4,96±1,47; p=0,04). Em relação às enzimas antioxidantes não houve diferença. Observa-se correlação entre as variáveis PaO_2/FiO_2 e TBARS (r = 0,4); SOD e PaO_2/FiO_2 (r = 0,51) e SOD e APACHE II (r = 0,56). Quanto ao desfecho da internação, 6 pacientes foram a óbito.

Conclusão: Pacientes submetidos à ventilação mecânica invasiva podem apresentar alteração do estado redox, marcado pelo aumento no TBARS e redução das enzimas antioxidantes.

Descritores: Estresse oxidativo; Unidades de terapia intensiva; Respiração artificial; Substâncias reativas com ácido tiobarbitúrico

REFERENCES

1. Emmerich JC. Suporte ventilatório: conceitos atuais. Rio de Janeiro: Revinter; 1998.
2. Andrade Júnior DR, Souza RB, Santos SA, Andrade DR. Os radicais livres de oxigênio e as doenças pulmonares. J Bras Pneumol. 2005;31(1):60-8.
3. Crapo JD. Morphologic changes in pulmonary oxygen toxicity. Annu Rev Physiol. 1986;48:721-31.
4. Barazzone C, Horowitz S, Donati YR, Rodriguez I, Piguet PF. Oxygen toxicity in mouse lung: pathways to cell death. Am J Respir Cell Mol Biol. 1998;19(4):573-81.
5. Barazzone C, White CW. Mechanisms of cell injury and death in hyperoxia: role of cytokines and Bcl-2 family proteins. Am J Respir Cell Mol Biol. 2000;22(5):517-9.
6. Feijó CA, Leite Júnior FO, Martins AC, Furtado Júnior AH, Cruz LL, Meneses FA. Gravidade dos pacientes admitidos à unidade de terapia intensiva de um hospital universitário brasileiro. Rev Bras Ter Intensiva. 2006;18(1):18-21.
7. Kruse JA, Thill-Baharozian MC, Carlson RW. Comparison of clinical assessment with APACHE II for predicting mortality risk in patients admitted to a medical intensive care unit. JAMA. 1988;260(12):1739-42.
8. Salvador M, Henriques JA. Radicais livres e a resposta celular ao estresse oxidativo. Canoas: ULBRA; 2004.
9. Durak I, Yalçin S, Burak Cimen MY, Büyükkoçak S, Kaçmaz M, Oztürk HS. Effects of smoking on plasma and erythrocyte antioxidant defense systems. J Toxicol Environ Health A. 1999;56(6):373-8.
10. Misra HP, Fridovich I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. J Biol Chem. 1972;247(10):3170-5.
11. Aebi H. Catalase in vitro. Methods Enzymol. 1984;105:121-6.
12. Rocha MS, Caetano JA, Soares E, Medeiros FL. Caracterização da população atendida em unidade de terapia intensiva: subsídio para a assistência. Rev Enferm UERJ. 2007;15(3):411-6.
13. Baio TH, Fioretto JR, Nakatami BT, Ronchi CF, Kurokawa CS, Ferreira AL. Efeitos de diferentes técnicas de ventilação mecânica e do óxido nítrico inalatório sobre o estresse oxidativo em lesão pulmonar aguda induzida experimentalmente. Botucatu: Faculdade de Medicina da Universidade Estadual de São Paulo; 2011.
14. Souza Jr TP, Oliveira PR, Pereira B. Exercício físico e estresse oxidativo: efeitos do exercício físico intenso sobre a quimioluminescência urinária e malondialdeído

plasmático. Rev Bras Med Esporte. 2005;11(1):91-6.
15. Costa-Hong V, Bortolotto LP, Jorgetti V, Consolim-ColomboI F, Krieger EM, Lima JJ. Estresse oxidativo e disfunção endotelial na doença renal crônica. Arq Bras Cardiol. 2009;92(5):413-8.
16. Barbosa KB, Costa NM, Alfenas RC, de Paula SO, Minim VP, Bressan J. Estresse oxidativo: conceito, implicações e fatores modulatórios. Rev Nutr. 2010;23(4):629-43.
17. Halliwell B, Gutteridge JM. Free radicals in biology and medicine. Oxford: Clarendon Press; 1989.
18. Andrades M, Ritter C, Moreira JC, Dal-Pizzol F. Oxidative parameters differences during non-lethal and lethal sepsis development. J Surg Res. 2005;125(1):68-72.
19. Carvalho CR, Toufen Junior C, Franca SA. III Consenso Brasileiro de Ventilação Mecânica. Ventilação mecânica: princípios, análise gráfica e modalidades ventilatórias. J Bras Pneumol. 2007;33(Supl 2):S54-70.
20. Dernaika TA, Keddissi JI, Kinasewitz GT. Update on ARDS: beyond the low tidal volume. Am J Med Sci. 2009;337(5):360-7.
21. Llesuy SF. Introducción y especies activas de oxígeno. In: Marroni NP, organizadora. Estresse oxidativo e antioxidantes. Canoas: ULBRA; 2002. p. 21-32.
22. Gaetani GF, Galiano S, Canepa L, Ferraris AM, Kirkman HN. Catalase and glutathione peroxidase are equally active in detoxification of hydrogen peroxide in human erythrocytes. Blood. 1989;73(1):334-9.
23. Wieacker P, Mueller CR, Mayerova A, Grzeschik KH, Ropers HH. Assignment of the gene coding for human catalase to the short arm of chromosome 11. Ann Genet. 1980;23(2):73-7.
24. Guerreiro MO, Petronilho F, Andrades M, Constantino L, Mina FG, Moreira JC, et al. Plasma superoxide dismutase activity and mortality in septic patients [corrected]. J Trauma. 2010;69(6):E102-6. Erratum in: J Trauma. 2011;70(6):1582.