BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902022e20827X

Article

# Protective effect of dexmedetomidine on lung injury during one-lung ventilation in elderly patients undergoing radical esophagectomy

**Juanjuan Miao[1], Mengmeng Cai[1], Jiafeng Sun[1], Yi Gu[*1], Boxiang Du[1]**

*[1]Department of Anesthesiology, The Second Affiliated Hospital of Nantong University, Nantong 226001, China*

This study investigated the protective effect of dexmedetomidine (Dex) on lung injury during one-lung ventilation (OLV) in elderly patients undergoing radical esophagectomy with remote ischemic preconditioning (RIPC). Fifty-four esophageal cancer patients undergoing radical esophagectomy were divided into control, RIPC and RIPC+Dex group. During the anesthesia and ventilation in surgery, the RIPC was performed in RIPC group, and the intravenous infusion of Dex based on RIPC was conducted in RIPC+Dex group. At the time immediately before OLV beginning (T1), 60 min of OLV (T2) and end of surgery (T3), the oxygenation index (OI) and respiratory index (RI) were recorded, and the serum superoxide dismutase (SOD), malondialdehyde (MDA), tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) levels were determined. Results showed that, compared with RIPC group, in RIPC+Dex group the OI at T2 and T3 increased, the RI at T2 and T3 decreased, the serum SOD level at T3 increased, the serum MDA level at T3 decreased, the serum TNF-α and IL-6 levels at T2 and T3 decreased (all $P < 0.05$). In conclusion, for elderly patients undergoing radical esophagectomy with RIPC, Dex can effectively inhibit the oxidative stress and inflammatory response during OLV, thus alleviating the lung injury and reducing the postoperative complications.

**Keywords:** Dexmedetomidine. Ischemic preconditioning. Lung injury. Inflammatory reaction. Oxidative stress.

## INTRODUCTION

Esophageal cancer is one of the most common malignant tumors in digestive tract. Most esophageal cancer patients are middle-aged and elderly (Mak *et al.*, 2010). They often suffer from the malnutrition and metabolic disorders, and have many complications in circulatory and respiratory systems. The reserve function of important organs such as heart and lung is poor, and the tolerance to surgery and anesthesia is low. The radical esophagectomy is the common used method for treating the esophageal cancer (Nishimaki *et al.*, 1998). One-lung ventilation (OLV) technology is widely used in the radical esophagectomy, which can provide a good surgical field. However, OLV can increase the intrapulmonary shunt and induce the local and systemic inflammatory response, which easily leads to the hypoxemia and lung injury, especially in elderly patients with pulmonary insufficiency (Ojima *et al.*, 2007). Therefore, it is particularly important to alleviate the pulmonary complications in OLV. Studies have shown that, the remote ischemic preconditioning (RIPC) is a kind of preconditioning that can mobilize the body's anti-injury ability, and has protective effect on lung injury (Olguner *et al.*, 2006; Li *et al.*, 2014). Dexmedetomidine (Dex) is a new highly selective adrenergic receptor agonist, which can stabilize the hemodynamics (Talke *et al.*, 2000), alleviate the stress response (Sulaiman *et al.*, 2012), and inhibit the inflammatory response (Bulow *et al.*, 2016). The mechanisms of RIPC and Dex in alleviating lung injury are different, and it is not clear whether the combination of Dex and RIPC has synergistic effect in preventing the lung

***Correspondence:** Y. Gu. Department of Anesthesiology. The Second Affiliated Hospital of Nantong University. 6 North Haierxiang Road. Nantong 226001, China. Phone: +86-513-85061315. E-mail: guyi2020@126.com. ORCID: https://orcid.org/0000-0003-2820-6257

injury during OLV in radical esophagectomy. This study aimed to investigate the protective effect of Dex on lung injury during OLV in elderly patients undergoing radical esophagectomy with RIPC and explored the related mechanism. The objective was to provide a reference for clinical application of this strategy.

## PATIENTS AND METHODS

### Patients

Fifty-four esophageal cancer patients undergoing radical esophagectomy from June 2017 to December 2018 in The Second Affiliated Hospital of Nantong University were enrolled in this study. Their age ranged from 61 to 75 years, with an average age of 67.41±8.38 years. There were 43 males and 11 females. The body mass index (BMI) was 22.15±2.73 kg/m$^2$. In American Society of Anesthesiologists (ASA) grade, there were 42 cases of grade I and 12 cases of grade II. The surgery duration was 169.52±29.87 min. The OLV duration was 139.73±18.55 min. The patients were divided into control group, RIPC group and RIPC+Dex group, 18 cases in each group. This study was approved by the Ethics Committee of The First Affiliated Hospital of Nanchang University. All patients signed the informed consent.

### Inclusion criteria and exclusion criteria

The inclusion criteria were as follows: undergoing radical esophagectomy; without history of diabetes, obesity, anemia or serious cardiovascular or cerebrovascular disease. The exclusion criteria were as follows: with incomplete medical records; had the radiotherapy, chemotherapy or immunotherapy within 1 month before surgery; had pulmonary infection within 2 weeks before surgery.

### Anesthesia and ventilation

After admission for radical esophagectomy, the blood pressure, heart rate, electrocardiogram and blood oxygen saturation were monitored routinely. The anesthesia induction was performed by intravenous injection of midazolam (0.05 mg/kg), sufentanil (0.8 μg/kg), propofol (1-2 mg/kg), and cisatracurium (0.15 mg/kg). The left double-lumen bronchial catheter was intubated and the position of the catheter was determined by fiberoptic bronchoscopy. The catheter was connected to the anesthesia machine for mechanical ventilation. The inspiratory to expiratory ratio was 1: 2. The respiratory frequency of two-lung ventilation was 12-14 times/min, with tidal volume of 8-10 ml/kg. The respiratory frequency of OLV was 14-16 times/min, with tidal volume of 6-8 ml/kg. The $P_{ET}CO_2$ was maintained as 35-45 mmHg. The anesthesia maintenance was performed by intravenous infusion of propofol (5-8 mg/(kg·h)) and intermittent injection of cisatracurium (0.05 mg/kg) and sufentanil (0.2 μg/kg). During the surgery, the mean arterial pressure fluctuation was maintained less than 20% of the baseline value, with blood oxygen saturation > 95%, airway pressure < 40 cm$H_2O$ and bispectral index of 40-55. In RIPC group, at 10 min after tracheal intubation, the lower limb blood flow was blocked for 5 min, followed by restoring for 5 min, repeated for three times, and the ischemic preconditioning was performed. In RIPC+Dex group, at the time of ischemic preconditioning beginning, Dex was infused intravenously at a load of 0.5 μg/kg for 15 min, and then Dex was infused intravenously at a rate of 0.5 μg/(kg·h) until the end of surgery. In control group, only normal saline with equal volume was infused intravenously. After the surgery, the catheter was extubated only after the patient's consciousness was clear and the spontaneous breathing was completely restored. The patients were sent to anesthesia recovery room for observation. The oxygen inhalation by mask and routine monitoring were performed.

### Observation indexes

Ten milliliter of blood sample from radial artery was collected immediately before OLV beginning (T1), at 60 min of OLV (T2) and at the end of surgery (T3), respectively. Four milliliter of blood sample was analyzed by blood gas analyzer. The oxygenation index (OI) and respiratory index (RI) were recorded. Three milliliter of blood sample was used to measure the oxidative stress indexes. The serum superoxide dismutase (SOD) level was measured by xanthine oxidase method and the malondialdehyde (MDA) level was measured

by thiobarbituric acid method. Three milliliter of blood sample was used to measure the inflammatory markers. The serum tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) levels were determined using the enzyme-linked immunosorbent assay. The kits were provided by Nanjing Senbeija Biotechnology Co., Ltd. (Nanjing, China). In addition, the postoperative complications of all patients were observed.

### Statistical analysis

All statistical analysis was carried out using SPSS 23.0 software (SPSS Inc., Chicago, USA). The enumeration data were presented as number, and were compared using $\chi^2$ test. The measurement data were presented as mean±standard deviation, and were compared using single-factor analysis of variance with SNK-q test. A P value of less than 0.05 was considered statistically significant.

## RESULTS

### General information of patients

The general information of patients in three groups was shown in Table I. There was no significant difference in age, gender, BMI, ASA grade, surgery duration or OLV duration among three groups (P > 0.05).

**TABLE I -** General information of patients in three groups

| Group | Control | RIPC | RIPC+Dex | P |
|---|---|---|---|---|
| n | 18 | 18 | 18 | |
| Age (months) | 67.45±8.65 | 68.32±9.12 | 66.68±8.44 | > 0.05 |
| Gender (n) | | | | > 0.05 |
| Male | 14 | 16 | 13 | |
| Female | 4 | 2 | 5 | |
| BMI (kg/m$^2$) | 23.82±2.52 | 22.05±2.17 | 21.49±3.33 | > 0.05 |
| ASA grade (n) | | | | > 0.05 |
| I | 14 | 12 | 16 | |
| II | 4 | 6 | 2 | |
| Surgery duration (min) | 178.45±27.45 | 160.78±23.57 | 167.12±28.12 | > 0.05 |
| OLV duration (min) | 146.16±18.27 | 132.62±18.18 | 140.33±17.83 | > 0.05 |

BMI, body mass index; OLV, one-lung ventilation.

### Comparison of OI and RI among three groups

At T1, there was no significant difference of OI or RI among three groups (P > 0.05). At T2 and T3, the OI in each group was significantly lower than that at T1, respectively (P < 0.05), and that at T3 was significantly higher than that at T2 (P < 0.05). At T2 and T3, the RI in each group was significantly higher than that at T1, respectively (P < 0.05), and that at T3 was significantly lower than that at T2 (P < 0.05). Compared with control group, the OI in RIPC and RIPC+Dex groups at T2 and T3 was significantly increased, respectively (P < 0.05), and the RI was significantly decreased (P < 0.05). Compared with RIPC group, the OI in RIPC+Dex group at T2 and T3 was significantly increased, respectively (P < 0.05), and the RI was significantly decreased (P < 0.05) (Figure 1).

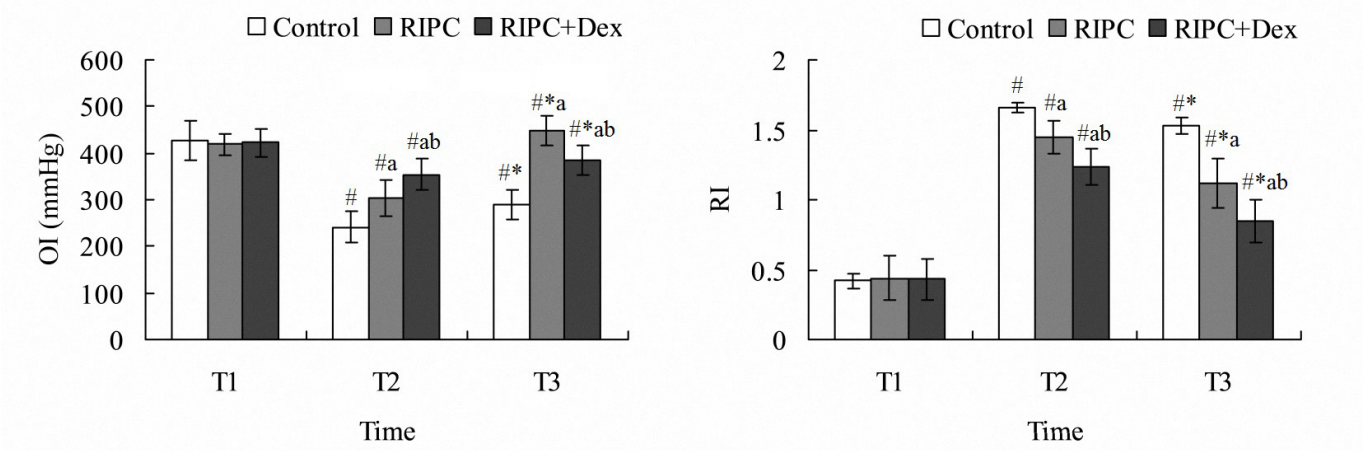


**FIGURE 1 -** Comparison of OI and RI among three groups. #P < 0.05 compared with T1; *P < 0.05 compared with T2; aP < 0.05 compared with control group; bP < 0.05 compared with RIPC group. OI, oxygenation index; RI, respiratory index.

### Comparison of serum SOD and MDA levels among three groups

In each group, there was no significant difference of serum SOD or MDA level between T1 and T2 (P > 0.05). Compared with T1 and T2, in each group the SOD level at T3 was significantly decreased, respectively (P < 0.05), and the MDA level was significantly increased (P < 0.05). At T1 and T2, there was no significant difference in serum SOD or MDA level among three groups (P > 0.05). At T3, compared with control group, the SOD level in RIPC and RIPC+Dex groups was significantly increased, respectively (P < 0.05), and the MDA level was significantly decreased (P < 0.05). Compared with RIPC group, the SOD level in RIPC+Dex group was significantly increased (P < 0.05), and the MDA level was significantly decreased (P < 0.05) (Figure 2).

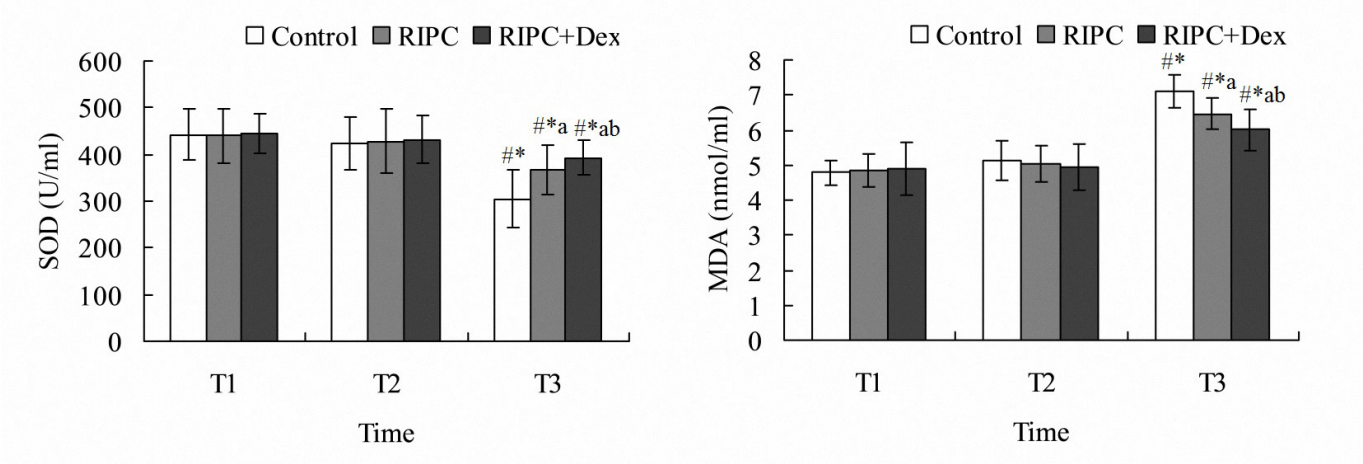


**FIGURE 2 -** Comparison of serum SOD and MDA levelsamong three groups. #P < 0.05 compared with T1; *P < 0.05 compared with T2; aP < 0.05 compared with control group; bP < 0.05 compared with RIPC group. SOD, superoxide dismutase; MDA, malondialdehyde.

### Comparison of serum TNF-α and IL-6 levels among three groups

At T1, there was no significant difference in serum TNF-α or IL-6 level among three groups ($P > 0.05$). At T2 and T3, the TNF-α and IL-6 levels in each group were significantly lower than that at T1, respectively ($P < 0.05$), and those at T3 were significantly higher those at T2, respectively ($P < 0.05$). Compared with control group, the TNF-α and IL-6 levels in RIPC and RIPC+Dex groups at T2 and T3 were significantly decreased, respectively ($P < 0.05$). Compared with RIPC group, the TNF-α and IL-6 levels in RIPC+Dex group at T2 and T3 were significantly decreased, respectively ($P < 0.05$) (Figure 3).

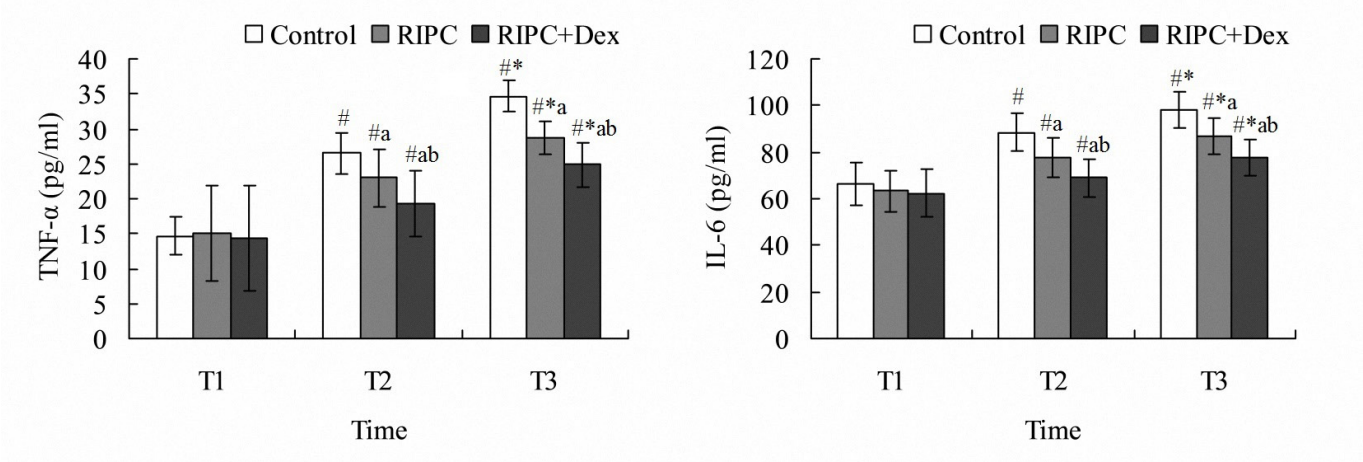


**FIGURE 3 -** Comparison of serum TNF-α and IL-6 levelsamong three groups. $^{\#}P < 0.05$ compared with T1; $^{*}P < 0.05$ compared with T2; $^{a}P < 0.05$ compared with control group; $^{b}P < 0.05$ compared with RIPC group. TNF-α, tumor necrosis factor α; IL-6, interleukin 6.

### Postoperative pulmonary complications

There was no serious adverse pulmonary reaction in the three groups during the surgery. After surgery, there were 7, 3 and 1 cases of pulmonary infection in control, RIPC and RIPC+Dex groups, respectively, with incidence of 38.89, 16.67% and 5.56%, respectively. There was significant difference among three groups ($\chi^2 = 6.393$; $P = 0.041$). In all patients, the pulmonary infection was cured aftertreatment.

## DISCUSSION

OLV is often used for anesthesia in radical esophagectomy. However, the long-term OLV and special surgical position and will cause the ischemia-reperfusion injury of lung (Gothard, 2006). RIPC is a method to mobilize the body to resist injury by utilizing endogenous protective phenomena after reperfusion injury. At present, it is known that RIPC has certain protective effect on heart, lung, kidney and other organs, but the specific mechanism is not clear (Zhou *et al*., 2010; Pedersen *et al*., 2012). Dex is an α2 adrenergic receptor agonist, which can improve microcirculation during pulmonary ventilation, thereby alleviating the lung injury (Gu *et al*., 2011). This study investigated the protective effect of Dex on lung injury during OLV in elderly patients undergoing radical esophagectomy with RIPC. Results showed that, compared with control group, the OI in other two groups at T2 and T3 was significantly increased, and the RI was significantly decreased. Compared with RIPC group, the OI in RIPC+Dex group was significantly increased, and the RI was significantly decreased. This indicates that, the single RIPC has the protective effect on lung injury during OLV, and Dex can further enhance the protective effect of RIPC.

During OLV, the non-ventilated lung collapses, resulting in ischemia and hypoxia of lung tissue and decreased oxygen free radical scavenging function. After restoring of two-lung ventilation, the re-expansion of atrophic alveoli induces the oxidative stress and production of a large number of oxygen free radicals (Misthos *et al*., 2005). Studies (Birdas, 2006; Yuluğ *et al*., 2007) have found that, the oxidative stress may be one of the important mechanisms for mediating the acute lung injury during OLV. Oxygen free radicals act with the unsaturated fatty acids on cell membranes, leading to the peroxidation. MDA is an important product of lipid peroxidation. The content of MDA in body can indirectly reflect the activity of oxygen free radicals (Davenport, Hopton, Bolton, 1995). SOD is an important antioxidant enzyme in the body. It can catalyze the transformation of oxygen free radicals to hydrogen peroxide, thus avoiding the damage to cells (Southard *et al*., 1987). The activity of SOD in body can reflect the level of antioxidant reaction. Therefore, the dynamic changes of SOD and MDA can reflect the degree of lung injury. Results of this study showed that, compared with control group, the SOD level in other two groups at T3 was significantly increased, and the MDA level was significantly decreased. Compared with RIPC group, the SOD level in RIPC+Dex group was significantly increased, and the MDA level was significantly decreased. This suggests that, RIPC can alleviate the oxidative stress during OLV, thus preventing the lung injury, and Dex can further alleviate the oxidative stress, thus improving the protective effect.

It is found that the excessive expansion of alveoli and the shear stress caused by repeated opening and closing of alveoli and the atrophy of local lungs during mechanical ventilation can induce the inflammatory response in the lungs (Stüber *et al*., 2002). TNF-α is produced by monocytes and macrophages. It plays an important role in the inflammatory response, and can cause the necrosis of tumor cells (Salas *et al*., 2000). In addition, TNF-α has the function of anti-infection and immune regulation (Mancusi *et al*., 2018). It is one of the most influential inflammatory mediators in the early stage of inflammation. IL-6 is a cytokine that increases the biological function. It can promote the aggregation, activation and differentiation of T and B lymphocytes, and participate in cellular and humoral immune processes (Saito *et al*., 1998). At the same time, IL-6 is also a pro-inflammatory factor. When the inflammation occurs, IL-6 can not only stimulate the production of C-reactive protein in the liver, but also directly mediate the inflammatory response to cause the tissue damage. It is the main index reflecting the severity of tissue injury (Pereira *et al*., 2014). Results of this study showed that, compared with control group, the TNF-α and IL-6 levels in other two groups at T2 and T3 were significantly increased. Compared with RIPC group, the TNF-α and IL-6 levels in RIPC+Dex group were significantly decreased. This indicates that, RIPC and Dex have the synergistic effect in reducing the inflammatory response during OLV, thus alleviating the lung injury.

In conclusion, for elderly patients undergoing radical esophagectomy, Dex and RIPC have the synergistic effect during OLV. The combined use of them can effectively inhibit the oxidative stress and inflammatory response, thus alleviating the lung injury and reducing the postoperative complications. This study still has some limitations. Firstly, the sample size of this study is relatively small. Larger sample size will make the results more convincing. In further studies, the sample size should be further enlarged for obtaining more satisfactory outcomes. Secondly, the time points of index observation are a little less. Thirdly, there may be other mechanisms for the protective effect of Dex on lung injury, and more indexes should be detected in further studies.

## ACKNOWLEDGMENTS

This work was supported by the Science and technology program of Nantong (JC2020059) .

## REFERENCES

Birdas TJ. Oxidative stress and one-lung ventilation. Eur J Cardiothorac Surg. 2006;30(2):412-413; author reply 413.

Bulow NM, Colpo E, Pereira RP, Correa EF, Waczuk EP, Duarte MF, et al. Dexmedetomidine decreases the

This is an open-access article distributed under the terms of the Creative Commons Attribution License.



inflammatory response to myocardial surgery under mini-cardiopulmonary bypass. Braz J Med Biol Res. 2016;49(4):e4646.

Davenport A, Hopton M, Bolton C. Measurement of malondialdehyde as a marker of oxygen free radical production during renal allograft transplantation and the effect on early graft function. Clin Transplant. 1995;9(3 Pt 1):171-175.

Gothard J. Lung injury after thoracic surgery and one-lung ventilation. Curr Opin Anaesthesiol. 2006;19(1):5-10.

Gu J, Chen J, Xia P, Tao G, Zhao H, Ma D. Dexmedetomidine attenuates remote lung injury induced by renal ischemia-reperfusion in mice. Acta Anaesthesiol Scand. 2011;55(10):1272-1278.

Li C, Xu M, Wu Y, Li YS, Huang WQ, Liu KX. Limb remote ischemic preconditioning attenuates lung injury after pulmonary resection under propofol-remifentanil anesthesia: a randomized controlled study. Anesthesiology. 2014;121(2):249-259.

Mak RH, Mamon HJ, Ryan DP, Miyamoto DT, Ancukiewicz M, Kobayashi WK, et al. Toxicity and outcomes after chemoradiation for esophageal cancer in patients age 75 or older. Dis Esophagus. 2010;23(4):316-323.

Mancusi A, Piccinelli S, Velardi A, Pierini A. The effect of TNF-α on regulatory T cell function in graft-versus-host disease. Front Immunol. 2018;9:356.

Misthos P, Katsaragakis S, Milingos N, Kakaris S, Sepsas E, Athanassiadi K, et al. Postresectional pulmonary oxidative stress in lung cancer patients. The role of one-lung ventilation. Eur J Cardiothorac Surg. 2005;27(3):379-382; discussion 382-383.

Nishimaki T, Suzuki T, Suzuki S, Kuwabara S, Hatakeyama K. Outcomes of extended radical esophagectomy for thoracic esophageal cancer. J Am Coll Surg. 1998;186(3):306-312.

Ojima H, Kuwano H, Kato H, Miyazaki T, Nakajima M, Sohda M, et al. Relationship between cytokine response and temporary ventilation during one-lung ventilation in esophagectomy. Hepatogastroenterology. 2007;54(73):111-115.

Olguner C, Koca U, Kar A, Karci A, Işlekel H, Canyilmaz M, et al. Ischemic preconditioning attenuates the lipid peroxidation and remote lung injury in the rat model of unilateral lower limb ischemia reperfusion. Acta Anaesthesiol Scand. 2006;50(2):150-155.

Pedersen KR, Ravn HB, Povlsen JV, Schmidt MR, Erlandsen EJ, Hjortdal VE. Failure of remote ischemic preconditioning to reduce the risk of postoperative acute kidney injury in children undergoing operation for complex congenital heart disease: a randomized single-center study. J Thorac Cardiovasc Surg. 2012;143(3):576-583.

Pereira LH, Machado JR, Olegário JG, Rocha LP, Silva MV, Guimarães CS, et al. Interleukin-6 and C-reactive protein are overexpressed in the liver of perinatal deaths diagnosed with fetal inflammatory response syndrome. Dis Markers. 2014;2014:252780.

Saito K, Ishikura H, Kishimoto T, Kawarada Y, Yano T, Takahashi T, et al. Interleukin-6 produced by pancreatic carcinoma cells enhances humoral immune responses against tumor cells: a possible event in tumor regression. Int J Cancer. 1998;75(2):284-289.

Salas A, Sans M, Soriano A, Reverter JC, Anderson DC, Piqué JM, et al. Heparin attenuates TNF-alpha induced inflammatory response through a CD11b dependent mechanism. Gut. 2000;47(1):88-96.

Southard JH, Marsh DC, McAnulty JF, Belzer FO. Oxygen-derived free radical damage in organ preservation: activity of superoxide dismutase and xanthine oxidase. Surgery. 1987;101(5):566-570.

Stüber F, Wrigge H, Schroeder S, Wetegrove S, Zinserling J, Hoeft A, et al. Kinetic and reversibility of mechanical ventilation-associated pulmonary and systemic inflammatory response in patients with acute lung injury. Intensive Care Med. 2002;28(7):834-841.

Sulaiman S, Karthekeyan RB, Vakamudi M, Sundar AS, Ravullapalli H, Gandham R. The effects of dexmedetomidine on attenuation of stress response to endotracheal intubation in patients undergoing elective off-pump coronary artery bypass grafting. Ann Card Anaesth. 2012;15(1):39-43.

Talke P, Chen R, Thomas B, Aggarwall A, Gottlieb A, Thorborg P, et al. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. Anesth Analg. 2000;90(4):834-839.

Yuluğ E, Tekinbas C, Ulusoy H, Alver A, Yenilmez E, Aydin S, et al. The effects of oxidative stress on the liver and ileum in rats caused by one-lung ventilation. J Surg Res. 2007;139(2):253-260.

Zhou W, Zeng D, Chen R, Liu J, Yang G, Liu P, et al. Limb ischemic preconditioning reduces heart and lung injury after an open heart operation in infants. Pediatr Cardiol. 2010;31(1):22-29.

Received for publication on 03rd September 2020
Accepted for publication on 17th October 2020