



ORIGINAL ARTICLE

Effects of dexmedetomidine on the function of distal organs and oxidative stress after lower limb ischaemia–reperfusion in elderly patients undergoing unilateral knee arthroplasty

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Aims: This study aims to evaluate the effects of dexmedetomidine on organ function, inflammation response, and oxidative stress in elderly patients following iatrogenic lower limb ischaemia–reperfusion (IR) during unilateral total knee arthroplasty.

Methods: Following unilateral total knee arthroplasty, 54 elderly patients were randomized to receive either intraoperative intravenous injection of dexmedetomidine ($n = 27$) or equivalent volume of 0.9% saline ($n = 27$). Blood samples were harvested at 5 minutes before lower limb tourniquet release (baseline); and 1, 6 and 24 hours after tourniquet release. Surrogate markers of cardiac, pulmonary, hepatic and renal function, oxidative stress, inflammatory response, along with parasympathetic and sympathetic activity were recorded and analysed.

Results: The levels of blood xanthine oxidase, creatine kinase, lactic acid and respiratory index increased in patients following tourniquet-induced lower limb IR injury. Dexmedetomidine administration decreased the respiratory index ($P = .014$, $P = .01$, and $P = .043$) and the norepinephrine level ($P < .001$) at 1, 6 and 24 hours; and decreased the xanthine oxidase level ($P = .049$, $P < .001$) at 6 and 24 hours after tourniquet release compared with the Control group. Other measurements, including creatine kinase isoenzyme, lactate dehydrogenase, creatinine, urea nitrogen, glutamic–oxalacetic transaminase, glutamic–pyruvic transaminase, malondialdehyde, interleukin-1, interleukin-6 and tumour necrosis factor- α , were not statistically significantly different between the 2 groups.

Conclusions: Intraoperative dexmedetomidine administration in elderly patients dampens the deterioration in respiratory function and suppresses the oxidative stress response in elderly patients following iatrogenic lower limb IR injury.

KEYWORDS

dexmedetomidine, elderly patients, iatrogenic ischaemia–reperfusion, oxidative stress

PI Statement: The authors confirm that the PI for this paper is Jianteng Gu, who had direct clinical responsibility for patients.

Sunshan Lu and Xingtong Chen contributed equally and should be considered as co-first authors.

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1 | INTRODUCTION

An aging population imposes great challenges on global healthcare service provision,¹ with this demographic more likely to require surgical intervention for chronic health problems such as total knee arthroplasty (TKA) for arthropathies.² The use of tourniquets can reduce intraoperative bleeding and achieve a better visualization during the TKA procedure. However, tourniquet application would inevitably induce ischaemia–reperfusion injury (IRI) in the lower limb, subsequently leading to remote organ injuries due to inflammatory cytokines and oxidative metabolites released from the limb undergoing ischaemia–reperfusion.³ Indeed, cardiopulmonary complications after TKA have been reported in elderly patients whose preoperative cardiopulmonary functions were apparently normal,⁴ indicating that this population is especially vulnerable to IR. These perioperative complications will prolong length of hospitalization, in turn increasing the risk for nosocomial infections and other forms of perioperative morbidity. Therefore, there is a growing imperative to understand the ensuing remote organ dysfunction, systemic inflammation and oxidative stress induced by tourniquet application in elderly patients undergoing TKA, as well as to explore potential protective measures.

Dexmedetomidine (Dex), an α_2 -adrenoceptors agonist, is increasingly used as a sedative in anaesthesia and intensive care unit setting. Dex primarily acts on noradrenergic neurons in the locus coeruleus of the pons, and results in dose-dependent inhibition of norepinephrine (NE) release.⁵ This is likely to be implicated in blocking the aggregation of inflammatory cells in the nerve system, reducing neuronal injury caused by the immune response and the incidence of surgical complications such as the stress response and postoperative cognitive impairment.⁶ In addition, Dex also promotes the release of acetylcholine (ACh) and increases parasympathetic activation, thereby inhibiting the excitability of the central nervous system,⁷ and regulates the immune system by dampening the T-cell and natural killer cell response.^{8,9} Furthermore, Dex exerts protective effects on vital organs during IRI previously reported by our group^{7,10,11} and by others.^{12–14} To our knowledge, most evidence arises from preclinical experiments, and the association of Dex in remote organ dysfunction following lower limb IRI is less reported. Thus, we performed a small randomized controlled trial to assess the effect of intraoperative intravenous Dex on oxidative stress, inflammation and autonomic activity, as well as its impact on cardiac pulmonary, hepatic and renal function in elderly patients undergoing TKA.

2 | METHODS

2.1 | Study design

The present study was a single-blinded (study participants), prospectively randomized, placebo-controlled, single-centre trial. Patients who were aged 60–90 years with American Society of Anaesthesiologist (ASA) grade I/II, and a diagnosis of advanced

What is already known about this subject

- Dexmedetomidine has been reported to exert organoprotective effects against ischaemia–reperfusion injury (IRI) during the perioperative period.
- Elderly patients undergoing total knee arthroplasty have less tolerance to tourniquet-induced IRI due to a reduced functional capacity.

What this study adds

- Intravenous injection of dexmedetomidine potentially dampens the deterioration in respiratory function and suppresses the oxidative stress response in elderly patients following iatrogenic lower limb IRI.

osteoarthritis undergoing a primary unilateral TKA with combined spinal–epidural anaesthesia, were screened for study recruitment between July 2018 and March 2019. Patients were excluded if they met any of the following criteria: cardiac function NYHA grade 3 or above; Child–Pugh level grade B or C; estimated glomerular filtration rate <60 mL/min/1.73 m²; a history of chronic obstructive pulmonary disease or asthma, oxygen saturation below 95 at rest on room air; coagulopathy; hypoalbuminaemia; and participating in other clinical trials. Eligible patients were randomly divided into 2 groups as a 1:1 ratio by a random number table. The patients were randomized to receive Dex (the Dex group) or 0.9% saline (the Control group). Patients in the Dex group received an intravenous bolus injection of Dex at initial loading dose of 1 μ g/kg over 10 minutes before tourniquet application, then an infusion at a maintenance dose of 0.5 μ g/kg/h until the end of surgery. Patients in the Control group received of 0.9% saline in an identical regimen as the Dex group.

The study was approved by the Ethics Committee and Institutional Review Board of Southwest Hospital of Third Military Medical University (Army Medical University), China. The trial was registered in the Chinese Clinical Trials Registry (ChiCTR-TRC-12002111). All patients provided informed written consent to participate in the study.

2.2 | Anaesthetic regimen

The patients were fasted for 8 hours before admitting to the operating room where they underwent noninvasive blood pressure measurement, electrocardiography and pulse oximetry. After the initial vital signs were measured, oxygen 2–3 L/min was administered via a face mask. Invasive blood pressure monitoring via the

radial artery was also established using a 20-gauge catheter. Spinal anaesthesia was performed at the L3–4 intervertebral space using a needle-through-needle technique in the lateral position, after which 1.5 mL of 0.75% bupivacaine diluted by 10% glucose solution to 3 mL was injected into the intrathecal space within 30 seconds followed by the insertion of an epidural catheter advanced 3–4 cm into the epidural space. When bilateral sensory blockade had been achieved up to the T10 dermatome, a tube line was cannulated near the femoral nerve under the guidance of a nerve stimulator, which was used for postoperative self-controlled analgesia management with 0.2% ropivacaine at a background dose of 3–5 mL/h for up to 72 hours after the surgery. Ephedrine was administered intravenously to maintain systolic blood pressure when its reduction was >20% of the baseline value. Bradycardia was defined as a heart rate of ≤ 50 beats/min, whereby intravenous atropine was administered.

2.3 | Postoperative care

The patients were transferred into the postanesthesia care unit to receive standardized care for at least 1 hour postoperatively. If the patient remained haemodynamically stable, they were returned to the general ward. All patients were cared under the first-degree nursing in the first postoperative 24 hours. The invasive blood pressure via the arterial catheter, oxygen saturation and electrocardiography were monitored for up to 24 hours after the surgery. All patients routinely received oxygen therapy through a nasal catheter for at least 24 hours.

2.4 | Outcome assessments

The changes of xanthine oxidase (XOD) reflecting oxidative stress were taken as the primary outcome. The biomarkers of pulmonary (respiratory index, RI), cardiac (creatinine kinase, CK; CK isozyme, CKMB; lactate dehydrogenase, LDH), renal (creatinine, Crea; urea nitrogen, Urea) and hepatic (alanine transaminase, ALT; aspartate aminotransferase, AST) functions, and lactic acid (cLac) were taken as the secondary outcomes, reflecting the changes of distal organ functions. Inflammatory cytokines (tumour necrosis factor- α , TNF- α ; interleukin-1, IL-1; interleukin-6, IL-6) and other biomarker measurements including malondialdehyde (MDA), Ach and NE were also taken as secondary outcomes. The clinical characteristics of patients and surgical details are regarded as other measurements.

The primary outcome and the secondary outcomes were assessed by blood samples. An arterial blood sample (5 mL) was obtained from the radial artery of each patient at 5 minutes before the tourniquet withdraw (baseline), and 1, 6 and 24 hours after tourniquet release. A 0.5-mL aliquot of the arterial blood sample was analysed by blood gas analyser (GEM3000, Beckman Coulter Life Science, IN, USA). The partial arterial oxygen pressure, alveolar–arterial oxygen partial pressure difference, lactic acid (cLac) were measured and recorded. The RI was

calculated based on the ratio of alveolar–arterial oxygen partial pressure difference to partial arterial oxygen pressure. The remaining 4.5 mL of arterial blood sample was transferred to 3 microcentrifuge tubes (1.5 mL, Eppendorf AG, Hamburg, German), then centrifuged at 1,000 \times g for 10 minutes. The serum supernatant were extracted and analysed by enzyme-linked immunoassay (Yueya Biotechnology Co., Ltd, Suzhou, China), with TNF- α , IL-1 and IL-6 for inflammatory reaction, CK, CKMB and LDH for cardiac function, creatinine and urea for renal function, ALT and AST for hepatic; MDA was derivatized using the thiobarbituric acid method (Jiancheng Bioengineering Research Institute, Nanjing, China); XOD was derivatized using the colorimetric method (Yueya Biotechnology Co., Ltd., Hefei, China). NE and Ach were derivatized using competitive method (Yueya Biotechnology Co., Ltd., Hefei, China). Other measurements were collected by an electronic case system (Mediston Medical Technology, Suzhou, China).

2.5 | Statistical analysis

PASS 15.0 (NCSS, LLC, USA) was used for sample size analysis. Our preliminary investigation had shown that the level of XOD increased at 24 hours after the tourniquet release. Data were expressed as mean \pm standard deviation (SD). The level of XOD for 2 groups were 13.9 ± 2.8 U/L (the Control group) and 12.1 ± 1.4 U/L (the Dex group) respectively at 24 hours after tourniquet release. The preliminary investigation revealed that a sample size of 27 patients per group would detect a significant difference with a power of 80% and an α -coefficient of 0.05.

SPSS 22.0 statistical software (SPSS, Chicago, IL, USA) was used for analysis. The primary and secondary outcomes were analysed by repeated measurement analysis of variance (ANOVA) within and between the 2 groups, and multiple comparisons (LSD) were carried out between 4 time points. The results of primary and secondary outcomes are shown as mean [95% confidence interval, CI]. Independent Student *t*-test and χ^2 test were used to analyse other measurements, and the results are expressed as mean \pm SD or ratio. A *P* value of $< .05$ was considered to be significant.

3 | RESULTS

3.1 | Clinical characteristics of patients

Sixty-six patients were assessed for eligibility and 12 were excluded in the initial patient selection (3 did not meet the inclusion criteria, 7 met the exclusion criteria and 2 refused to participate). No patient was withdrawn during the trial. Therefore, a total of 54 patients enrolled and all patients completed the trial. The details of the patient enrolment are summarized in Figure 1. The clinical characteristics of patients and surgical details (other measurements) are shown in Table 1. There was no significant difference between the 2 groups at baseline.

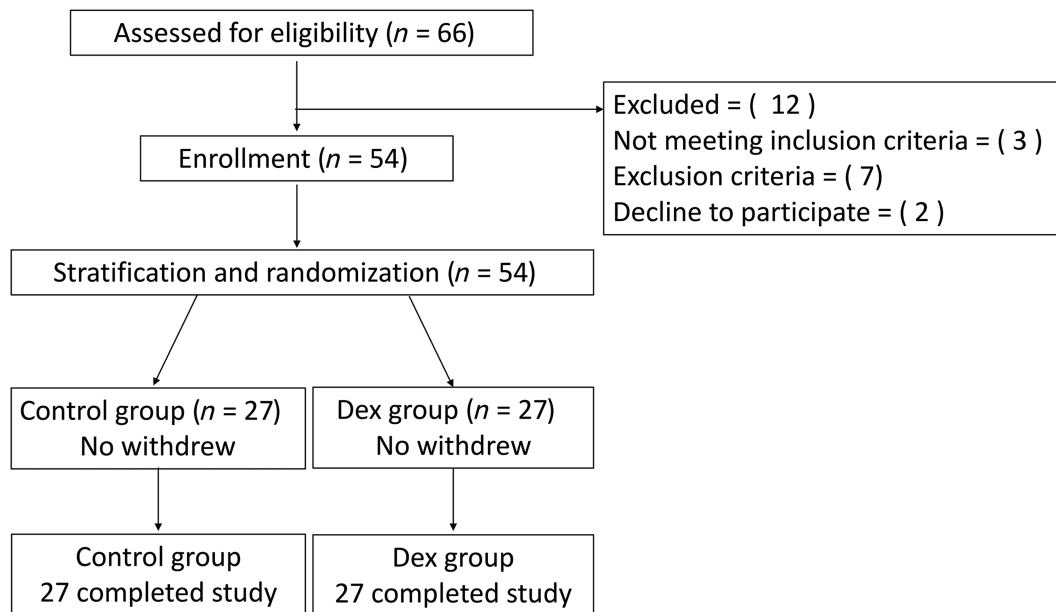


FIGURE 1 The flow chart of patient enrolment. Dexmedetomidine (Dex) group = 27 cases; Control group = 27 cases

TABLE 1 Clinical characteristics of patients

	Control group (n = 27)	Dex group (n = 27)	P values
Demographics			
Age (y)	71.4 ± 7.8	68.1 ± 5.8	.32
Male/Female	10/17	8/19	.55
Body weight (kg)	65.0 ± 9.1	60.5 ± 7.1	.10
Comorbidity (n/27)			
Hypertension	7/27	10/27	.38
Diabetes	11/27	9/27	.57
Hyperlipidaemia	6/27	8/27	.54
Intraoperative data			
Operation time (min)	95.0 ± 17.3	113.3 ± 15.1	.72
Tourniquet pressure (mmHg)	300.0 ± 15.2	298.3 ± 5.8	.73
Tourniquet time (min)	61.1 ± 11.8	75.3 ± 15.0	.35
Intraoperative fluids (mL)	1066.7 ± 207.1	1016.7 ± 135.4	.28
Blood loss (mL)	179.2 ± 39.6	200 ± 36.9	.32
Postoperative data			
Length of hospital stay (d)	6.15 ± 1.38	6.59 ± 1.58	.28
Suspected postoperative infection (n/27)	1/27	1/27	> .99

3.2 | The changes of systemic oxidative stress, inflammation and autonomic activity

Systematic oxidative stress response (XOD and MDA) was measured in this study. XOD, as the primary outcome, was significantly increased at 6 hours (23.76, 95% CI [20.75, 26.78], $P = .009$) and 24 hours (28.91, 95% CI [25.96, 31.87], $P < .001$) after tourniquet release compared with baseline (18.45, 95% CI [15.70, 21.21]) in the Control group, while Dex administration decreased XOD elevation at

6 hours (19.47, 95% CI [16.46, 22.49], $P = .049$) and 24 hours (15.97, 95% CI [13.02, 18.92], $P < .001$) after tourniquet release compared with the Control group (Figure 2A). Otherwise, there was no statistically significant difference within or between the 2 groups in terms of MDA (Figure 2B). TNF- α , IL-1 and IL-6 were detected for evaluating systemic inflammation, while there was no significant difference within or between the 2 groups (Figure 2C-E).

The NE level decreased in the Control group at 6 hours (455.35, 95% CI [418.62, 492.08], $P = .03$) and 24 hours (443.04, 95% CI

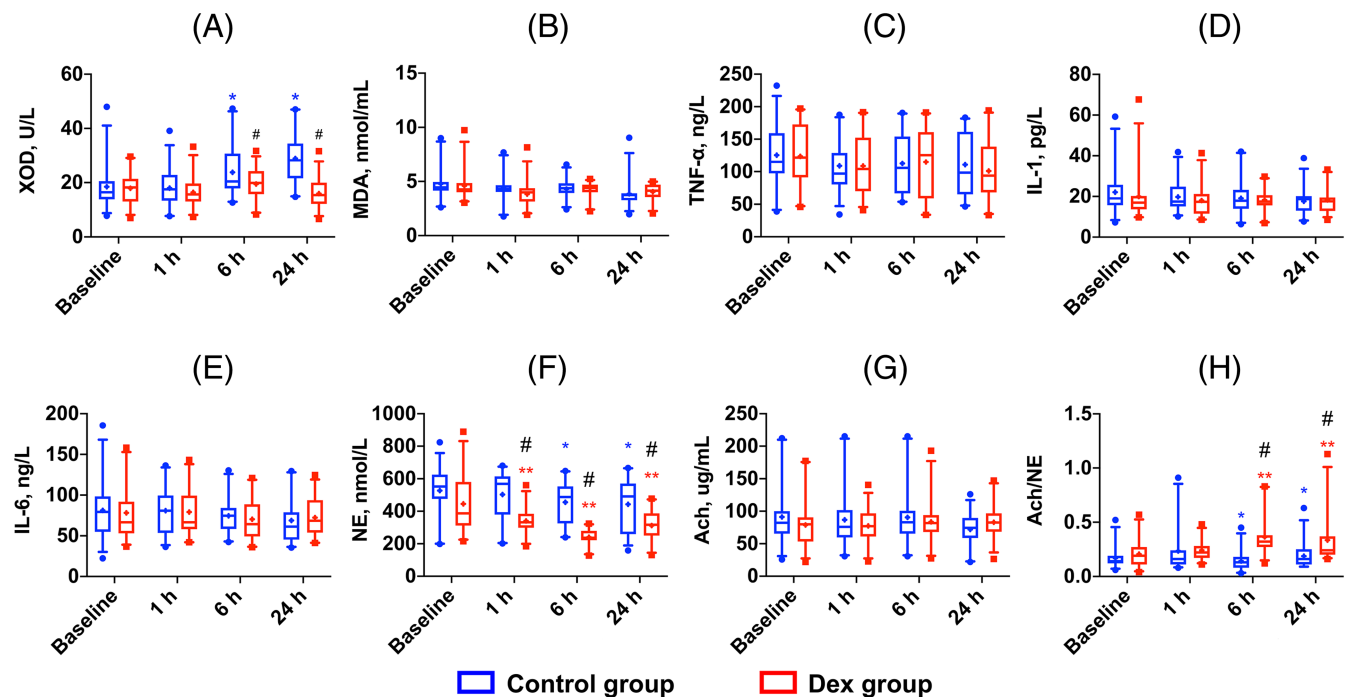


FIGURE 2 The changes of systemic oxidative, inflammation, and autonomic activity. (A) Xanthine oxidase, XOD; (B) malondialdehyde, MDA; (C) tumour necrosis factor- α , TNF- α ; (D) interleukin-1, IL-1; (E) interleukin-6, IL-6; (F) norepinephrine, NE; (G) acetyl choline, Ach; (H) the ratio of Ach/NE. Data are presented as box with whiskers, mean values are shown by the plus sign, 95% confidence interval by the whiskers, median values are shown by the horizontal line inside the box, interquartile range by the top and bottom of the boxes, and values were outside the 5th and 95th percentiles by dots and squares. * $P < .05$ vs. the baseline in the Control group; ** $P < .05$ vs. the baseline in the dexmedetomidine (Dex) group; # $P < .05$ vs. the Control group at the corresponding time point

[393.01, 493.06], $P = .046$) after tourniquet release from the baseline (527.49, 95%CI [466.74, 588.25]). Dex administration further reduced the NE at 1 hour (340.07, 95%CI [293.14, 387.00], $P < .001$), 6 hours (240.34, 95%CI [203.61, 277.07], $P < .001$), and 24 hours (311.77, 95%CI [261.75, 361.80], $P < .001$) compared with the Control group (Figure 2F). There was no significant change in Ach level within or between the 2 groups (Figure 2G). The ratio of Ach/NE decreased at 6 hours (0.14, 95%CI [0.09, 0.20], $P = .035$) and 24 hours (0.19, 95%CI [0.12, 0.25], $P = .042$) after tourniquet release in the Control group, and Dex administration increased the ratio at 6 hours (0.36, 95%CI [0.31, 0.42], $P < .001$) and 24 hours (0.33, 95%CI [0.27, 0.40], $P = .003$) compared with the Control group (Figure 2H).

3.3 | Organ dysfunction

The RI in the Control group was increased at 1 hour (0.63, 95%CI [0.49, 0.78], $P = .01$), 6 hours (0.76, 95%CI [0.62, 0.89], $P < .001$), and 24 hours (0.57, 95%CI [0.51, 0.63], $P = .0002$) compared with the baseline (0.41, 95%CI [0.32, 0.50]). Dex administration was shown to reduce the RI at 1 hour (0.38, 95%CI [0.23, 0.52], $P = .014$), 6 hours (0.49, 95%CI [0.36, 0.63], $P = .01$), and 24 hours (0.48, 95%CI [0.42, 0.54], $P = .043$) compared with the Control group (Figure 3A). The CK level increased at 1 hour (102.47, 95%CI [84.101, 20.85], $P < .001$), 6 hours (271.28, 95%CI [188.96, 353.60], $P < .001$), and 24 hours

(290.35, 95%CI [163.89, 416.82], $P = .001$) in the Control group; and at 6 hours (146.78, 95%CI [64.46, 229.10], $P = .037$) and 24 hours (159.86, 95%CI [33.40, 286.32], $P = .018$) in the Dex group (Figure 3B). However, there was no significant difference in the changes between the groups. The secondary outcomes CKMB (Figure 3C), LDH (Figure 3D), AST (Figure 3E), ALT (Figure 3F), Crea (Figure 3G) and Urea (Figure 3H) had shown no significant difference within or between the 2 groups.

In addition, tourniquet application increased the cLac level at 1 hour (1.56, 95%CI [1.35, 1.77], $P = .006$), 6 hours (2.06, 95%CI [1.70, 2.42], $P < .001$), and 24 hours (1.98, 95%CI [1.72, 2.24], $P < .001$) in the Control group. Dex administration reduced the cLac at 6 hours (1.50, 95%CI [1.14, 1.86], $P = .019$) and 24 hours (1.45, 95%CI [1.19, 1.71], $P = .006$) compared with the Control group (Figure 3I).

4 | DISCUSSION

The main findings of the present study demonstrated that intravenous injection of Dex in elderly patients that underwent lower limb IRI during TKA reduced oxidative stress by decreasing the level of XOD, attenuated sympathetic activation by decreasing the level of NE and potentially increased the Ach/NE ratio. Dex also reduced the deterioration of respiratory function by decreasing the RI. However, as these metabolic and functional changes remained within normal limits, the

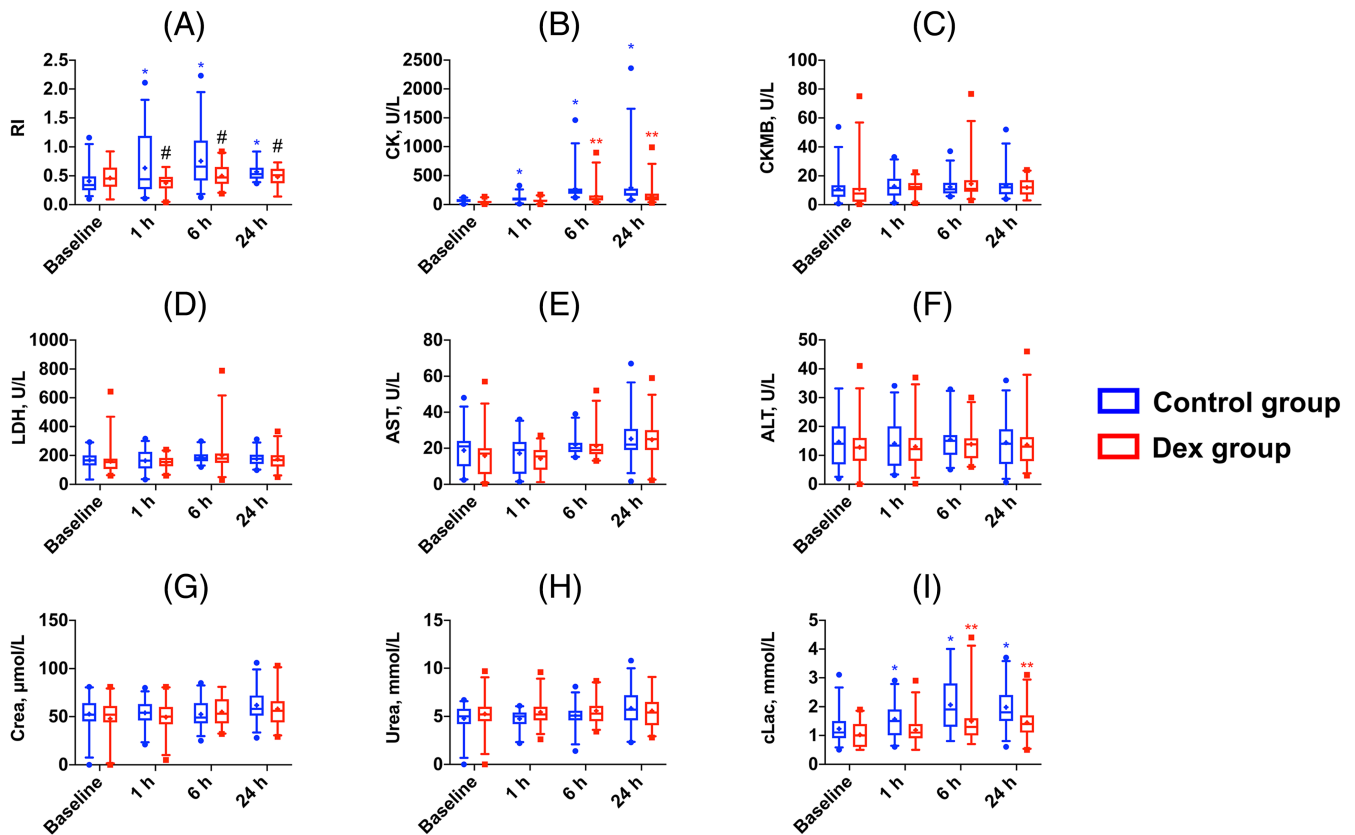


FIGURE 3 The changes of vital organs function. (A) Respiratory index, RI; (B) creatine kinase, CK; (C) CK isoenzyme, CKMB; (D) lactate dehydrogenase, LDH; (E) glutamic oxalacetic transaminase, AST; (F) glutamic-pyruvic transaminase, ALT; (G) creatinine, Crea; (H) urea nitrogen, Urea and (I) lactic acid, cLac. Data are presented as box with whiskers, mean values are shown by the plus sign, 95% confidence interval by the whiskers, median values are shown by the horizontal line inside the box, interquartile range by the top and bottom of the boxes, and values were outside the 5th and 95th percentiles by dots and squares. * $P < .05$ vs. the baseline in the Control group; ** $P < .05$ vs. the baseline in the dexmedetomidine (Dex) group; # $P < .05$ vs. the Control group at the corresponding time point

clinical importance of this finding is questionable. Other measurements including cardiac function indicators (CK, CKMB, LDH), kidney function indicators (Crea, Urea), hepatic function indicators (ALT, AST), inflammatory factors (IL-1, IL-6, TNF- α) between the 2 groups were not statistically different.

TKA is a reliable procedure for end-stage osteoarthritis and has excellent clinical outcomes with a low complication rate, resulting in an overall improved quality of life for patients.¹⁵ Despite the demonstrated advantages of TKA, lower limb tourniquet-induced IRI is a potent generator of local skeletal muscles necrosis and systemic inflammation, which is associated with limb swelling, development of deep venous thrombosis, neural deficit, the releasing of inflammatory factors and reactive oxygen species.^{3,16} Circulating toxic metabolites released by IRI can activate leucocytes and endothelial cells in remote organs, results in leucocyte-dependent microvascular injury.¹⁷ Furthermore, IRI-induced leucocytes trafficking to multiple organs also lead to systemic inflammatory mediators releasing, thus increase the possible development of the systemic inflammatory response syndrome.¹⁸ Indeed, IRI-induced systematic microvascular injury and inflammatory factors release have been described in most remote organs and is recognized as a serious problem during a variety of

surgical procedures. Elderly patients are particularly at risk due to a reduced functional capacity, due to both age and baseline comorbidities, and therefore are at an increased vulnerability to IRI, resulting in a higher rate of postoperative complications.¹⁹ In the present study, a widely used sedative agent, Dex, was administered to determine its potential organoprotective properties on lower limb IRI in elderly patients undergoing TKA.

One of the most susceptible organs after limb IRI is the lung.¹⁸ Circulating toxic metabolites released by injured skeletal muscle can induce alveolar cell death via necrosis, autophagy and apoptosis, subsequently causing pulmonary interstitial and diffuse damage. RI is a sensitive index of pulmonary gas exchange and breathing rate, with an increased RI representing oxygen exchange dysfunction. In this study, after tourniquet release, the RI increased and reached a peak value at 6 hours, and followed by a gradual reduction at 24 hours, suggesting that tourniquet-induced IRI may lead to deterioration in gas exchange. Since our study was conducted in elderly patients without severe pre-existing cardiopulmonary comorbidities, the RI in both groups was <1 and no significant clinical changes of respiratory dysfunction occurred. It cannot be firmly stated that Dex certainly play a role in lung protection, we could only infer that elderly patients treated with Dex have a

smaller degree of deterioration of their lung function from the baseline state. We posit that for elderly patients with pre-existing pulmonary dysfunction, tourniquet-induced IRI may exacerbate pulmonary function and Dex would have a greater positive value in alleviating this. However, Dex should not be considered for routine use to prevent remote organ damage in patients with good preoperative physical condition.

IRI-induced cardiac function damage is also very common. CK, CKMB, and LDH are commonly used clinical biochemical indicators to reflect cardiac function. CKMB is mainly present in myocardial cells and its concentration has a higher sensitivity and specificity for diagnosing myocardial damage; LDH can catalyse the dehydrogenation of cLac to generate pyruvate, which is widely present in the body; CK is widely distributed in smooth muscle throughout the body, followed by the myocardium.^{20,21} The present study showed that CK levels increased significantly after lower limb IRI, while CKMB and LDH levels did not change, indicating that increased CK value may be caused by skeletal muscle injury rather than myocardial injury. In other studies, Dex administration could reduce the serum CK levels during limb extremity surgery.^{22,23} However, the CK levels

in our study showed a declining trend in the Dex group compared with the Control group, but there was no statistically significant difference.

Tourniquet-induced IRI also causes the release of oxygen free radicals and their metabolites, such as MDA and XOD. In the early phase of IRI, MDA and XOD can exacerbate many aspects of injury process, such as increasing the production of inflammatory mediators and neutrophil activation.²⁴ The present study found that although inflammation-related cytokines IL-1, IL-6 and TNF- α had no significant change, XOD concentration continued increasing after tourniquet release. Previous studies have shown that XOD activity in the serum may be an early index in acute lung, liver, and heart injury, and correlates with the degree of organ damage due to oxidative stress.²⁵ Our results reflected that XOD is a better indicator than inflammatory cytokines for the early detection of organ damage during TKA. Furthermore, the increase in XOD level was significantly attenuated by Dex treatment, indicating that the cellular oxidative response could be partially reduced. We speculate that the protective effects of Dex may relate to the inhibition of oxygen free radical-mediated lipid peroxidation, as well as through the reduction of inflammatory cytokine

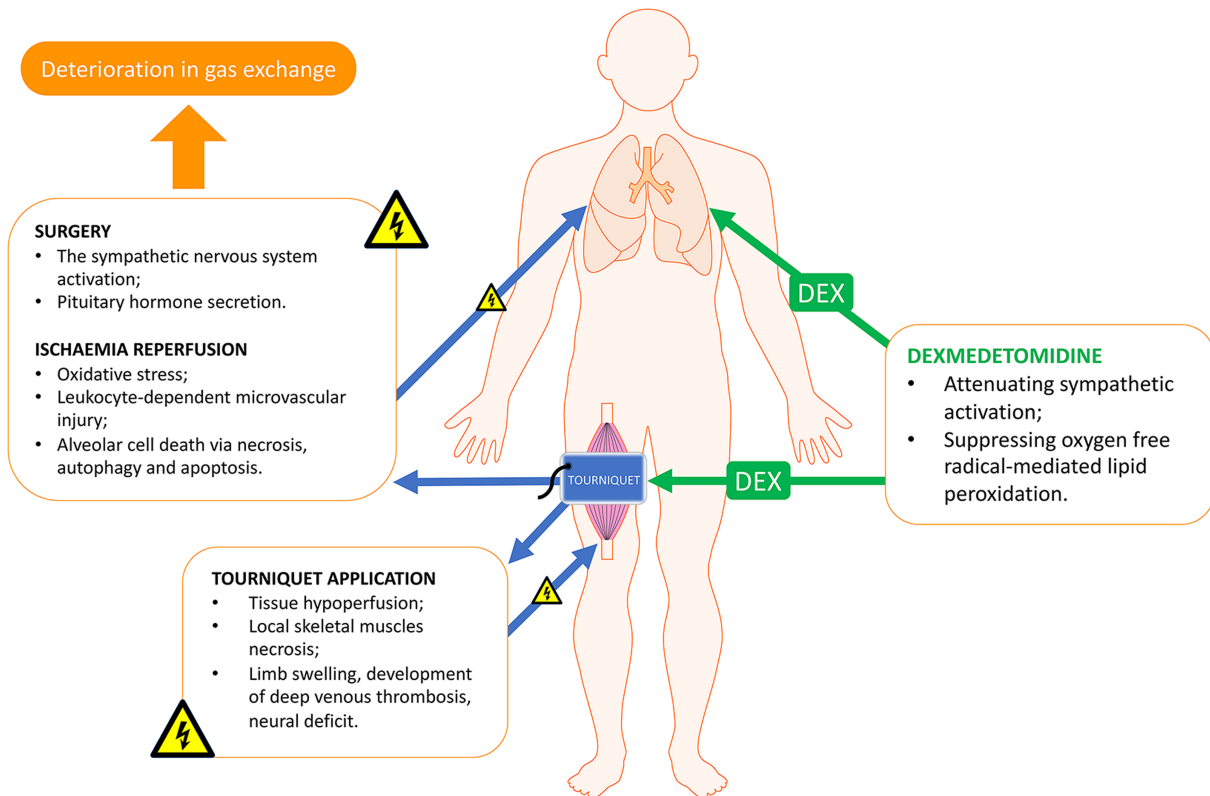


FIGURE 4 Schematic visualization of total knee arthroplasty (TKA)-induced pulmonary gas exchange deterioration and the potential protective effects of dexmedetomidine. TKA surgery itself activates sympathetic nervous system and promotes pituitary hormone secretion. Lower limb tourniquet-induced ischaemia–reperfusion injury (IRI) during TKA results in the release of oxygen free radicals and inflammatory factors. The circulation of these mediators, in turn, will induce leukocyte-dependent microvascular injury and alveolar cell death in lungs. The lung is highly susceptible to injury caused by circulating proinflammatory mediators released upon IRI. Tourniquet application also leads to tissue hypoperfusion and local skeletal muscles necrosis, and potentially leads to limb swelling, deep venous thrombosis development, and neural deficit. Elderly patients undergoing iatrogenic lower limb IRI with the intervention of intraoperative dexmedetomidine are potentially able to have a dampened deterioration in respiratory function and less oxidative stress response following surgery

release. Of note, the level of MDA did not rise as expected as XOD after tourniquet release in this study. This observation may be related to the otherwise good health of the elderly patients, or that XOD is more sensitive than MDA in demonstrating oxidative stress under lower limb IRI.

Surgical stimulus activates the sympathetic nervous system to initiate a cascade of stress responses and pituitary hormone secretion. Attenuation of sympathetic activation to reduce stress response during surgery has been shown to be beneficial for postoperative outcomes.²⁶ In this study, the level of NE was significantly attenuated after tourniquet release in the Dex group than that of the Control group, indicating that the sympathetic activation induced by IRI was effectively dampened by Dex treatment. Since plasma NE does not penetrate the blood–brain barrier well, release from the adrenal medulla in response to sympathetic stimulation is effectively distinct from that of the central nervous system.²⁶ We, therefore, speculate that Dex mainly inhibit the release of NE from peripheral presynaptic sympathetic nerve terminals. In addition, although the Ach level was unaffected, the ratio of Ach/NE increased by the administration of Dex in our study. The ratio of Ach/NE, which constitutes a sensitive measure of cholinergic phenotype acquisition, was used to simulate the assessment of parasympathetic and sympathetic activity. These results indicate that there was a relatively increased activity in the parasympathetic system. However, whether this activity is a direct result of the cholinergic anti-inflammatory and organ-protective effects of Dex warrants further study.

This study has several limitations. Firstly, the single-blinded nature makes it difficult to prevent bias from the investigators. We tried to minimize this bias by randomizing, and strictly following the standard operating procedures for quality control. Additionally, considering that anaesthesia and surgery itself may affect organs function in elderly patients, further data of patients' physical function at baseline would be useful. However, as the main aim of this study is to evaluate the changes of systemic response and organs function before and after tourniquet induced-IRI, data prior to tourniquet release can theoretically be used as a baseline reference. Moreover, because only elderly patients with ASA I/II were enrolled in this study, these patients were expected to be less vulnerable to IRI. This may explain why there were no significant clinical changes. However, our results indicated that the lungs may be the most susceptible organ during TKA, patients with respiratory dysfunction or pulmonary comorbidities require further medical attention prior to the surgery. Additionally, the effects of Dex in elderly patients with ASA III and above in this setting warrants further investigation. Furthermore, our small sample size may undermine the reliability of our results; these results do indicate that a larger sample size is warranted to clarify the effect of Dex on tourniquet-induced lower limb IRI in elderly patients.

In conclusion, iatrogenic lower extremity IRI could cause oxidative stress in elderly patients undergoing TKA, and their respiratory function was observed to deteriorate from the baseline state after tourniquet release. This may have occurred secondary to the oxidative stress during IRI. Intravenous injection of Dex could reduce the

detrimental impact of IRI on lung function and reduce the sympathetic activation and suppress oxygen free radical-mediated lipid peroxidation. Therefore, elderly patients undergoing iatrogenic lower limb IRI with the intervention of intraoperative Dex are potentially able to have a dampened deterioration in respiratory function and less oxidative stress response following surgery (Figure 4).

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COMPETING INTERESTS

The authors declare no competing interests.

CONTRIBUTORS

Jianteng Gu and Kaizhi Lu: designed the study, Sunshan Lu, Xingtong Chen, Jiaolin Ning, Lili Hu and Jian Cao: conducted the study, Yan Chen and Bin Yi: analysed and interpreted the data, Sunshan Lu and Xingtong Chen: wrote the draft, Qian Chen and Zhen Cahilog: revised the article, All authors: final approval of the version to be submitted.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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