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Effects of different doses of ulinastatin on organ protection of deep hypothermic circulatory arrest in rats

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Abstract

Background Deep hypothermic circulatory arrest (DHCA) can cause systemic inflammatory response (SIR) and ischemia-reperfusion (I/R) injury, potentially exacerbating organ failure. Ulinastatin (UTI) is a frequently employed anti-inflammatory medication in clinical practice, but different timing and dosage may influence its protective efficacy.

Methods 24 rats were randomly divided into four groups. Three different doses of UTI ($3/10/30\times10^4$ U/kg; low/medium/high dose) were administered in the DHCA rat model, with a control group that underwent DHCA without UTI administration. Inflammatory markers and routine clinical indicators of myocardial, hepatic, and renal tissue injury were evaluated. All rats underwent the standard DHCA procedure.

Results Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and neutrophil elastase (ELA-2) levels in rats exposed to DHCA gradually increased after rewarming. Compared with the DHCA-only group, both the low dose of UTI (UTI-L) and the medium dose of UTI (UTI-M) significantly reduced IL-6 ($p=0.017$, $p=0.022$), TNF-α ($p=0.003$, $p<0.001$), ELA-2 levels ($p=0.018$, $p=0.001$), and elevated IL-10 levels ($p<0.001$, $p<0.001$) 4 h post-weaning from cardiopulmonary bypass (CPB). In addition, compared with the DHCA group, both the UTI-L and UTI-M group showed significantly lower levels of cardiac troponin I ($p=0.001$, $p=0.001$), creatine kinase muscle and brain isoenzyme (CK-MB) ($p<0.001$, $p<0.001$), creatinine ($p<0.001$, $p<0.001$), blood urea nitrogen ($p=0.002$, $p=0.021$), aspartate transaminase ($p<0.001$, $p<0.001$) and alanine aminotransferase ($p<0.001$, $p<0.001$) at the end of the experiment. The hematoxylin-eosin staining results of kidney and liver tissue damage were alleviated in the UTI-L and UTI-M groups. The high dose of UTI (UTI-H) group did not exhibit dose-dependent anti-inflammatory effects and was associated with aggravated injury to the heart, liver, and kidney.

Conclusion This study demonstrated that the administration of low to medium doses of UTI during DHCA significantly attenuated the levels of IL-6, TNF-α, and ELA-2, elevated the level of the anti-inflammatory factor IL-10, and provided protective effects on myocardial, hepatic, and renal tissues.

Keywords Deep hypothermic circulatory arrest, Ulinastatin, Inflammation

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Introduction

As a special procedure of cardiopulmonary bypass (CPB), deep hypothermic circulatory arrest (DHCA) has long been employed in the repair of complex aortic arch surgeries and congenital defects to create a clear surgical field and protect brain function [1–3]. However, DHCA is a non-physiological process. The interaction between blood and the circuit surface, along with hemodilution, hypothermia, and ischemia-reperfusion (I/R) injury, can trigger inflammatory responses and activate the coagulation pathway, leading to alterations in endothelial cell functionality [4]. These factors significantly increase the vulnerability of organs such as the lungs, liver, and kidneys to injury, potentially leading to prolonged hospitalization and adversely affecting patient prognosis [5, 6].

Ulinastatin (UTI) is a protease inhibitor isolated from the urine of healthy individuals. It exerts its effects by inhibiting various serine proteases, including neutrophil elastase, trypsin and fibrinolytic enzyme, while also stabilizing lysosomal and cell membranes [7]. Clinically, UTI has been effectively applied in treating inflammatory diseases such as acute pancreatitis and sepsis [8, 9]. In cardiac surgery, some studies showed that UTI could reduce postoperative bleeding and red blood cell transfusion, protect platelet function, as well as lower the incidence of acute kidney injury [10, 11]. However, UTI has a relatively short half-life of approximately 40 min, and its administration following pulmonary I/R injury exhibits a dose-dependent suppression of the systemic inflammatory response (SIR) [12]. Therefore, variations in the timing and dosage of UTI administration may influence the therapeutic goals and organ protection effect of UTI in cardiac surgery. In this study, we investigated the protective effects of different UTI doses on multiple organs in a DHCA rat model to identify the optimal dosage.

Materials and methods

Animals

This study was reviewed and approved by the Animal Experimental Ethics Committee of Fuwai Hospital (FW-2022-0001). Male Sprague Dawley (SD) rats, weighing between 400 and 600 g and aged 12–14 weeks (HFK Bioscience, China), were housed under standard laboratory conditions, with free access to food and water (at the Fuwai Animal Center). Twenty-four rats were randomly divided into four groups: the DHCA group ($n=6$), the low-dose UTI-treated (3×10^4 U/kg) DHCA group (UTI-L, $n=6$), the middle-dose UTI-treated (10×10^4 U/kg) DHCA group (UTI-M, $n=6$), and the high-dose UTI-treated (30×10^4 U/kg) DHCA group (UTI-H, $n=6$). UTI powder (Guangdong Techpool Bio-pharma Co., Ltd, Guangzhou, Guangdong, China) was dissolved in 2 mL of normal saline. Half of the dose was added to the CPB priming solution and the other half was administered after rewarming. The whole study followed the animal research: reporting of in vivo experiments (ARRIVE) guidelines.

CPB and DHCA process

The main workflows of the entire experimental procedure was consistent with previously reported method [13]. Briefly, rats were anesthetized with 2–3% sevoflurane and endotracheal intubation was performed. The left femoral artery was cannulated to monitor mean arterial blood pressure (MAP). CPB was establishment through catheterization of the tail artery and right external jugular vein. After injection of 500 IU/kg of heparin through the right external jugular vein, CPB was initiated. The CPB device consisted of a reservoir (modified from Murphy's dropper), a roller pump, a heat exchanger, a membrane oxygenator, connecting tubes, and a water tank. The CPB circuit was primed with 12 mL of 6% hydroxyethyl starch and 2 mL of saline containing 150 IU heparin. The initial flow rate of CPB was set at 160–180 mL/kg/min, and maintained for 10 min before cooling. The target temperature was set at 18 °C. DHCA was then induced by draining the blood into the reservoir and lasted for approximately 45 min, confirmed by a MAP of zero. During the rewarming phase, the circulation was first restored and the rectal temperature was gradually increased to 34 ℃. Then, after 30 min of full-flow assistance, the CPB was weaned off. During rewarming, MAP was maintained above 50 mmHg. Finally, the rats were observed under anesthesia and mechanical ventilation for 4 h before being euthanized. Liver and kidney tissues were quickly harvested and preserved in formaldehyde. Baseline physiological parameters, including MAP, heart rate (HR) and rectal temperature were continuously monitored throughout the operation. All rats survived until the end of the experiment.

Blood gas analysis

Arterial blood samples (0.2 mL) were collected for blood gas analysis (i-STAT, Chicago, IL, USA) at five time points: after anesthesia (T1), 10 min after initiating CPB (T2), during rewarming (T3), at weaning from CPB (T4), and 4 h post-weaning from CPB (T5). Ventilator parameters and electrolyte levels were adjusted according to the blood gas results of rats.

Enzyme-Linked immunosorbent assay

Blood samples were drawn at T2, T4 and T5. Serum Interleukin (IL)-6, IL-10, tumor necrosis factor-α (TNF-α), and neutrophil elastase (ELA-2) levels were quantified using enzyme-linked immunosorbent assay.

Detection of myocardial, hepatorenal function

The plasma samples at T2, T4 and T5 was collected to measure the levels of creatine kinase muscle and brain isoenzyme (CK-MB), cardiac troponin I (cTnI), creatinine, blood urea nitrogen (BUN), aspartate transaminase (AST) and alanine aminotransferase (ALT) using a fully automated biochemical analyzer.

Tissue specimen

Euthanasia was performed through cervical dislocation under deep anesthesia by increasing the output concentration of sevoflurane (8%). After euthanizing the rats, liver and kidney coronal Sect. (1 mm × 2 mm × 2 mm) were quickly obtained and fixed in 4% formaldehyde for 2 h, and then stored in a refrigerator at 0–4℃. After dehydration, embedding, slicing, baking and hematoxylin-eosin (HE) staining, the tissue morphology was observed under microscope. The hepatic, and renal pathological scores were determined by an expert pathology specialist in a blinded manner. The scoring rules are shown in Supplementary Table 1.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 9.0 (GraphPad San Diego, CA, USA) and SPSS 27.0 (SPSS Inc., Chicago, IL). The Shapiro-Wilk test was used to assess the normality of continuous variables. Values were expressed as mean ± standard deviation. Repeated measures analysis of variance (ANOVA) was used for inter group comparison and parameter comparisons at different time points within a group. A Pvalue < 0.05 (two-tailed) indicates statistically significant.

Results

Changes of MAP, HR and blood gas analysis

The basic hemodynamic measurements and blood gas analysis results are shown in Fig. 1. During the process of cooling, the MAP and HR of rats gradually decreased, and subsequently recovered upon rewarming (Fig. 1A, B). The MAP of UTI-L and UTI-M groups was higher compared to the normal DHCA group at T4 ($p < 0.001$, $p < 0.001$) and T5 ($p = 0.017$, $p = 0.001$). In contrast, the UTI-H group had a significantly lower MAP than the normal DHCA group at T4 ($p < 0.001$) and T5 ($p < 0.001$).

The establishment of CPB within 10 min was a process for rats to adapt to CPB, and at this time point, there were no significant differences in blood gas results among the four groups. During DHCA, ischemia and hypoxia led to the accumulation of anaerobic metabolites. After rewarming, the concentration of lactate significantly increased. With sufficient blood flow support, the concentration of lactate showed a decreasing trend. In addition, there were no significant differences in basic blood gas parameters between the DHCA group and the other three groups that received varying dosages of UTI at the end of the experiment (Fig. 1C-F).

Changes of inflammatory factors

The levels of IL-6, TNF-α, ELA-2, and IL-10 in DHCA rats gradually increased after the DHCA procedure (Fig. 2, Supplementary Table 2). Compared with the DHCA-only group, both UTI-L and UTI-M significantly reduced IL-6 ($p = 0.017$, $p = 0.022$), TNF-α ($p = 0.003$, $p < 0.001$) and ELA-2 levels ($p = 0.018$, $p = 0.001$) 4 h post-weaning from CPB (Fig. 3A, B,C). The IL-10 levels in UTI-L and UTI-M group were significantly higher than that in the DHCA group ($p < 0.001$, $p < 0.001$) (Fig. 3D). There was no statistically significant difference in the levels of IL-6, TNF-α, ELA-2, and IL-10 between the UTI-H group and the DHCA group at T5 ($p = 0.086$, $p = 0.292$, $p = 0.226$, $p = 0.728$, respectively).

Myocardial, liver and kidney function

The changes in cTnI, CK-MB, creatinine, BUN, AST and ALT after DHCA were measured to assess the impact of DHCA on myocardial, liver and kidney function in rats. In the rats undergoing DHCA, the above indicators gradually increased 4 h post-weaning from CPB (Fig. 4). Compared with the DHCA group, both the UTI-L and UTI-M group showed significantly lower levels of cTnI ($p = 0.001$, $p = 0.001$), CK-MB ($p < 0.001$, $p < 0.001$), creatinine ($p < 0.001$, $p < 0.001$), BUN ($p = 0.002$, $p = 0.021$), AST ($p < 0.001$, $p < 0.001$) and ALT ($p < 0.001$, $p < 0.001$) at T5 (Fig. 5A-F). The UTI-H group exhibited elevated levels of cTnI ($p = 0.002$), CK-MB ($p = 0.009$), creatinine ($p < 0.001$), BUN ($p < 0.001$), and ALT ($p < 0.001$) at T5 compared to the DHCA group. Consequently, the administration of a high dose of UTI resulted in more pronounced impairment of liver and renal function in DHCA rats.

Pathological results

Representative HE staining images of renal and hepatic tissues in each group are described. The DHCA and UTI-H groups exhibited pathological injury in the renal tissues of rat, including tubular cell flattening, tubular lumen dilation, and detachment of renal tubular epithelial cells (Fig. 6). Additionally, the HE staining images of the hepatic tissues in the UTI-H group revealed swollen hepatocytes, disordered arrangement, and disruption of the liver lobule structure (Fig. 7). Compared with the DHCA group, the UIT-L and UTI-M groups significantly reduced tubular injury scores (2.33 ± 0.52 vs. 3.83 ± 0.41, $p < 0.001$; 1.17 ± 0.41 vs. 3.83 ± 0.41, $p < 0.001$) (Fig. 8A) and liver injury scores (1.83 ± 0.75 vs. 3.50 ± 0.55, $p < 0.001$; 1.50 ± 0.55 vs. 3.50 ± 0.55, $p < 0.001$)(Fig. 8B).

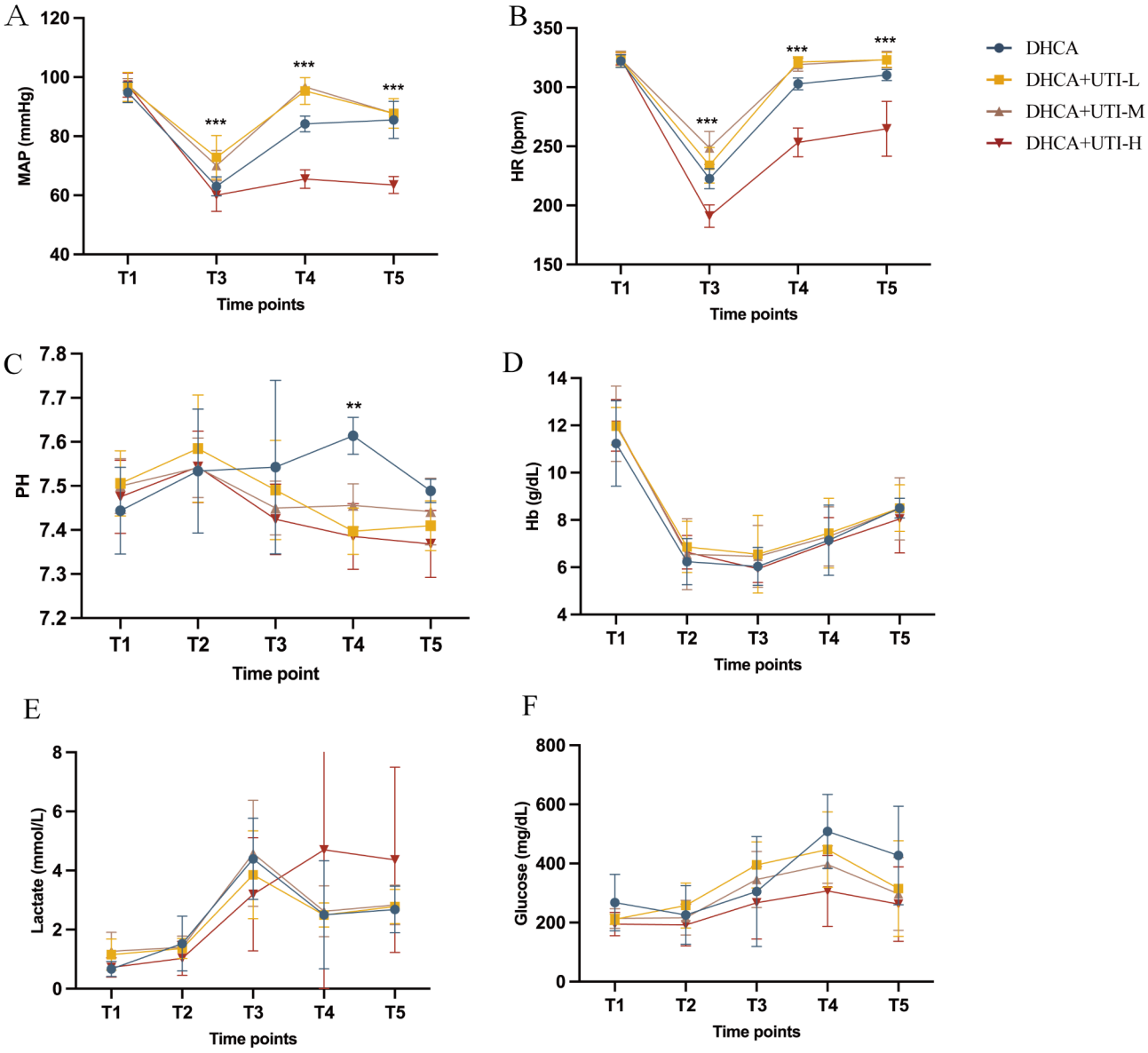

Fig. 1 Effects of ulinastatin on Hemodynamics and Blood Gas Analysis in DHCA Rats. Mean arterial blood pressure (MAP) (**A**) and heart rate (HR) (**B**) were monitored throughout the experiment. PH (**C**), hemoglobin (**D**), lactate (**E**) and glucose (**F**) were measured at predefined time-points for four groups of rats. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. DHCA, deep hypothermic circulatory arrest; UTI, ulinastatin. UTI-L, low dose UTI-treated; UTI-M, middle dose UTI-treated; UTI-H, high dose UTI-treated

Discussion

DHCA can induce a strong inflammatory response and ischemia-reperfusion injury, which can easily lead to multiple organ dysfunction. This study demonstrated that administering low to medium doses of UTI effectively decreased postoperative levels of IL-6, TNF-α, and ELA-2 while enhancing IL-10 release in DHCA rats, thereby exerting protective effects on myocardial, hepatic, and renal tissues. However, excessive doses of UTI not only failed to reduce inflammatory response, but also increased functional damage to major organs.

The DHCA rat model could activate specific signal transduction pathways to induce SIR [14, 15]. In this study, IL-6, TNF-α and ELA-2 levels increased significantly after DHCA, which was consistent with the results of previous studies [14, 16, 17]. Engels et al. found that

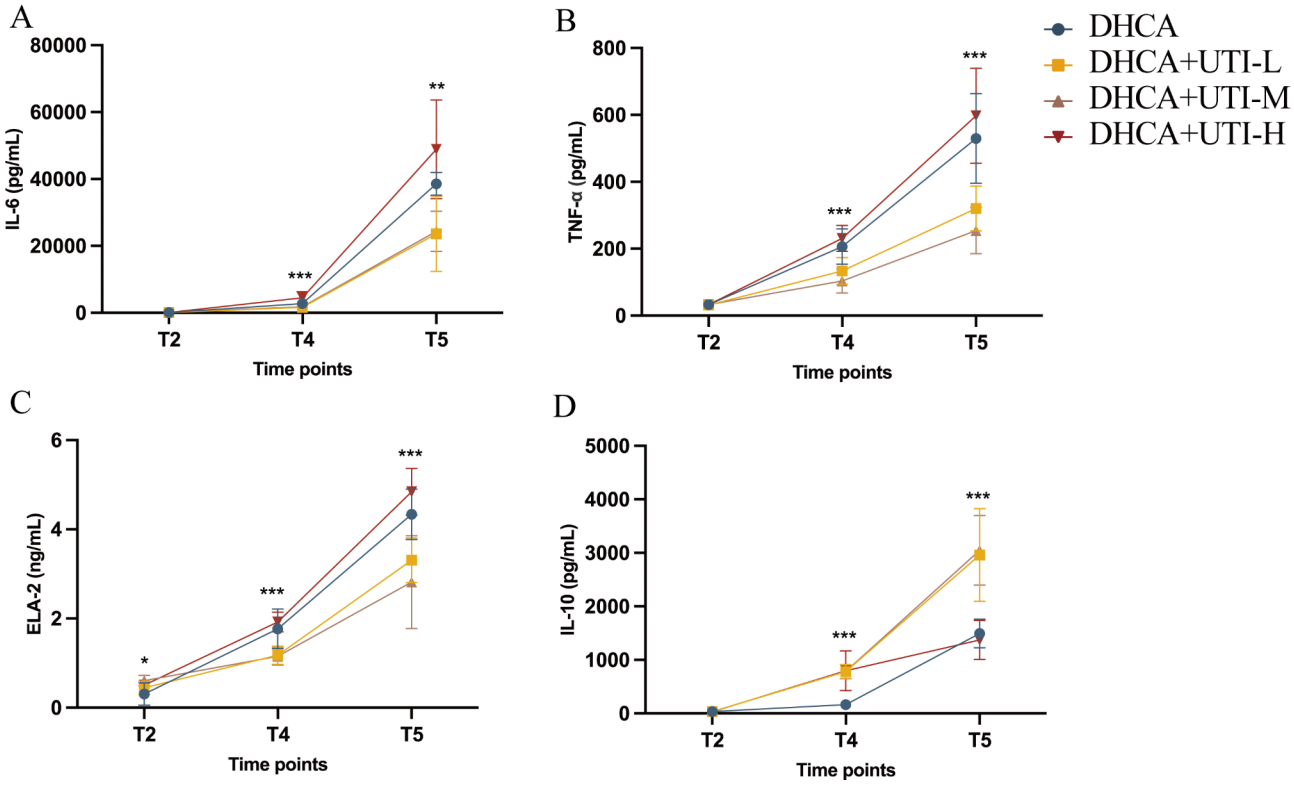

Fig. 2 Changes in inflammatory factors in rats treated with ulinastatin and DHCA at different time. IL-6 (**A**), TNF-α (**B**), ELA-2 (**C**), IL-10 (D) were measured by ELISA. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. DHCA, deep hypothermic circulatory arrest; UTI, ulinastatin. UTI-L, low dose UTI-treated; UTI-M, middle dose UTI-treated; UTI-H, high dose UTI-treated

SIR seemed not to be provoked during the cooling procedure but was elicited mainly during reperfusion, and the mechanism and molecular pathway involved were not completely clear [14]. Previous literature suggested that the overproduction of inflammatory and oxidative factors during the reperfusion phase was thought to play a key role in both I/R and SIRS [18].

UTI is a widely used protease inhibitor in clinical settings. Previous clinical trials have provided strong evidence that UTI can reduce the release of typical inflammatory biomarkers after cardiac surgery with CPB, which are beneficial for improving patient prognosis [19–21]. In this study, a low to medium dose UTI resulted in significantly elevated MAP after DHCA. Furthermore, the levels of pro-inflammatory factors (IL-6, TNF-α, and ELA-2) decreased and IL-10 increased after the whole experiment in the UTI-L and UTI-M groups. IL-6 is an important early inflammatory factor. TNF-α plays a role in both the release of IL-6 and IL-8 after I/R injury as well as the reduction of vascular tension and cardiac contractility. These actions are part of the major pathway in the cytokine cascade during SIR. IL-10 acts as an anti-inflammatory cytokine, suppressing the production of proinflammatory cytokines and inhibiting neutrophil–endothelial interactions [22]. Moreover, the interaction between reactive oxygen species and proteases released by neutrophils after activation can mediate endothelial cell damage [23]. Elastase is a highly cytotoxic protease that can decompose connective tissue components and increase the risk of capillary leakage [24, 25]. Therefore, administration of low to medium doses of UTI effectively suppresses inflammatory responses and promotes hemodynamic stability.

The dosage of UTI exhibits significant variation in both animal trials and human clinical research. Furthermore, the timing and dosage of UTI can influence its effectiveness. In the treatment of patients with acute respiratory distress syndrome (ARDS), it has been reported that the regimen of UTI ranges from 20 to 60×10^4 U, 1–2 times per day [26]. In addition, the tolerance of UTI in

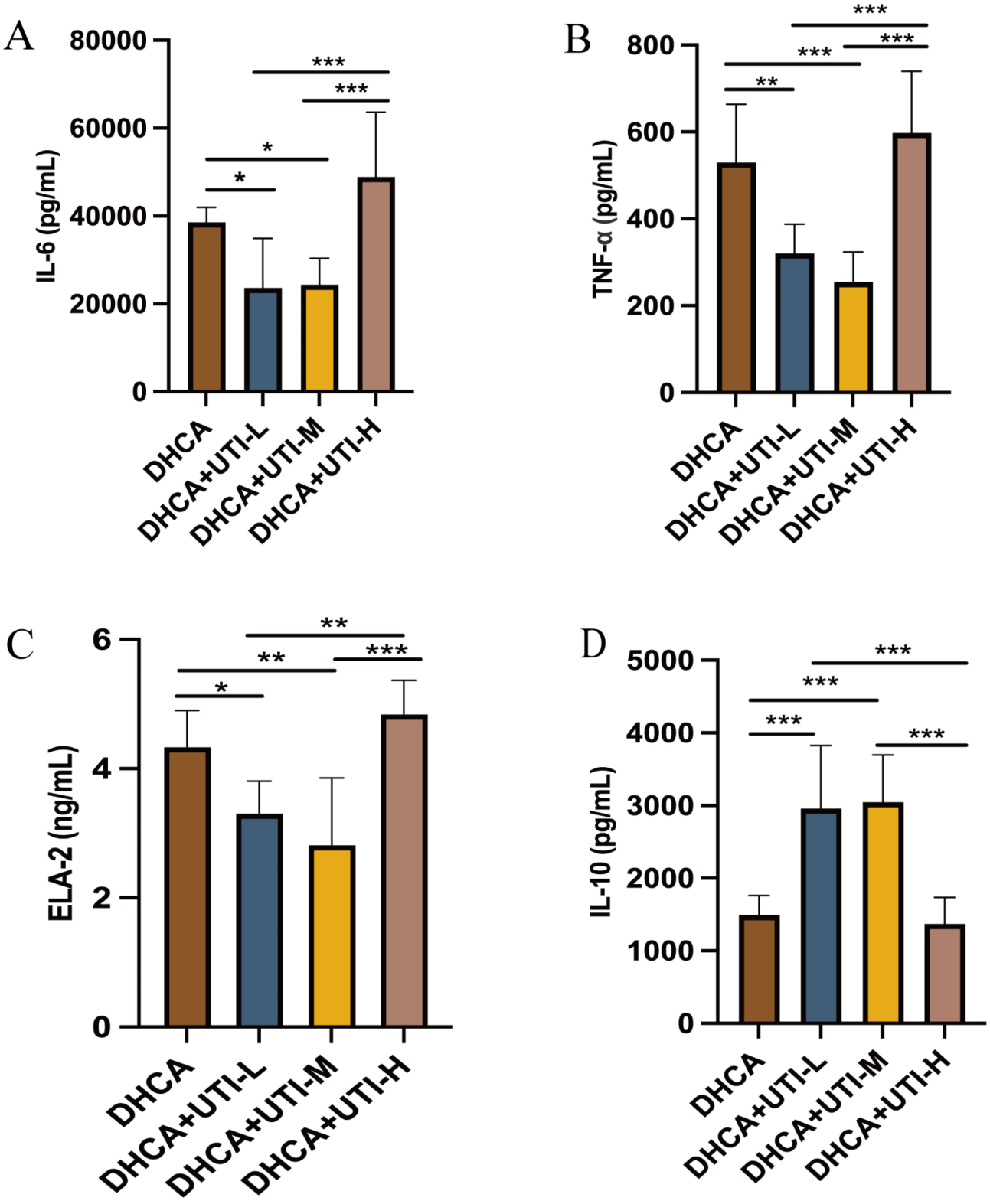

Fig. 3 Changes in inflammatory factors in rats treated with ulinastatin and DHCA at 4 h post-weaning from CPB. IL-6 (**A**), TNF-α (**B**), ELA-2 (**C**), IL-10 (D) were measured. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. DHCA, deep hypothermic circulatory arrest; UTI, ulinastatin. UTI-L, low dose UTI-treated; UTI-M, middle dose UTI-treated; UTI-H, high dose UTI-treated

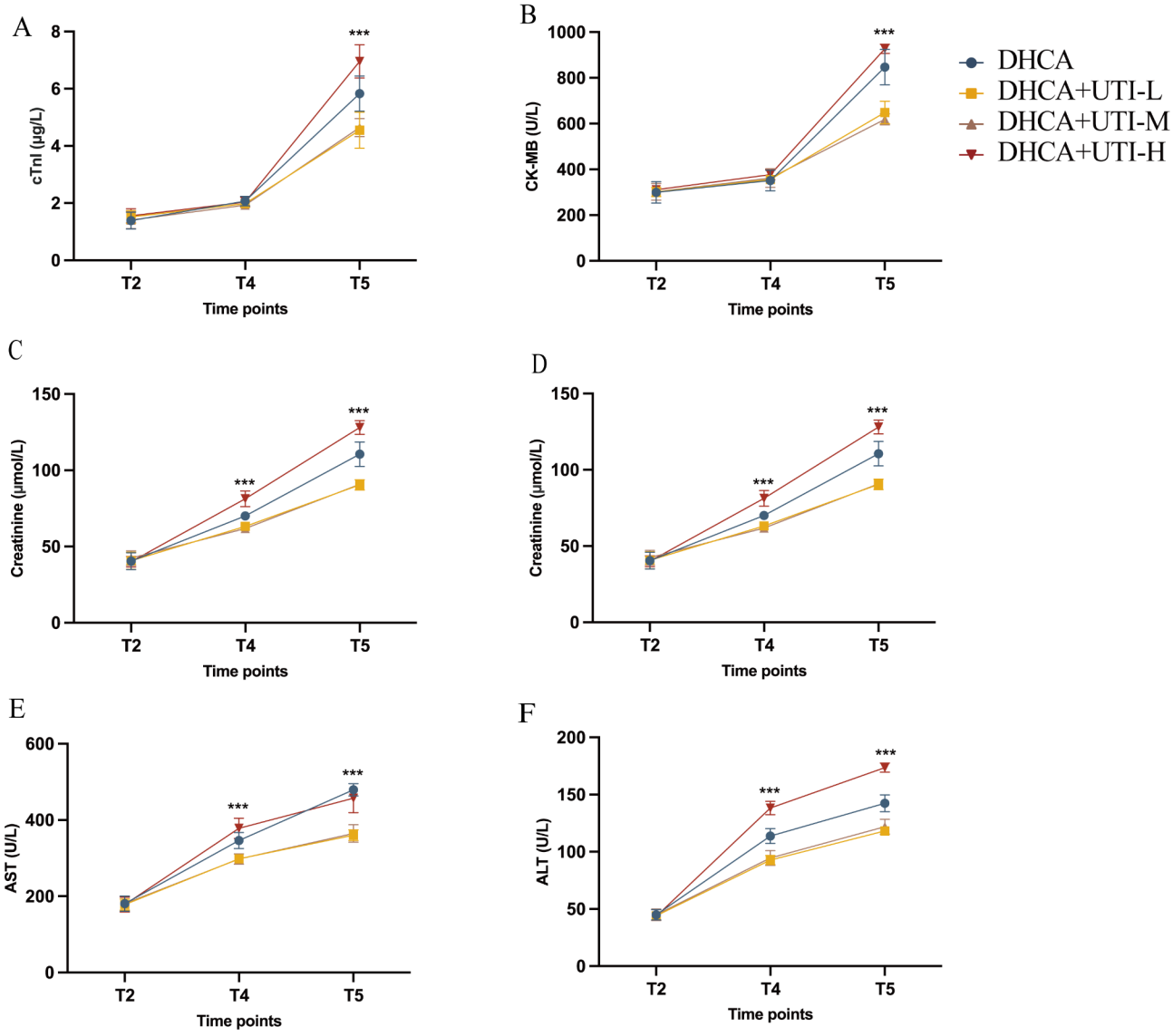

Fig. 4 Changes in functional indicators of myocardial, hepatic, and renal tissues at different time. cTnI (**A**), CK-MB (**B**), creatinine (**C**), BUN (**D**), AST (**E**) and ALT (**F**) were measured. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. DHCA, deep hypothermic circulatory arrest; UTI, ulinastatin. UTI-L, low dose UTI-treated; UTI-M, middle dose UTI-treated; UTI-H, high dose UTI-treated

51 healthy volunteers was evaluated in a single-center, double-blind, randomized, placebo-controlled clinical trial [27]. As a result, the concentration of UTI injected intravenously within 2 h in healthy subjects ranged from 3 to 80×10^5 U, demonstrating good tolerability. Mild adverse effects, such as dizziness, injection site pain, and leukopenia, were the most frequently reported. In patients undergoing cardiac surgery, UTI doses are typically administered within the range of $0.5–2 \times 10^4$ U/kg [10]. Based on the above doses, He et al. conducted a meta-analysis of 15 randomized studies involving 646 patients who underwent cardiac surgery with CPB [28]. They reported a significant reduction in TNF-α, IL-6, and IL-8 levels, along with an increase in IL-10 levels at 6 and 24 h after UTI treatment, which aligns with our findings. Similarly, Liu et al. demonstrated that postoperative

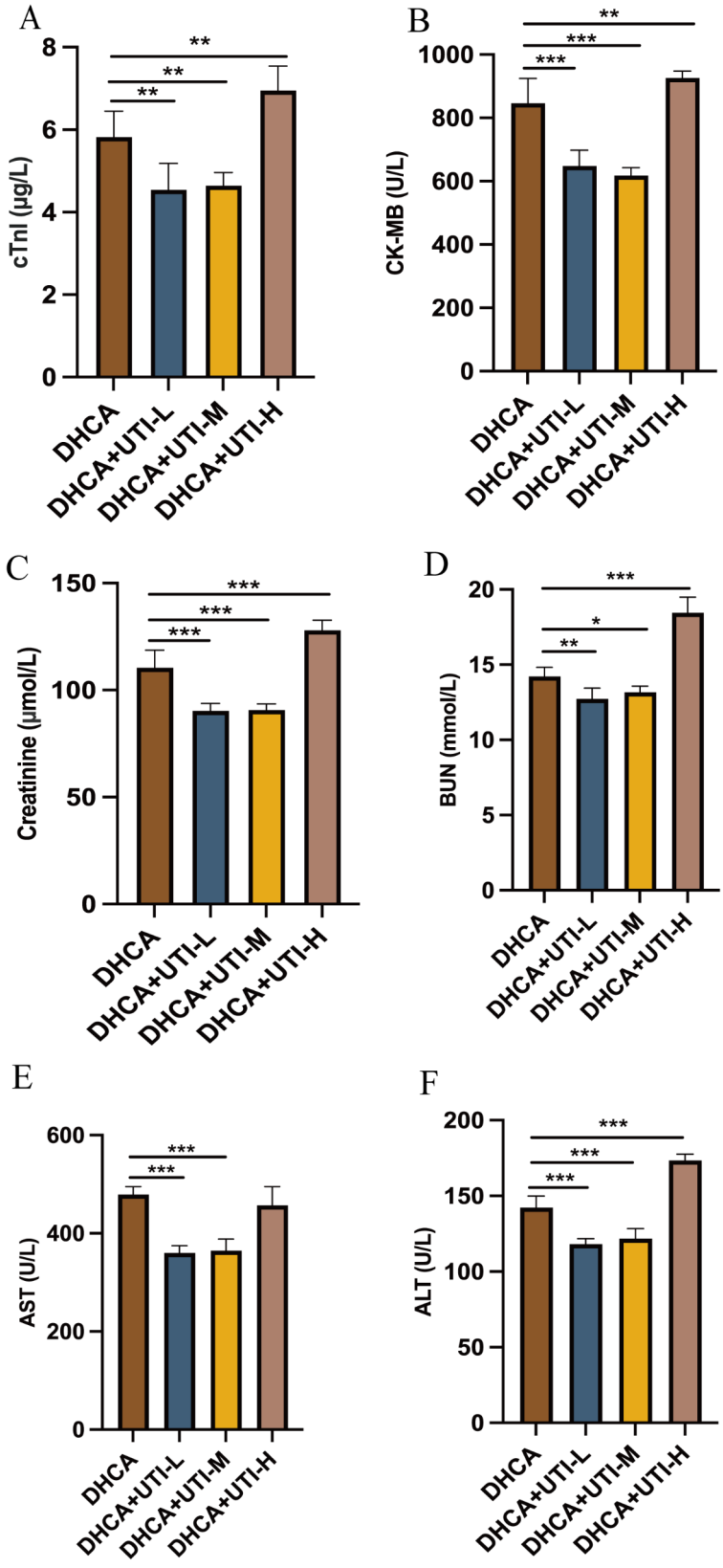

Fig. 5 Comparison of myocardial, hepatic, and renal functions in four groups of rats at 4 h post-weaning from CPB. cTnI (**A**), CK-MB (**B**), creatinine (**C**), BUN (**D**), AST (**E**) and ALT (**F**) were compared. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. DHCA, deep hypothermic circulatory arrest; UTI, ulinastatin. UTI-L, low dose UTI-treated; UTI-M, middle dose UTI-treated; UTI-H, high dose UTI-treated

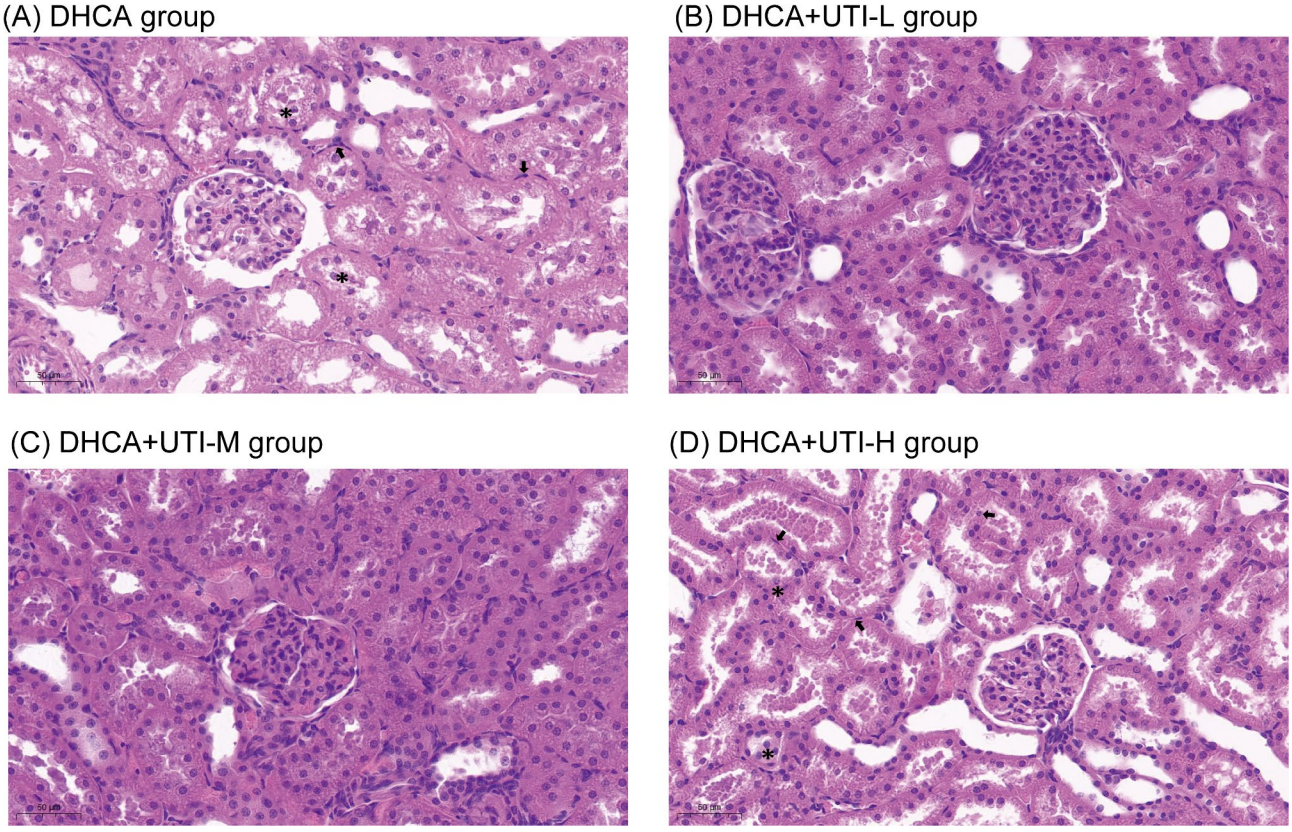

Fig. 6 Representative hematoxylin and eosin staining images of renal tissues from the four experimental groups. The pathological results of (**A**) DHCA group, (**B**) DHCA + UTI-L group, (**C**) DHCA + UTI-M group and (**D**) DHCA + UTI-H group were described. Significant flattening of renal tubular cells, dilation of renal tubular lumen, and detachment of renal tubular epithelial cells were observed in the DHCA group (**A**) and UTI-H group (**D**). Black arrow: flattening renal tubular cells; Black asterisk: renal tubular epithelial cells shedding

inflammatory cytokine levels in CPB patients receiving 6×10^4 U/kg UTI were significantly lower compared to those receiving $2–4 \times 10^4$ U/kg [29]. Given the pronounced inflammatory response and organ damage induced by DHCA, our study suggests that UTI at doses of $3–10 \times 10^4$ U/kg can be safely and effectively utilized in a DHCA rat model.

In this study, the high dose of UTI (30×10^4 U/kg) did not result in a reduction of the inflammatory response following DHCA, but instead led to an increase in cTnI, CK-MB, creatinine, BUN and ALT levels. In addition, rats in the high-dose UTI group showed lower MAP and PH after undergoing DHCA. We hypothesize that these effects may result from the toxic impact of drug overdose at 30×10^4 U/kg UTI, which impaired myocardial contraction, reduced HR, exacerbated ischemia-reperfusion injury, amplified inflammatory response activation, and aggravated acidosis, as well as hepatic and renal damage. Consequently, the high dose of UTI hindered the full expression of its anti-inflammatory and antioxidant efficacy.

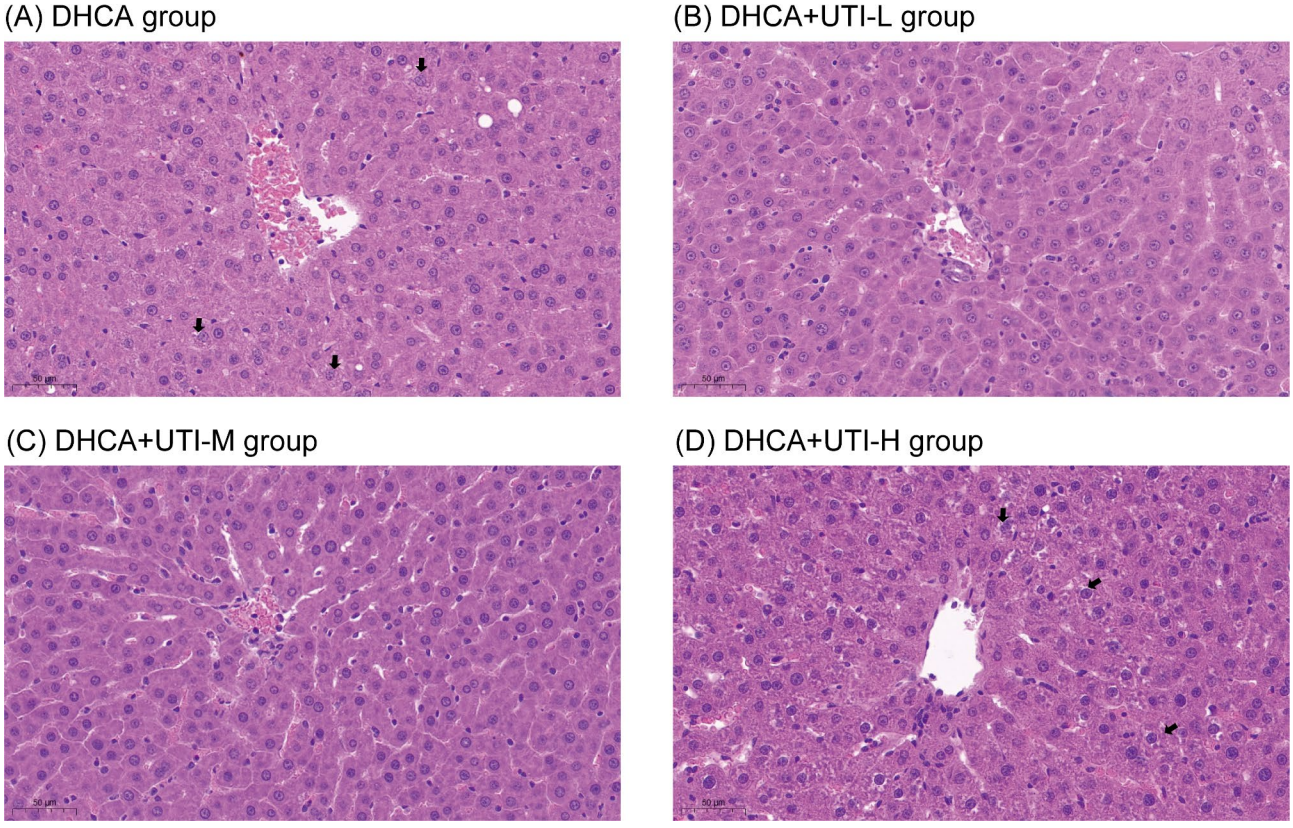

Fig. 7 Representative hematoxylin and eosin staining images of hepatic tissues from the four experimental groups. The pathological results of (**A**) DHCA group, (**B**) DHCA + UTI-L group, (**C**) DHCA + UTI-M group and (**D**) DHCA + UTI-H group were described. The UTI-H group (**D**) revealed swollen hepatocytes, disordered arrangement, and disruption of the liver lobule structure. Black arrow: Liver cells swelling and degeneration

There were several limitations in this study. First, owing to the limited blood volume in rats and financial constraints, proteins associated with cellular signaling pathways and inflammatory pathways were not analyzed, nor were additional inflammatory markers (e.g., IL-1β and IL-8). Consequently, the molecular mechanisms underlying the action of UTI could not be fully elucidated; Second, all the rats in this study were in a healthy baseline state and had not undergone thoracotomy, which may result in differences when compared to inflammatory stimulation in clinical practice; Third, the rats were euthanized 4 hours after surgery, and the long-term effects of low to medium doses of UTI were not observed. A longer observation period is needed in the future to comprehensively evaluate the long-term benefits of UTI. Furthermore, in this study, UTI doses were used at 3×10^4, 10×10^4 and 30×10^4 U/kg. Further experimental confirmation should be conducted in the future to determine whether UTI doses of 10 to 30×10^4 U/kg can reduce inflammatory responses and protect liver and kidney function.

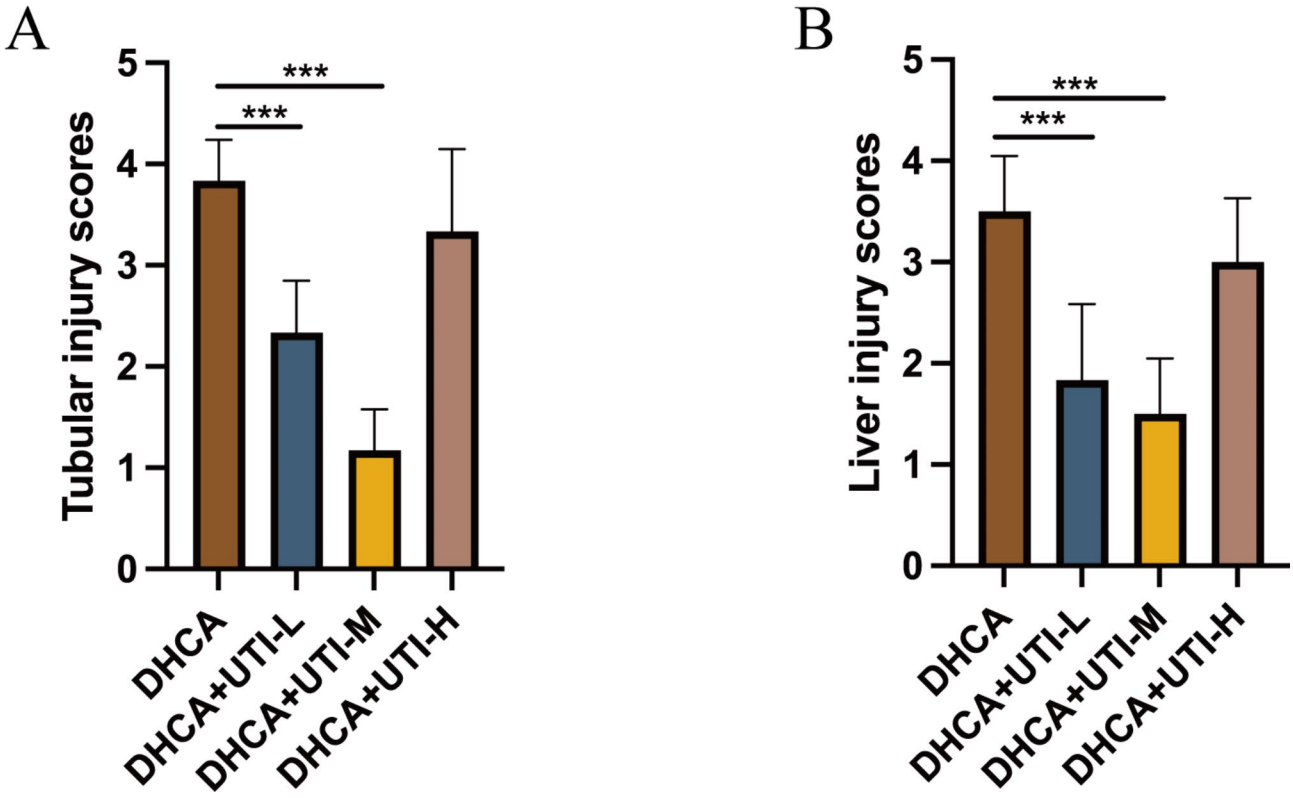

Fig. 8 Graphical presentation of the pathologic scores. The renal tubular injury scores (**A**) and the liver injury scores of four groups of rats are shown. *** $p < 0.001$. DHCA, deep hypothermic circulatory arrest; UTI, ulinastatin. UTI-L, low dose UTI-treated; UTI-M, middle dose UTI-treated; UTI-H, high dose UTI-treated

Conclusions

DHCA can induce a strong inflammatory response and ischemia-reperfusion injury. Adding a low and medium dose of UTI could safely and effectively reduce the levels of inflammatory factors IL-6, TNF - α, and ELA-2, and increase the level of anti-inflammatory factor IL-10. Conversely, the administration of UTI at a high dose of 30×10^4 U/kg did not exhibit a dose-dependent suppression of the inflammatory response. Instead, it increased damage to myocardial, hepatic and renal function. The optimal dose and treatment time of UTI need to be further investigated in the future.

Abbreviations

DHCA	Deep hypothermic circulatory arrest
CPB	Cardiopulmonary bypass
UTI	Ulinastatin
SIR	Systemic inflammatory response
MAP	Mean arterial blood pressure
HR	Heart rate
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor-α
CK-MB	Creatine kinase muscle and brain isoenzyme
cTnI	Cardiac troponin I
BUN	Blood urea nitrogen
AST	Aspartate transaminase
ALT	Alanine aminotransferase
HE	Hematoxylin-eosin
ARDS	Acute respiratory distress syndrome

Supplementary information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

YT and QH designed the study, extracted the data and drafted the manuscript. JW and TW performed the statistical analysis. ZB and YY provided help and performed the research. BJ and GG provided help in the establishment of animal models. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Data availability

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

Declarations

Ethics approval and consent to participate

This study was approved by the Animal Experimental Ethics Committee of Fuwai Hospital (FW-2022-0001). All experimental procedures complied with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health.

Consent for publication

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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