

Original Article

The protective effects of dexmedetomidine on the liver and kidney injury in heat stroke rats

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Abstract: The current study aimed to explore whether dexmedetomidine could attenuate heat-induced liver and kidney injury in rats and the possible mechanism. Forty eight male anesthetized SD rats were randomly divided into following three groups (n=16): blank control group (group C), heat stroke model group (group HS) and dexmedetomidine group (group Dex). The model and dexmedetomidine groups were subjected to heat stress ($40\pm0.5^{\circ}\text{C}$) to induce heat stroke. A bolus injection of normal saline or dexmedetomidine ($25\text{ }\mu\text{g/kg}$) was administrated intraperitoneally immediately after the onset of heat stroke. Blood samples were gained at 1 h (T1) and 6 h (T6) after injection, the serum concentrations of ALT, AST, Cr, BUN, IL-1 β , IL-6 and TNF- α were measured. The serum concentrations of liver and kidney injury markers (ALT, AST, BUN, Cr) and inflammatory cytokines (IL-1 β , IL-6, TNF- α) in group HS were significantly higher than in group C in T1 and T6 ($P<0.05$). In addition, the concentrations of ALT, AST, BUN, Cr, IL-1 β , IL-6 and TNF- α in group Dex were lower than in group HS in two time points ($P<0.05$). Systemic delivery of dexmedetomidine at the time point of onset of heat stroke may ameliorate the liver and kidney injury by regulating inflammation and decreasing the inflammatory cytokines.

Keywords: Dexmedetomidine, heat stroke, inflammation, cytokine

Introduction

Heat stroke is a life-threatening illness which is characterized by nervous and circulatory system dysfunction and severe hyperthermia induced by high temperature environment [1]. Multi-organ dysfunction including liver and kidney injury may occur in heat stroke patients. In spite of lowering the temperature, fluid infusing and multi-organ supporting, the mortality of heat stroke patients was still high [2]. So far, there were no satisfactory drugs.

Systemic inflammation occurs during heat stroke in rats. Several studies have shown that the serum concentrations of cytokines and chemokines in heat stroke rats or patients [3]. These studies suggest that some inflammatory mediators may play an important role in the pathogenesis of heat stroke. Therefore, inhibiting the production of these mediators may alle-

viate the multi-organ injury in heat stroke patients [4, 5].

Dexmedetomidine is a novel alpha-2 adrenergic agonist with high selectivity. It has sedative, antisympathic and slight analgesic effects while has little effect in hemodynamics and has no inhibitive effect in breathing, and was generally used in ICU [6]. Recently, several studies indicated that dexmedetomidine could regulate the inflammation and has multi-organ protective effects in sepsis and ischemic reperfusion injury animal model [7, 8]. The pathophysiological process of heat stroke is similar with sepsis in many respects, and they both exist severe systemic inflammatory response [9].

Thus, we hypothesized dexmedetomidine may have protective effects on heat stroke. In order to verify our hypothesis, the effect of dexmedetomidine on serum concentrations of inflammatory mediators and liver and kidney injury

Table 1. The time of reaching the heat stress end and the weight change of before and after the heat stress between the two group ($\bar{x} \pm s$, $n=16$)

Treatment group	Using time	Weight changing
Group HS	81.25 $\pm$ 3.42	4.13 $\pm$ 0.72
Group Dex	80.31 $\pm$ 3.86	3.94 $\pm$ 0.77
<i>T</i>	0.728	0.711
<i>P</i>	0.472	0.483

markers in heat-stress induced heat stroke rat model were investigated.

Materials and methods

Experimental animals

Forty eight adult male SD rats were provided by Experimental Animal Center of the Chinese people's liberation army 304 hospital. The animals were housed at ambient temperature of 24°C with free access to water and food. All the rats were allowed to conform in this environment for at least seven days. This experiment was authorized by the Institutional animal Care and Use Committee of the Chinese people's liberation army 304 hospital and complied with the guidelines for the care and use of laboratory animals (National Institute of Health Guide for the Care and Use of Laboratory Animals, NIH Publications No. 80-23, revised 1996).

Preparation of heatstroke model

All rats were anesthetized with intraperitoneally injected sodium pentobarbital (45 mg/kg), which also abolished the corneal and pain reflexes. Rats were placed in a pre-warmed incubator maintained at 40.0 $\pm$ 0.5°C. The rectal temperature (representing of the core temperature) was monitored every 5 minutes, and the heat stress was terminated when the core temperature reached 42°C [10].

Grouping and treatment

Rats were randomly divided into 3 groups ($n=16$). Control group (group C): the rats were put into the cage at a room temperature of 24°C after anesthetizing. Heat stroke model group (group HS): the rats were administrated intraperitoneal immediately with normal saline when their core temperature reached 42°C, then were migrated to a room temperature of 24°C. Dexmedetomidine group (group Dex): the

rats were administrated intraperitoneal immediately with dexmedetomidine (25 ug/kg) [11-13] (Batch number: 14010632, Jiangsu Hengrui limited liability company, China) when their core temperature reached 42°C, then were migrated to a room temperature of 24°C. The time of the core temperature reaching 42°C and the weight of the rats before or after setting up the heat stroke model was recorded.

Measurements of liver and kidney injury markers and cytokines in serum

Blood samples were obtained from rats through cardiac puncture in first hour and sixth hour after administration. Serum concentrations of ALT, AST, Cr and BUN were measured by automatic biochemical analyzer (Hitachi 2600-010, Japan). The concentrations of IL-1 β , IL-6 and TNF- α in serum of rats were measured by using ELISA kits (Shanghai Xitang Biological Technology limited liability company, China).

Statistical analysis

Statistical analyses were performed using SPSS16.0. Results are presented as means $\pm$ SD. Between-group comparisons were assessed by one-way analysis of variance (ANOVA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

General condition

The time of reaching the heat stress end and the weight change of before and after the heat stress between group HS and group Dex were no statistically significant ($P>0.05$), as shown in **Table 1**.

Effects of dexmedetomidine on liver and kidney injury markers

Compared with group C, the concentrations of ALT, AST, BUN and Cr in serum were increased in group HS in T1 and T6 ($P<0.05$); the concentrations of ALT, AST, BUN, Cr in group Dex were lower than that in group HS in two time points ($P<0.05$), as shown in **Figure 1**.

Effects of dexmedetomidine on cytokines

Compared with group C, the serum levels of IL-1 β , IL-6, TNF- α were increased in group HS in

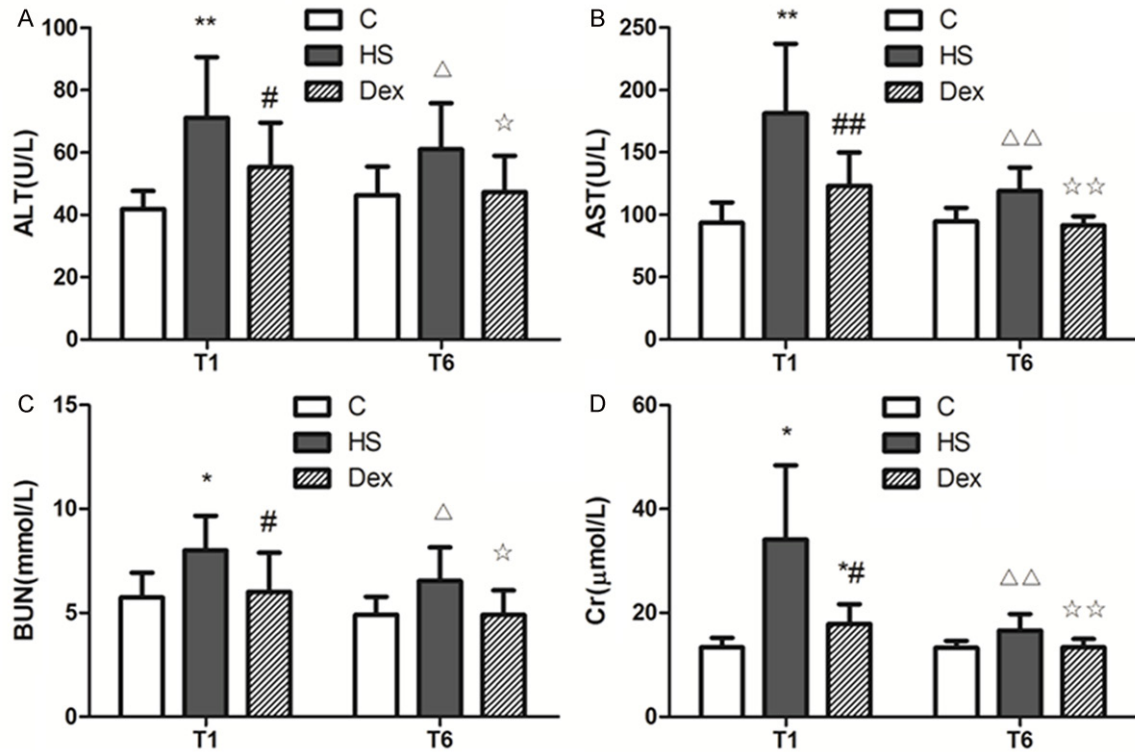


Figure 1. The comparison of liver and kidney injury markers in serum between groups. In T1, compared with group C, * $P < 0.05$, ** $P < 0.01$; compared with group HS, # $P < 0.05$, ## $P < 0.01$. In T6, compared with group C, $\Delta P < 0.05$, $\Delta\Delta P < 0.01$; compared with group HS, ☆ $P < 0.05$, ☆☆ $P < 0.01$.

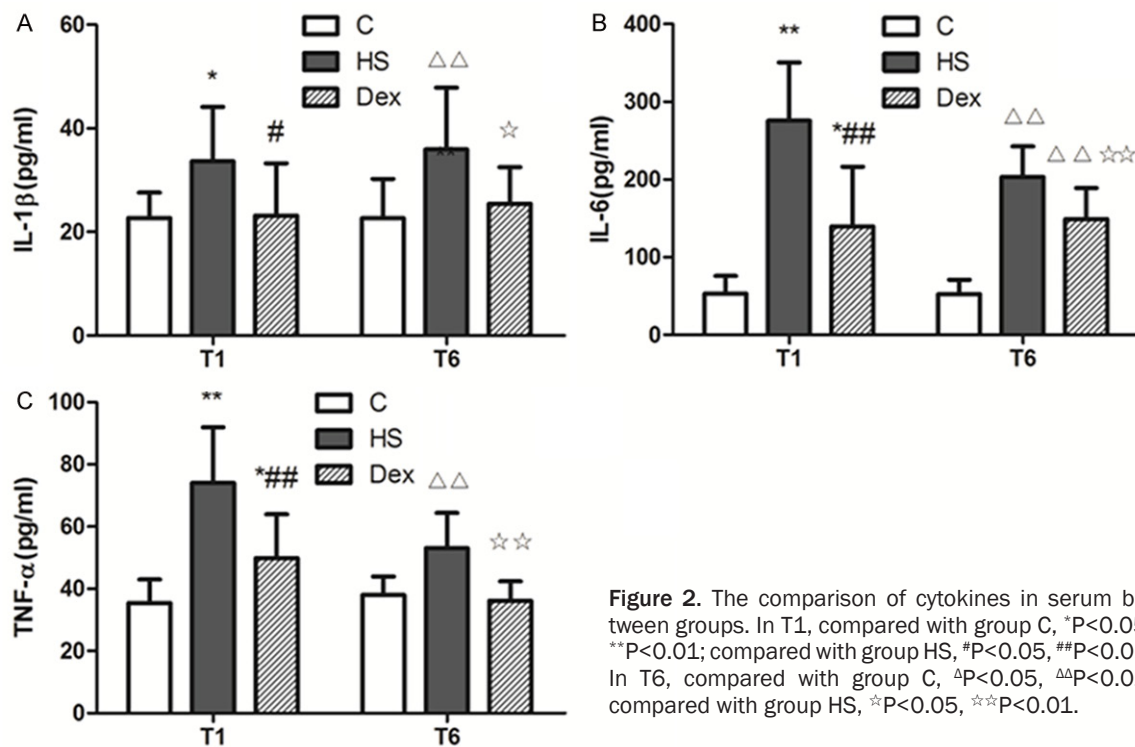


Figure 2. The comparison of cytokines in serum between groups. In T1, compared with group C, * $P < 0.05$, ** $P < 0.01$; compared with group HS, # $P < 0.05$, ## $P < 0.01$. In T6, compared with group C, $\Delta P < 0.05$, $\Delta\Delta P < 0.01$; compared with group HS, ☆ $P < 0.05$, ☆☆ $P < 0.01$.

T1 and T6 ($P<0.05$); the serum levels of IL-1 β , IL-6, TNF- α in group Dex were lower than that in group HS in two time points ($P<0.05$), as shown in **Figure 2**.

Discussion

The systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) in heat stroke animals were caused by the over production of inflammatory mediators including IL-6 and TNF- α . The past studies indicated that the pathophysiology of heat stroke was that heat stress induced blood from non-vital central organs to the periphery, resulted in the increasing in vascular intestinal permeability. Then, LPS activated mononuclear macrophages and other immune cells when leaked into blood. The immune cells released massive inflammatory mediators which induced inflammation, resulted in MODS [14]. Hagiwara et al. [4, 5] found that the serum concentrations of cytokines (such as TNF- α , IL-1 β and IL-6) were increased and multi-organ function was damaged in the heat-induced heat stroke rat model. Moreover, the multi-organ injury can be mitigated, and the outcome also can be improved through decreasing the levels of inflammatory cytokines. Therefore, we investigated the mechanism of the potential protective effects of dexmedetomidine on the heat stroke rats through detecting the serum concentrations of TNF- α , IL-1 β , IL-6.

Heat stroke induced multi-organ dysfunction including liver, kidney, intestine, lung, brain and skeletal muscle and so on [15, 16]. The concentrations of ALT, AST in serum of heat stroke patients were increased markedly. So ALT and AST can be used as indexes to judge the condition and outcome in heat stroke patients, they were also generally used as indexes to access the liver function in clinic. Otherwise, BUN and Cr were generally used as kidney functional indexes. Therefore, we measured the serum concentrations of ALT, AST, BUN and Cr to access the liver and kidney injury in heat stroke rats. In this study, we found that the levels of ALT, AST, BUN, Cr, TNF- α , IL-1 β and IL-6 in group HS were increased compared with group C. Consistent with the results of Chen and colleagues [17], our data indicated that the heat stroke rats occurred liver and kidney injury and this injury were related with the increased cytokines.

Dexmedetomidine, a novel sedative with an affinity for a 2-adrenoceptor, was normally used as anaesthetic adjunct [18]. Multiple studies have shown that dexmedetomidine may prevent the release of inflammatory mediators including IL-6 and TNF- α [8, 19, 20]. In vitro, dexmedetomidine prevented the infiltration, accumulation and activation of neutrophil, induced neutrophil apoptosis and inhibited the inflammation [21]. Increasing numbers of investigations reported that dexmedetomidine has beneficial effects in experimental models of septic shock and many other inflammatory diseases through regulating inflammation [8, 22, 23]. The current study indicated that treatment with dexmedetomidine (25 $\mu\text{g/kg}$) decreased the levels of systemic inflammatory mediators (TNF- α , IL-1 β , IL-6) and liver and kidney injury markers (ALT, AST, BUN, Cr) ($P<0.05$). Therefore, dexmedetomidine mitigated liver and kidney injury, this may be related with it decreasing inflammatory cytokines and regulating systemic inflammation.

Overall, the present study suggested that treatment with dexmedetomidine (25 $\mu\text{g/kg}$) may ameliorate the liver and kidney injury by regulating inflammation and decreasing the inflammatory cytokines. These results provided evidence for dexmedetomidine may have potential protective effects in heat stroke patients.

Disclosure of conflict of interest

None.

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