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ORIGINAL ARTICLE

Basic Study

Low G preconditioning reduces liver injury induced by high +Gz exposure in rats

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Author contributions: Zhang HY and Shi B designed the research; Shi B and Li WB performed the research; Shi B and Feng ZQ analyzed the data; Shi B, Feng ZQ and Zhang HY wrote the paper.

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Abstract

AIM: To investigate the effect of repeated lower +Gz exposure on liver injury induced by high +Gz exposure in rats.

METHODS: Sixty male Wister rats were randomly divided into a blank control group, a low G preconditioning group (LG) (exposed to +4 Gz/5 min per day for 3 d before +10 Gz/5 min exposure), and a +10 Gz/5 min group (10G) (n = 20 in each group). Blood specimens and liver tissue were harvested at 0 h and 6 h after +10 Gz/5 min exposure. Liver function was analyzed by measuring serum alanine transaminase (ALT) and aspartate aminotransferase (AST) levels, and liver injury was further assessed by histopathological observation. Malondialdehyde (MDA), superoxide dismutase (SOD) and Na^+-K^+-ATPase were determined in hepatic tissue.

RESULTS: The group LG had lower ALT, AST, and MDA values at 0 h after exposure than those in group 10G. SOD values and Na^+-K^+-ATPase activity in the LG group were higher than in group 10G 0 h post-exposure. Hepatocyte injury was significantly less in group LG than in group 10G on histopathological evaluation.

CONCLUSION: It is suggested that repeated low +Gz exposure shows a protective effect on liver injury induced by high +Gz exposure in rats.

Key words: Positive acceleration (+Gz); Liver injury; Preconditioning; Animal centrifuge; Rat

Core tip: We conducted this experimental study to explore an optimized strategy of reducing liver injury induced by high +Gz exposure, and to observe more specific indices of liver function, such as alanine transaminase, aspartate aminotransferase, malondialdehyde, superoxide dismutase, Na^+-K^+-ATPase and hepatic pathology. We found that low G preconditioning

reduced oxidative stress and significantly improved Na^+-K^+-ATPase activity, inducing minimal liver injury.

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INTRODUCTION

Ischemic preconditioning (IPC) refers to a phenomenon in which the tissue can not only increase resistance to further ischemic injury but also reduce the degree of organ dysfunction or subsequent damage following ischemia reperfusion[1,2]. To some extent, ischemia of a brief period initiates an endogenous protection for the following sustained ischemic period[3]. At first, the protective effect of IPC was verified in the heart[4]. Although the potential mechanism is not fully understood, the protective effect of IPC in delaying cell injury of skeletal muscle[5], brain[6], kidney[7], liver[8] and small intestine[9] is generally accepted. More and more studies have demonstrated that many different stimuli can induce preconditioned status of the liver. Ren *et al*[10] reported that liver IPC played a beneficial role in hepatic graft function and intestinal barrier function, contributing to stabilization of intestinal microbiota in liver transplantation. Currin *et al*[11] found that IPC markedly reduced hepatocellular injury after aortic clamping and ameliorated the survival rate. Lee *et al*[12] showed that hepatic IPC directly reduced distant renal ischemia and reperfusion injury in animal experiments. Figueira *et al*[13] demonstrated that hepatic IPC could not only recover portal vein flow, but also relieve hepatocellular injury.

During a flight, pilots may experience high sustained +Gz acceleration that results in gravity load and hemodynamic changes. Repeated +Gz exposure can cause accumulative stress damage in the body[14], inducing organ dysfunction and triggering pathologic changes. For a long time, many researchers were interested in the problem and tried to figure out some useful safeguard measures[15]. Cao *et al*[16] found that repeated low +Gz preconditioning could obviously ameliorate memory and balance changes induced by high +Gz exposure in rats. It was also found that lower gravity preconditioning was able to dramatically improve rat learning and memory impairment induced by high gravity exposure[17]. Li *et al*[18]'s study showed that brain injury induced by high +Gz exposure could be remarkably alleviated by low +Gz exposures in rats. It was also found that the left ventricular contractility and secretions of vascular endotheliocytes in the heart of rats following high +Gz exposure were significantly improved by low G preconditioning[19]. Moreover, it was discovered that low G preconditioning was protective for several enzyme activities in myocardial tissue after high +Gz stress in rats[20].

The liver is the largest internal organ, and an important metabolic organ[21,22]. Without timely and effective preventive measures, the natural protective mechanism of the liver may be overpowered by continuous and repeated exposures to +Gz acceleration. In experimental studies, repeated +Gz exposure can transiently cause liver dysfunction and trigger pathologic changes. We are interested in whether low G preconditioning has a similar protective effect on liver injury and dysfunction induced by high +Gz stress. The aim of this study is to investigate the possible protective effect of repeated low +Gz exposure on liver injury induced by high +Gz exposure in rats.

MATERIALS AND METHODS

Experimental animals

Sixty male Wister rats (provided by the Experimental Animal Center of the Academy of Military Medical Science, Beijing, China), weighing between 250 and 300 g, were randomly divided into three groups: blank control group (group BC, n = 20), low G preconditioning group (group LG, n = 20) (exposed to +4 Gz/5 min per day for 3 d before +10 Gz/5 min exposure) and +10 Gz/5 min group (group 10G, n = 20). All rats were housed under standard experimental conditions: 12:12-h light-dark cycle, humidity 70%-80%, and room temperature 23-26 ℃. Standard laboratory chow and water were provided and rats were allowed to acclimatize for 7 d. The rats were fasting but had access to water for 12 h before the experiment to reduce experimental errors. All experiments were conducted between 8:00 am and 12:00 am. The experimental schemes were approved by the Animal Care and Use Committee of China PLA Air Force General Hospital and carried out according to the Guide for the Care and Use of Laboratory Animals.

Exposure of animals to acceleration and specimen collection

The animal centrifuge had an arm length of 2 m and was provided by the Air Force Aeromedicine Institute (Beijing, China), with an onset rate of 0.1-6 Gz/s, and acceleration range of 1-15 G. Each rat was placed inside a 15 cm × 5 cm × 3 cm cylindrical plastic restraint device which was mounted in the centrifuge arm with the head of the rat facing the axis of the centrifuge for +Gz orientation. In the +10 Gz/5min group, the rats were exposed to +10 Gz lasting for 5 min as reported elsewhere[23]. For the low G preconditioning group, the rats were exposed to +4 Gz/5 min every day for 3 d before +10 Gz/5 min exposure. The onset/offset rate of +Gz was set at +1 G/s. The rats in the blank control group were mounted on the arms of centrifuge, but were free from acceleration. After exposure to acceleration for 0 h and 6 h, general anesthesia, routine disinfection, and laparotomy were

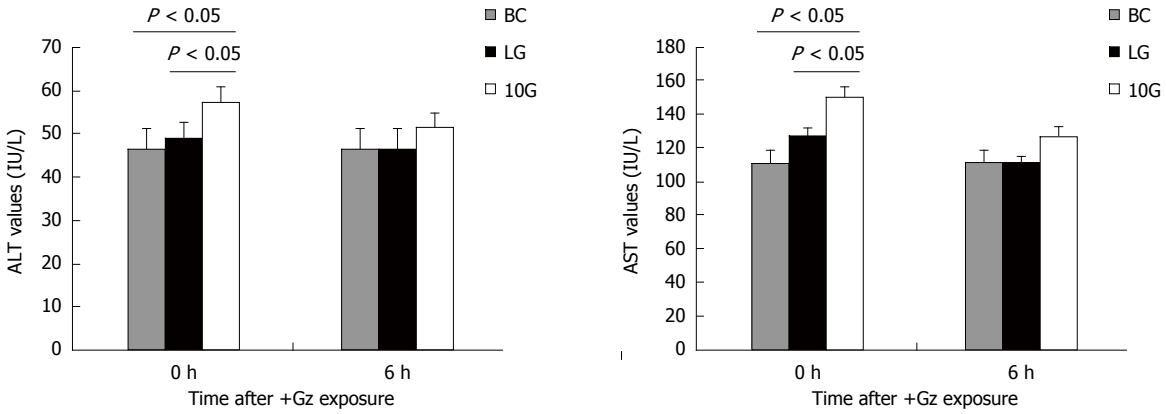

Figure 1 Comparison of rat serum alanine aminotransferase and aspartate aminotransferase levels at 0 and 6 h after +Gz exposures in the blank control group, low G preconditioning group and +10 Gz/5 min group. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in group low G preconditioning (LG) or group +10 Gz/5 min (10G) were higher than those in blank control group ($P < 0.05$ BC *vs* 10G) at 0 h after exposure, respectively. The rats in LG group showed lower ALT and AST levels than those in 10G group at 0 h after exposure ($P < 0.05$, LG *vs* 10G). BC: Blank control.

performed for specimen collection. A blood sample of about 2 mL was drawn from the inferior vena cava to measure serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Liver tissue was quickly removed and weighed. One part of the tissue was fixed in 4% formaldehyde for the histopathological examination, and the other part was immediately frozen in liquid nitrogen and stored under -80 ℃ for determination of malondialdehyde (MDA), superoxide dismutase (SOD) and Na^+-K^+-ATPase.

Blood sampling and analysis

Blood samples were obtained and separated by centrifugation (1500 rpm, 20 min). Activity changes of serum ALT and AST were measured using a serum analyzer (Cobas-Mira Plus; Roche Manheim, Germany).

Determination of oxidative stress markers

MDA level and SOD activity were measured spectrophotometrically using the corresponding kits (Nanjing Jiancheng Biotechnology Institute, Nanjing, China), respectively. Liver specimens were homogenized and treated in accordance with the manufacturer's recommendations. The results were expressed as nmol/mg protein for MDA, and U/mg protein for SOD.

Measurement of Na^+-K^+-ATPase activity levels

Na^+-K^+-ATPase activity in liver specimens was measured using an ATPase Assay Kit (Nanjing Jiancheng Biotechnology Institute, Nanjing, China) according to the manufacture's protocol. Na^+-K^+-ATPase activity was measured based upon the principle of inorganic phosphate measurement that was decomposed by adenosine triphosphate[24]. Changes of enzymatic activity indirectly indicated membrane damage or not. Na^+-K^+-ATPase activity was expressed as μmolPi/mg protein/h.

Histopathological analysis

After being fixed in 4% formaldehyde solution, the tissue samples were embedded in paraffin, cut into 5-μm-thick sections, and stained with hematoxylin-eosin (HE). The histological changes after repeated +Gz exposure were graded using Suzuki's criteria[25]. There were three features to assess the morphometric parameters: sinusoidal congestion, hepatocyte necrosis, and ballooning degeneration, graded from 0 to 4. A specific grading method was introduced: 0, none; 1, minimal congestion and ballooning degeneration as well as single cell necrosis; 2, minor congestion and ballooning degeneration as well as < 30% lobular necrosis; 3, moderate congestion and ballooning degeneration as well as 30%-60% lobular necrosis; 4, severe congestion and ballooning degeneration as well as > 60% lobular necrosis. The pathological changes were observed under microscope by an experienced blinded histologist.

Statistical analysis

The data was expressed as the mean ± SD. The unpaired *t*-test was used to compare low G preconditioning group and +10 Gz/5 min group. SPSS 13.0 software (SPSS, Chicago, IL, United States) was involved for data analysis, and $P < 0.05$ indicated significant difference.

RESULTS

Low G preconditioning reduced hepatocellular damage

Plasma ALT and AST levels were measured to assess liver damage at 0 and 6 h after exposure. ALT and AST values in the BC group were 46.7 ± 4.6 IU/L and 110.6 ± 7.4 IU/L, respectively. In group LG or group 10G, ALT and AST levels were higher than those in BC group ($P < 0.05$) at 0 h after exposure, respectively. However, the rats in LG group showed lower ALT

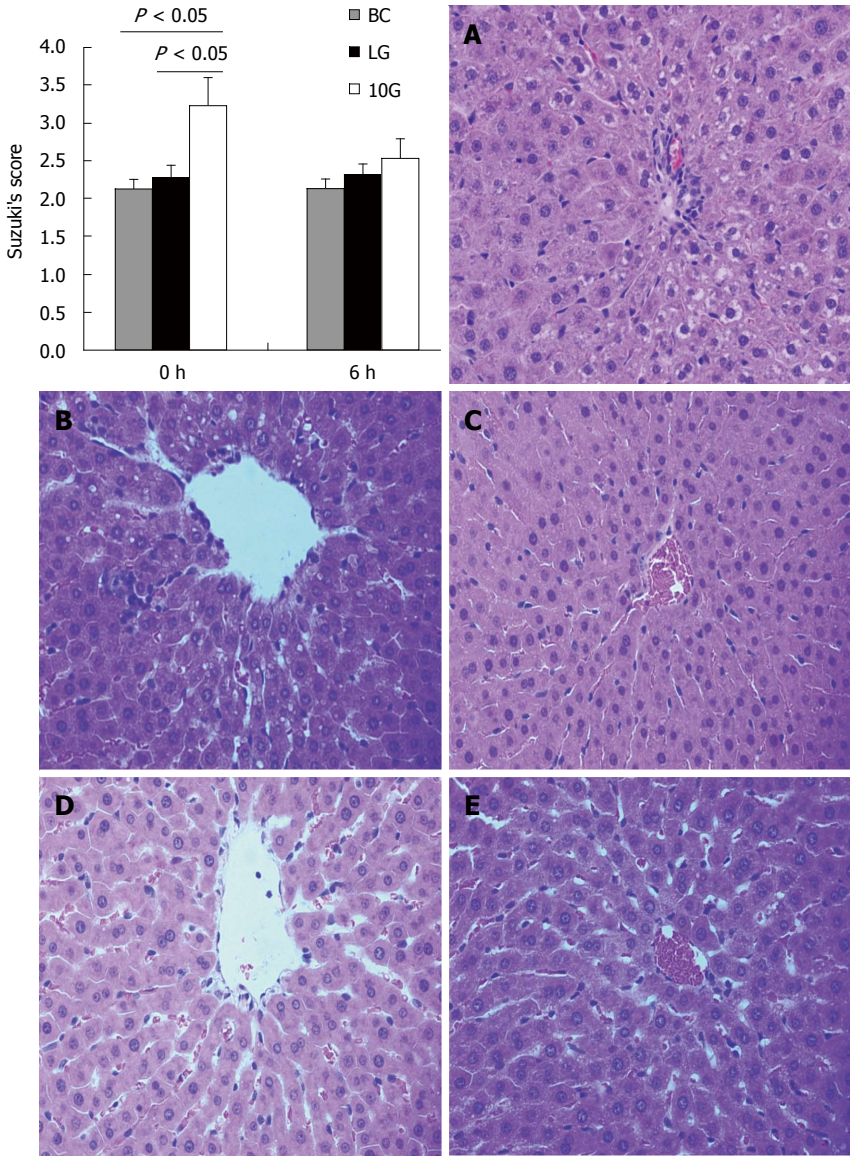

Figure 2 Pathological changes in the liver tissue at 0 and 6 h after +Gz exposures in the blank control group, low G preconditioning group and +10 Gz/5 min group. No significant injury was found in blank control group (A: Suzuki's score = 2.12 ± 0.13). At 0 h after exposure, there was disorderly hepatic sinus cord-like structure associated with hepatocyte edema in +10 Gz/5min (10G) group (B: Suzuki's score = 3.23 ± 0.37). In sharp contrast, there was regular liver lobule structure in low G preconditioning (LG) group (C: Suzuki's score = 2.28 ± 0.16). At 6 h after exposure, hepatocyte edema became lighter, and liver lobule structure had orderly arrangement in 10G group (E: Suzuki's score = 2.53 ± 0.25; $P < 0.01$). There was no significant difference between 0 and 6 h after exposure in LG group (C and D: Suzuki's score = 2.28 ± 0.16 *vs* 2.31 ± 0.14, $P < 0.01$). BC: Blank control.

and AST levels than those in 10G group at 0 h after exposure ($P < 0.05$). Group LG displayed normal ALT and AST levels at 6 h after exposure (Figure 1). These results demonstrate that low G preconditioning had a protective effect on liver function in rats after high G stress.

To analyze the extent of hepatocyte injury induced by high +Gz acceleration, liver sections were stained with HE at 0 and 6 h after exposure (Figure 2). No significant injury was found in the blank control group (Figure 2A; Suzuki's score = 2.12 ± 0.13). At 0 h after exposure, there was a disorderly hepatic sinus cord-like structure associated with hepatocyte edema in the 10GS group (Figure 2B; Suzuki's score = 3.23 ± 0.37). In sharp contrast, there was regular liver lobule structure in the LG group (Figure 2C; Suzuki's score = 2.28 ± 0.16). At 6 h after exposure, hepatocyte edema became lighter, and liver lobule structure was arranged in a more orderly manner in the 10GS group (Figure 2E; Suzuki's score = 2.53 ± 0.25; $P < 0.01$). There was no significant difference between 0 and 6 h after exposure in the LG group (Figure 2B and D; Suzuki's score = 2.28 ± 0.16 *vs* 2.31 ± 0.14; $P < 0.01$).

Low G preconditioning protected hepatocytes from damage of oxidative stress

To assess oxidative stress effect on hepatocytes induced by +Gz exposure, MDA and SOD were measured at 0 and 6 h after exposure. The MDA level in the BC group was 1.14 ± 0.25 nmol/mgprot. At 0

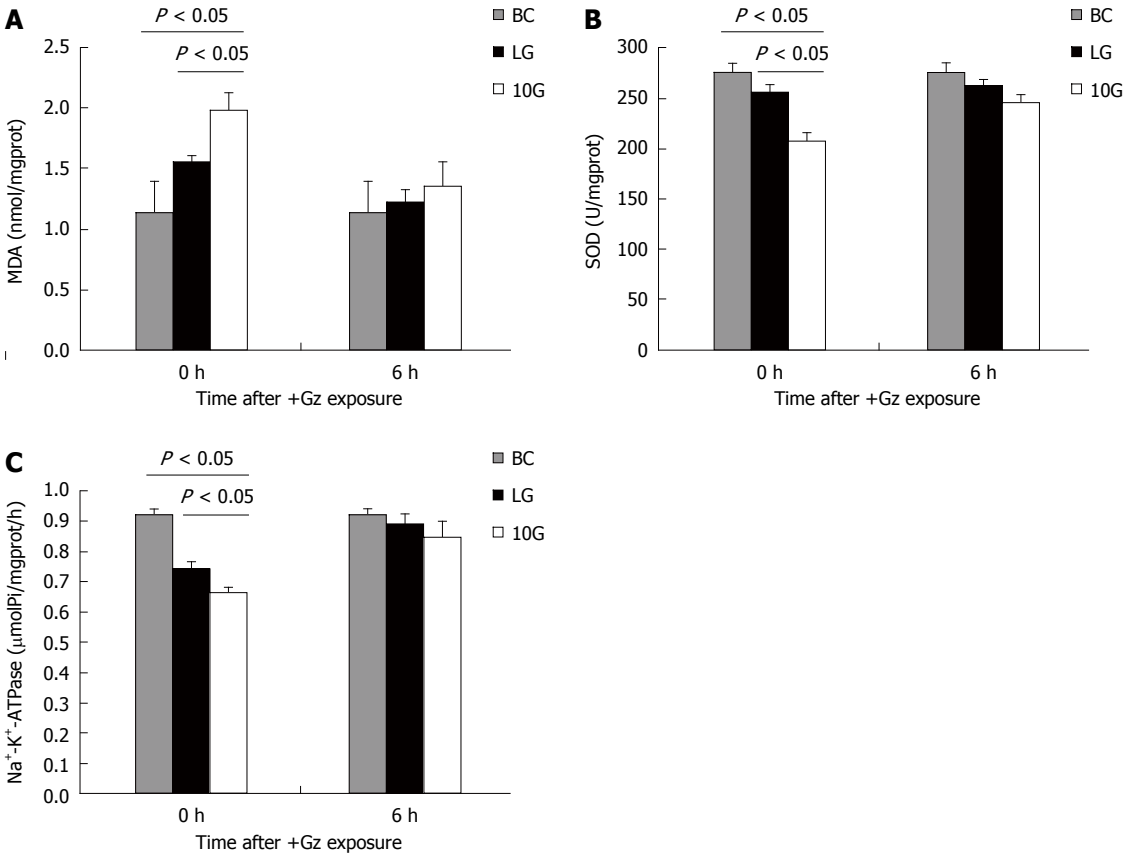

Figure 3 Comparison of the liver tissue malondialdehyde levels (A), the liver tissue superoxide dismutase levels (B) and the rat liver Na^+-K^+-ATPase activity (C) at 0 and 6 h after +Gz exposures in the blank control group, low G preconditioning group and +10 Gz/5min group. A: Malondialdehyde (MDA) level in liver tissue of group low G preconditioning (LG) or group +10 Gz/5 min (10G) was higher than that of blank control group at 0 h after exposure ($P < 0.05$, BC *vs* 10G). MDA level in liver tissue in LG group was lower than that in 10G group at 0 h after exposure ($P < 0.05$, LG *vs* 10G); B: Compared with blank control group, liver tissue superoxide dismutase (SOD) level in LG or 10G group reduced significantly at 0 h after exposure ($P < 0.05$, *vs* BC). Compared to 10G group, SOD level was higher in LG group at 0 h after exposure ($P < 0.05$, LG *vs* 10G); C: The Na^+-K^+-ATPase activity in LG group was higher than that in 10G group at 0 h after exposure ($P < 0.05$, LG *vs* 10G). BC: Blank control.

h after exposure, levels of MDA activity in the LG and 10G groups were 1.56 ± 0.05, 1.99 ± 0.14 nmol/mgprot, respectively, which were higher than that of the blank control group ($P < 0.05$). However, MDA level in liver tissue in the LG group was lower than that in the 10G group at 0 h after exposure. There was no significant difference between MDA level in liver tissue of LG and 10G groups at 6 h after exposure ($P > 0.05$, Figure 3A). Compared with the blank control group, liver tissue SOD level in the LG or 10G groups reduced significantly at 0 h after exposure (255.5 ± 8.15 U/mgprot *vs* 207.28 ± 8.36 U/mgprot, $P < 0.05$). Compared to the 10G group, SOD level was higher in the LG group at 0 h after exposure ($P < 0.05$). There was no significant difference between LG and 10G groups at 6 h after exposure ($P > 0.05$; Figure 3B). Therefore, low G preconditioning could reduce oxidative stress injury induced by high +Gz exposure in rats.

Low G preconditioning improved hepatic energy metabolism

The Na^+-K^+-ATPase activity in the liver tissue of the LG and 10G groups was decreased compared to that of the blank control group. The Na^+-K^+-ATPase activity in the LG group was higher than that in the 10G group at 0 h after exposure (0.742 ± 0.023 μmolPi/mgprot *vs* 0.666 ± 0.016 μmolPi/mgprot, $P < 0.05$). The difference between group LG and group 10G at 6 h after exposure was not significant ($P > 0.05$; Figure 3C).

DISCUSSION

With the progress of aviation science and technology, maneuverability of the fighter plane has been improved to a large extent. Modern aircrafts are capable of generating positive acceleration of +9 Gz range and +6 Gz/s rapid onset rate which is sustained for 15-45 s, which may exceed the human body's physical capabilities[26,27]. More attention should be paid to pilots' health and flight safety.

In clinical practice, IPC is a surgical tactic to increase tissue tolerance and reduce ischemia-reperfusion injury (I/R)[4,28]. Several studies support the safety and efficacy of IPC against liver IR[29,30]. During flight, direct action and stress response caused by repeated +Gz exposure may cause liver I/R injury. Several anti-G measures have been adopted

to reduce organism damage and build G tolerance, such as anti-G suit[31], anti-G straining maneuvers and positive pressure breathing[32], tilt-back seat[33], and comprehensive protection measures[34]. It is worth mentioning that centrifuge training is an important way of improving the strength and stamina of pilots[35]. Low G training might be a better way to help build endurance. In the field of gravitation physiology, other studies have shown that low G training could increase reserves of circulatory system and elevate the G tolerance of pilots[36]. In the preliminary experiments, it has been demonstrated that long-term exposure to the +4 G environment shows no harmful effects on liver morphology, which is the basis of selecting +4 G as the preconditioning condition in this study (data is not shown). The liver is a vital organ in the body. Liver injury after high +Gz exposure may be life threatening. Hence, we carried out the study to ascertain whether low G training could reduce liver injury induced by high +Gz exposure.

Both ALT and AST are markers of hepatic damage after +Gz exposure. Our results indicated that the rats in the LG group had lower serum ALT and AST level than those in the 10G group. Thereby, low Gz preconditioning was able to reduce liver injury induced by high +Gz exposure.

MDA is used widely as a sensitive marker of oxidative stress[37]. In our study, hepatic MDA in the LG group was lower compared to the 10G group. Furthermore, SOD activity was significantly decreased after +10 Gz/5 min exposure, indicating that liver tissue was vulnerable to oxidative damage. Our results showed that low G preconditioning may reduce the oxidative stress caused by high +Gz exposure and attenuate subsequent tissue damage.

Na^+-K^+-ATPase activity decreased significantly in liver tissue after +Gz exposures compared to the blank control group. Nevertheless, Na^+-K^+-ATPase activity in the LG group was significantly higher than that in the 10G group at 0 h after exposure, further supporting that low G preconditioning improved hepatic energy metabolism. Morphologically, our study of rat liver in the +Gz exposure model demonstrated that low +Gz preconditioning could reduce hepatocyte injury.

In summary, low G preconditioning is protective for liver injury induced by high +Gz exposure in rats, and the precise mechanism includes decrease of oxidative stress, preservation of hepatic energy metabolism and improvement of cellular morphology.

COMMENTS

Background

Many studies have shown that ischemic preconditioning can not only increase resistance to further ischemic injury but also reduce the degree of organ dysfunction or subsequent damage following ischemia reperfusion. In basic research, repeated +Gz exposure can transiently impair liver function and trigger pathologic changes. However, no experimental study has been carried out to investigate the possible protective effect of repeated low +Gz exposure on liver injury induced by high +Gz exposure in rats.

Research frontiers

Flight safety and the protective effect of low G preconditioning are the key research frontiers.

Innovations and breakthroughs

The authors established animal models to study the possible protective effect of lower +Gz exposures. The experimental results showed that low G preconditioning could decrease liver enzymes and malondialdehyde levels and improve superoxide dismutase and Na^+-K^+-ATPase activity.

Applications

Low G preconditioning shows a protective effect on liver injury induced by high +Gz exposure in rats.

Terminology

A low G preconditioning group was exposed to +4 Gz/5 min per day for 3 d before +10 Gz/5 min exposure.

Peer-review

This study result may provide an important method to combat liver injury induced by high +Gz exposure.

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