



## Research article

# Effect of different acupuncture sequences of *Huiyangjiuzhen* acupoints on blood glucose and hemorheology in the anesthetized rabbits

Peiying Pang<sup>a,1</sup>, Shen Zhuang<sup>a,1</sup>, Jiaqi Liu<sup>a</sup>, Li-jen Chang<sup>b,\*\*</sup>, Haoyan Yang<sup>a</sup>, Xiaoyu Fan<sup>a</sup>, Jie Mi<sup>c</sup>, Yongjun Zhang<sup>d</sup>, Yunpeng Fan<sup>a</sup>, Yingqiu Liu<sup>a</sup>, Weimin Zhang<sup>a</sup>, Wuren Ma<sup>a,c,\*</sup>

<sup>a</sup> College of Veterinary Medicine & Institute of Traditional Chinese Veterinary Medicine, Northwest A&F University, Yangling, 712100, PR China

<sup>b</sup> Department of Small Animal Clinical Sciences, Virginia Maryland College of Veterinary Medicine, Blacksburg, VA 24060, USA

<sup>c</sup> Xi'an Veterinary Teaching Hospital, Northwest A&F University, Xi'an, 710065, PR China

<sup>d</sup> Beijing Xiangyun Guanzhong Veterinary Hospital, Shunyi, 101318, PR China

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## ABSTRACT

**Background and objective:** Hemorheology and blood glucose are commonly used to estimate the risks of thrombosis and stress hyperglycemia after anaesthesia. The sequence of acupoint stimulation might influence the therapeutic effects of acupuncture. In the current study, we aimed at investigating the effect of different acupuncture sequences of “*Huiyangjiuzhen*” acupoints on the blood glucose and hemorheology in anesthetized rabbits.

**Methods:** Twenty-five rabbits were randomly divided into five groups, including the control group (CG), the positive-sequence group (PSG), the reverse-sequence group (RSG), the disorder-sequence group (DSG), and the random group (RG). Except for the CG and RG, the rabbits in other groups were acupunctured with different sequences of “*Huiyangjiuzhen*” acupoints when the rabbits were anesthetized. The acupoints in rabbits of the RG were chosen randomly. The levels of blood glucose and hemorheology indexes before and after anaesthesia was detected.

**Results:** In the PSG, Hgb 200/s, Mhb 30/s, Hqr 200/s, ERI, hematocrit and plasma viscosity levels were decreased, and the blood glucose level was not changed. In the DSG, the levels of Mhb 30/s and hematocrit were decreased, and the blood glucose was increased. In the CG, RSG and RG, no hemorheology indexes were changed and the blood glucose was increased.

**Conclusion:** “*Huiyangjiuzhen*” acupuncture could decrease the risks of post-operative thrombosis and stress hyperglycemia in anesthetized rabbits. This effectiveness depends on both acupuncture and acupuncture sequence at the “*Huiyangjiuzhen*” acupoints.

**Abbreviations:** EDI, Erythrocyte deformability index; EAI, erythrocyte aggregation index; ERI, erythrocyte rigidity index.

\* Corresponding author. College of Veterinary Medicine & Institute of Traditional Chinese Veterinary Medicine, Northwest A&F University, Yangling, 712100, PR China.

\*\* Corresponding author. Department of Small Animal Clinical Sciences, Virginia Maryland College of Veterinary Medicine, Blacksburg, VA, USA.

E-mail addresses: [ljchang@vt.edu](mailto:ljchang@vt.edu) (L.-j. Chang), [vetma@nwafu.edu.cn](mailto:vetma@nwafu.edu.cn) (W. Ma).

<sup>1</sup> Both authors contributed equally to this work.

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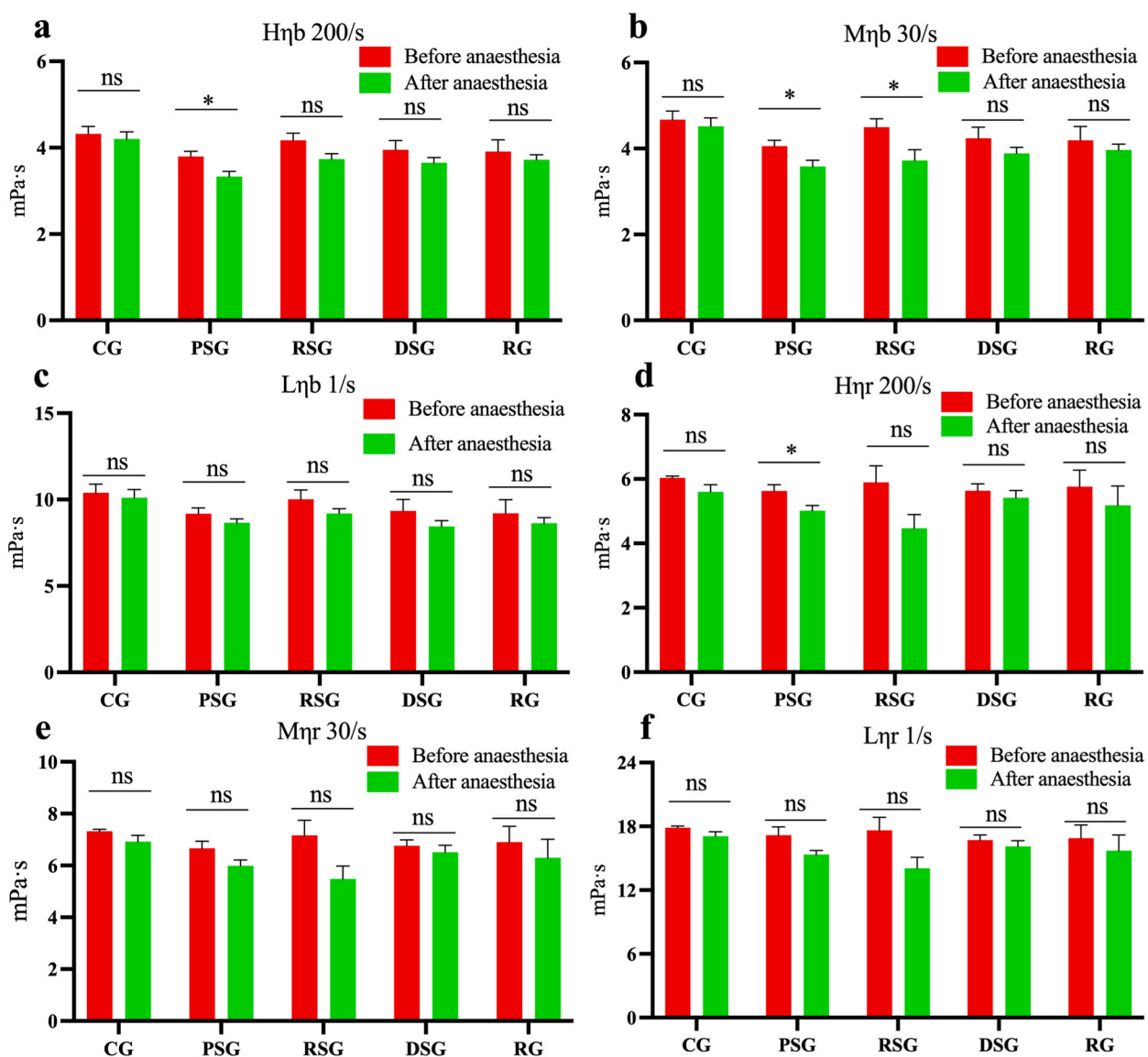
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## 1. Introduction

In the surgery, the general anaesthesia is a commonly used anesthetic method. It is beneficial for surgeon to finish the surgery successfully. However, adverse reactions after anaesthesia are inevitable. The adverse reactions are results from the pharmacological effects of the anesthetic, as well as could be caused by stress responses induced by anaesthesia [1,2].

Thrombosis is one of the severe complications in surgical patients, which might lead to the insufficient blood perfusion and oxygenation, in turn induce the dysfunction of organs and even death [3,4]. A study about emergency general surgery in America showed that the rate of thrombosis was approximately 2.5 % [5]. Lu et al. [6] compiled 8639 cases of noncompartmental knee arthroplasty and found that general anaesthesia has a higher incidence of deep vein thrombosis than other anesthetic techniques. Zhang et al. [7] analyzed the patients undergoing general anaesthesia from January 2021 to June 2022 in their hospital and found that the numbers of patient with and without postoperative thrombosis were 27 and 91, respectively. The occurrence of thrombosis is related to hyperviscosaemia, a clinicopathological syndrome characterized by abnormal parameters of hemorheology [8]. These parameters could be disturbed by the anaesthesia [4,9–11].

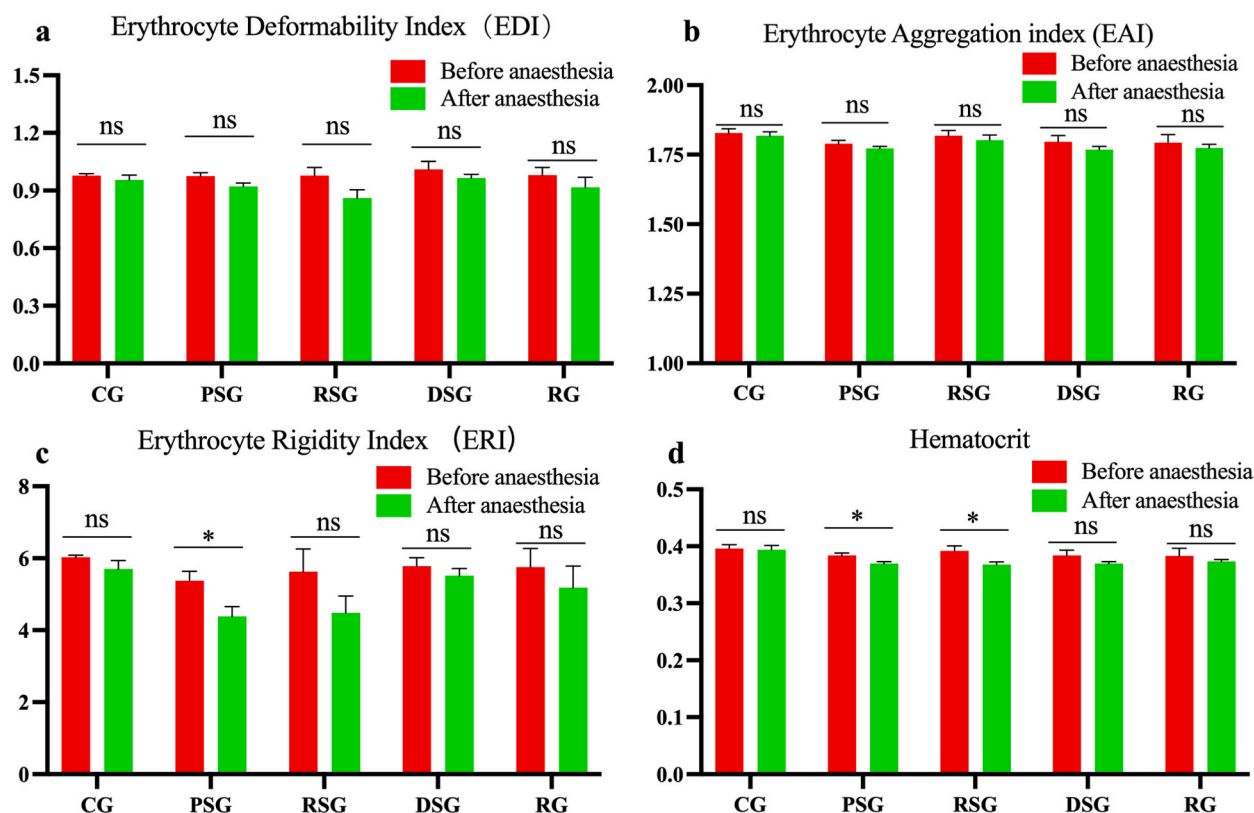


**Fig. 1.** The influence of different acupoint intervention sequence of “Huiyangjiuzhen” acupuncture on the whole blood viscosity. The levels of H<sub>nb</sub> 200/s before and after anaesthesia (a), the levels of M<sub>nb</sub> 30/s before and after anaesthesia (b), the levels of L<sub>nb</sub> 1/s before and after anaesthesia (c), The levels of H<sub>nr</sub> 200/s before and after anaesthesia (d), the levels of M<sub>nr</sub> 30/s before and after anaesthesia (e), the levels of L<sub>nr</sub> 1/s before and after anaesthesia (f). Each value is expressed as the mean ± SEM. The numerical value represents the difference between before and after anaesthesia in the same group.

Stress hyperglycemia is another severe complication during the anaesthesia. It not only contributes to the formation of thrombosis [12,13], but also an independent risk factor for postoperative morbidity and mortality [14,15]. The incidence of stress hyperglycemia is 20 %–38 % [16]. Sharma et al. [17] found that 65 % of patients had a postoperative blood glucose concentration which was higher than 7.8 mmol/L, and the ratio of the patients whose postoperative blood glucose concentration was higher than 10.0 mmol/L is 32.7 %. Umpierrez et al. [18] and Squires et al. [19] reports found that the patients without diabetes seem to have worse prognoses than diabetic patients.

Acupuncture has been widely used to treat many kinds of diseases as a result of its convincing therapeutic effects and rare adverse effects. It has been widely demonstrated that acupuncture assists anaesthesia, reduces anaesthesia complication, and promotes postoperative rehabilitation [20]. “*Huiyangjiuzhen*” acupuncture, which was first recorded in *ZhēnJiǔJùYīng* at Míng Dynasty, is an acupuncture technique that Ya-men (GV-15), Lao-gong (PC-8), San-yin-jiao (SP-6), Yong-quan (KID-1), Tai-xi (KID-3), Zhong-wan (CV-12), Huan-tiao (GB-30), Zu-san-li (ST-36) and He-gu (LI-4) were stimulated successively. Originally, it is used as a first-aid measure to save the patients with syncope, cold limbs and deep-sited pulse, and the syndrome of yang-depletion. The recent studies found that it could be used to treat the cerebral infarction [21], stroke hemiplegia [22], Alzheimer’s disease [23], cervical vertigo with vertebral artery [24], and so on. Our previous studies found that “*Huiyangjiuzhen*” acupuncture promoted postoperative recovery and hemorheology indexes in the anesthetized dogs [25].

According to Traditional Chinese Medicine theory, the acupuncture sequence might influence therapeutic effects. In recent years, some recent research have investigated this theory. Xu et al. [26] found that there were different therapeutic effects on blood viscosity of stroke patients in yin-syndrome between two different acupuncture sequence of “Twelve Jing points”. Jin et al. [27] found that different “host-guest” acupuncture sequence according to “Eight methods of the intelligent turtle” induced different tendencies on the levels of estradiol, progesterone, thrombosis B2 and 6-Keto-PGF1 $\alpha$  in the late pregnant rats. Thus, it is an interesting question whether changing the acupuncture sequence of “*Huiyangjiuzhen*” acupoints would influence their effects. Therefore, the purpose of the current study was to investigate the effects of “*Huiyangjiuzhen*” acupuncture on the levels of hemorheology indexes and the blood glucose and the role of acupuncture sequences of “*Huiyangjiuzhen*” acupoints in these effects.



**Fig. 2.** The influence of different acupoint intervention sequence of “*Huiyangjiuzhen*” acupuncture on the erythrocyte functions. The levels of EDI before and after anaesthesia (a), the levels of EAI before and after anaesthesia (b), the levels of ERI before and after anaesthesia (c), the levels of hematocrit before and after anaesthesia (d). Each value is expressed as the mean  $\pm$  SEM. The numerical value represents the difference between before and after anaesthesia in the same group.

## 2. Results

### 2.1. Effects of different acupuncture sequences of “Huiyangjiuzhen” on the levels of whole blood viscosity

Whole blood viscosity indexes, including high shear rate (H<sub>ηb</sub> 200/s), middle shear rate (M<sub>ηb</sub> 30/s) and low shear rate (L<sub>ηb</sub> 1/s), and whole blood reduction viscosity, including high shear rate (H<sub>ηr</sub> 200/s), middle shear rate (M<sub>ηr</sub> 30/s) and low shear rate (L<sub>ηr</sub> 1/s), were tested to reflect the general trends of hemorheology. In the PSG, the levels of H<sub>ηb</sub> 200/s, M<sub>ηb</sub> 30/s and H<sub>ηr</sub> 200/s after anaesthesia were lower than that before anaesthesia ( $P < 0.05$ , Fig. 1a, b & d), and there were no significant changes in the levels of L<sub>ηb</sub> 1/s, M<sub>ηr</sub> 30/s and L<sub>ηr</sub> 1/s between after and before anaesthesia ( $P > 0.05$ , Fig. 1c, e & f). In the RSG, the rabbits had a lower level of M<sub>ηb</sub> 30/s after anaesthesia compared with that before anaesthesia ( $P < 0.05$ , Fig. 1b), and the levels of other five indexes were not changed by anaesthesia ( $P > 0.05$ , Fig. 1a, c, d, e & f). In the CG, DSG and RG, the levels of these indexes were not changed significantly between after anaesthesia and before anaesthesia ( $P > 0.05$ , Fig. 1a-f).

### 2.2. Effects of different acupuncture sequences of “Huiyangjiuzhen” on the levels of erythrocyte-related indexes

Erythrocyte deformability index (EDI), erythrocyte aggregation index (EAI), erythrocyte rigidity index (ERI) and hematocrit are common indicators of erythrocyte to reflect the hemorheology. In the PSG, the results showed that there was a significant decrease in the levels of ERI and hematocrit between before and after anaesthesia ( $P < 0.05$ , Fig. 2c & d), and there were no significant changes in the levels of EDI and EAI ( $P > 0.05$ , Fig. 2a and b). In the RSG, the rabbits had a lower level of hematocrit after anaesthesia compared with that before anaesthesia ( $P < 0.05$ , Fig. 2d), and the levels of other indexes were not changed ( $P > 0.05$ , Fig. 2a-c). In the CG, DSG and RG, the levels of all indexes were not changed significantly ( $P > 0.05$ , Fig. 2a-d).

### 2.3. Effects of different acupuncture sequences of “Huiyangjiuzhen” on the levels of the plasma viscosity

The plasma viscosity is also an important factor that influences whole blood viscosity. In the PSG, the level of plasma viscosity index after anaesthesia was significantly lower than that before anaesthesia ( $P < 0.05$ , Fig. 3). However, there were no significant differences between before and after anaesthesia in the other four groups ( $P > 0.05$ , Fig. 3).

### 2.4. Effects of different acupuncture sequences of “Huiyangjiuzhen” on the levels of fibrinogen

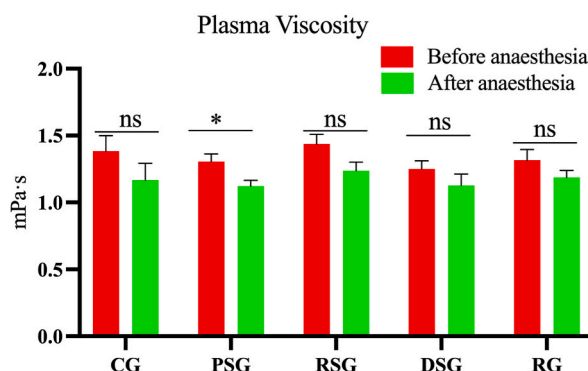
Fibrinogen is the most relevant macromolecule related to the plasma blood viscosity. The results showed that no changes were observed between before and after anaesthesia in all five groups ( $P > 0.05$ , Fig. 4).

### 2.5. Effects of different acupuncture sequences of “Huiyangjiuzhen” on the level of blood glucose

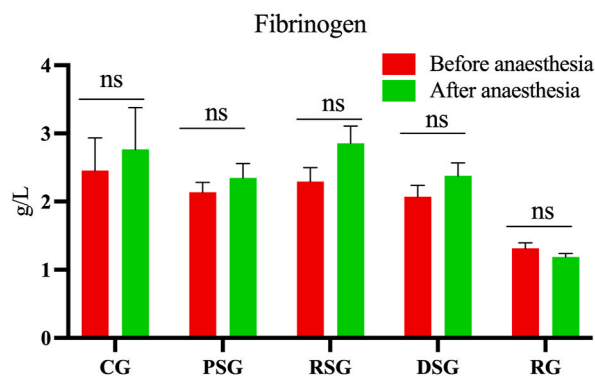
High blood glucose is not only a factor that contributes to the increase of blood viscosity, but also a risk factor for the life and health. The levels of blood glucose after anaesthesia were significantly higher than that before anaesthesia in the CG and the DSG ( $P < 0.05$ , Fig. 5), and there was an extremely significant difference in the blood glucose between before and after anaesthesia in the RSG ( $P < 0.01$ , Fig. 5). However, no significant increase was observed in the PSG ( $P > 0.05$ , Fig. 5).

## 3. Discussion

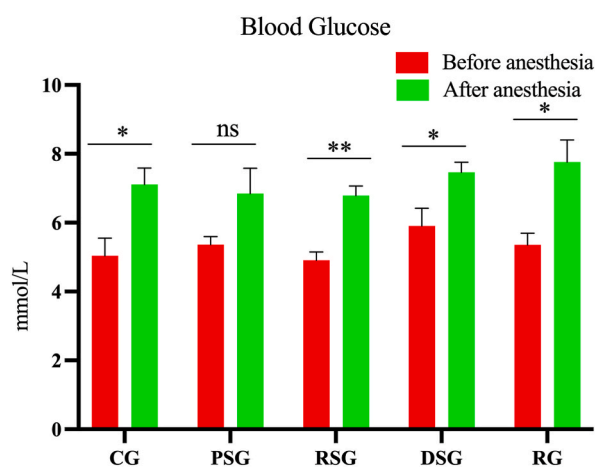
General anaesthesia is a common method which is widely used in surgery. It also brings the risks of thrombosis and stress



**Fig. 3.** The influence of different acupoint intervention sequence of “Huiyangjiuzhen” acupuncture on the levels of plasma viscosity before and after anaesthesia. Each value is expressed as the mean  $\pm$  SEM. The numerical value represents the difference between before and after anaesthesia in the same group.



**Fig. 4.** The influence of different acupoint intervention sequence of “*Huiyangjiuzhen*” acupuncture on the levels of fibrinogen before and after anaesthesia. Each value is expressed as the mean  $\pm$  SEM. The numerical value represents the difference between before and after anaesthesia in the same group.



**Fig. 5.** The influence of different acupoint intervention sequence of “*Huiyangjiuzhen*” acupuncture on the levels of blood glucose. Each value is expressed as the mean  $\pm$  SEM. The numerical value represents the difference between before and after anaesthesia in the same group.

hyperglycemia. Our previous study has found that “*Huiyangjiuzhen*” acupuncture improved the quality of recovery in dogs [25]. Its therapeutic effects and mechanisms still need more research.

Normal blood flow is a necessary precondition to prevent the formation of thrombosis. Anaesthesia could induce the abnormal blood viscosity to cause the decrease in the blood flow [4]. In the current study, rabbits treated with acupuncture by the positive sequence had a lower level of H<sub>1b</sub> 200/s, M<sub>1b</sub> 30/s and H<sub>1r</sub> 200/s after anaesthesia compared with that before anaesthesia, while the CG did not. These indicated that “*Huiyangjiuzhen*” acupuncture could decrease the whole blood viscosity and reduce the risk of postoperative thrombosis in the rabbits. However, these changes were not in complete accordance with our previous studies about the “*Huiyangjiuzhen*” acupuncture on dogs [25]. The rabbits had a higher risk of anesthetic-related death whose rate was 1.39 %, while this rate in dogs was 0.17 % according to a survey in UK [29]. One reasonable explanation is that the rabbits are timider and more sensitive than dogs and they exhibit a higher stressful response to the anaesthesia [30,31]. These indicated that the adverse responses in the anesthetized rabbits are more difficulties to be eliminated by the “*Huiyangjiuzhen*” acupuncture compared with these in the dogs. Because the rabbits are the third most popular pets [32], there would be clinical significance for the further research to verify this inference in the future.

It is widely believed that blood hematocrit, erythrocytes deformability, erythrocytes aggregation, plasma viscosity, and temperature are the mainly primary determinants of the blood rheological behavior [33]. In the current study, the positive sequence decreased the levels of ERI, hematocrit and plasma viscosity. The ERI is not only an indicator to reflex the erythrocytes’ deformability, but also a factor that whose increase could promote the incidence of thrombosis through elevating platelet margination [34]. Meanwhile, the change in high shear viscosity also reflects the erythrocytes deformability. Hematocrit is the proportion of erythrocyte concentration to the mean corpuscular volume. Its increase promotes the interaction between platelets and activated endothelium, which are beneficial for the formation of thrombosis [35,36]. Our results indicated that “*Huiyangjiuzhen*” acupuncture regulated the whole blood viscosity by improving erythrocytes deformability, decreasing hematocrit and plasma viscosity.

Stress induced by anaesthesia could lead to the activation of the sympathetic nerve, in turn induce the liver to release the stored

fibrinogen into the blood circulation system. Fibrinogen, a kind of high molecular weight protein in the plasma, plays a complex and important role in the formation of thrombosis. It converts into fibrin for blood clot formation when cleaved by thrombin [37] and is a major component which contributes to the plasma viscosity [38]. Meanwhile, it promotes the aggregate of erythrocytes, which induces an increase in the level of blood viscosity under low shear rate [39]. Our study showed that no significant changes were observed in the fibrinogen levels, indicating that “*Huiyangjiuzhen*” acupuncture ameliorated the blood viscosity not through regulating the levels of fibrinogen.

Stress hyperglycemia is an independent risk factor for postoperative complications and mortality. During the anaesthesia, stressful stimulation could increase sympathetic stimulation and subsequently rise the levels of cortisol, catecholamines, glucagon, and growth hormones, pro-inflammatory cytokines, and peripheral insulin resistance to induce the stress hyperglycemia [1,40]. In the current study, only positive sequence did not increase the level of postoperative blood glucose, indicating the rationality of acupuncture sequence of “*Huiyangjiuzhen*” acupoints. Meanwhile, positive sequence also decreased the rigidity of erythrocyte and the whole blood viscosity. Because hyperglycemia could activate the peroxidation of lipid and protein in erythrocyte, in turn induce a decrease in erythrocyte deformability [41], inhibition of increased blood glucose induced by “*Huiyangjiuzhen*” acupuncture might also prevent the increase of blood viscosity through preventing the loss of erythrocyte deformability.

Meanwhile, compared with the PSG, DSG and RSG, the RG did not induce any changes in the indexes of hemorheology and increased the levels of blood glucose, indicating that the combination of these nine acupoints in “*Huiyangjiuzhen*” acupuncture could prevent thrombosis and hyperglycemia induced by anaesthesia. Furthermore, the positive acupuncture sequence of “*Huiyangjiuzhen*” acupoints decreased the H<sub>9b</sub> 200/s, M<sub>9b</sub> 30/s, H<sub>9r</sub> 200/s, ERI, hematocrit and plasma viscosity levels, and inhibited the increase in the blood glucose. By contrast, the reverse acupuncture sequence of “*Huiyangjiuzhen*” acupoints only changed the levels of M<sub>9b</sub> 30/s and hematocrit and did not inhibit the increase in the blood glucose, while the disordered acupuncture sequence did not change the indexes of hemorheology and increase the blood glucose. These results reflected that the positive sequence had a better effect on the prevention of postoperative thrombosis and stress hyperglycemia than other sequence, indicating that the acupuncture sequence of “*Huiyangjiuzhen*” acupoints played a considerable role on the anti-thrombosis and hypoglycemic effects during the anaesthesia, which was the evidence that the effectiveness of “*Huiyangjiuzhen*” acupuncture depended on its sequence.

#### 4. Conclusion

In conclusion, “*Huiyangjiuzhen*” acupuncture has an ability to decrease the risks of postoperative thrombosis and hyperglycemia in anesthetized rabbits. This effectiveness is a result of the acupuncture at the “*Huiyangjiuzhen*” acupoints, as well as depends on the acupuncture sequence of these acupoints.

#### 5. Materials and methods

##### 5.1. Animals

All experimental procedures and animal care were approved by the Institutional Animal Care and Use Committee and Ethics Committee of Northwest A&F University (approval number: NWLA-2021-063). All animal experiments were handled in strict accordance with the guidelines for laboratory animals of Animal Care and Use Committee of Northwest A&F University.

Twenty-five female rabbits (3–4 months old) weighing  $2.14 \pm 0.27$  kg were selected. They were kept in a climate-controlled environment at  $20 \pm 1$  °C, a relative humidity of  $45 \pm 5$  % with 12 h light/dark cycles and allowed ad libitum to food and water. After two weeks of adaptive feeding, the experiment was started after ensuring that the rabbits were in healthy status.

##### 5.2. Treatment procedure and acupuncture

The rabbits were randomly divided into five groups: the control group (CG), the positive-sequence group (PSG), the reverse-sequence group (RSG), the disorder-sequence group (DSG), and the random group (RG).

After the adaptive feeding, the rabbits were weighed, and the indwelling venous catheter needle was placed in the marginal ear vein of each rabbit. For all treatment groups, the rabbits were initially anesthetized with propofol at a dose of 1 mg/kg which was injected through marginal ear vein injection. When the pain response and the eyelid reflex disappeared, anaesthesia was successful. Then the rabbits were fixed on the operating table and anaesthesia respirators were used for assisted respiration. During the treatment, manipulate lightly and softly to avoid the stress on the rabbits. Meanwhile, Isoflurane was inhaled through anaesthesia respirators to avoid the possible agitation of rabbits.

There was no acupuncture treatment in CG. The other four groups, the acupuncture was handled after anaesthesia. In the PSG, the acupuncture sequence was from Ya-men (GV-15), Lao-gong (PC-8), San-yin-jiao (SP-6), Yong-quan (KID-1), Tai-xi (KID-3), Zhong-wan (CV-12), Huan-tiao (GB-30), Zu-san-li (ST-36) and He-gu (LI-4), which were positive to the sequence recorded in the *ZhēnJiūJùYīng*. In the RSG, the acupuncture sequence was from He-gu (LI-4), Zu-san-li (ST-36), Huan-tiao (GB-30), Zhong-wan (CV-12), Tai-xi (KID-3), Yong-quan (KID-1), San-yin-jiao (SP-6), Lao-gong (PC-8), and Ya-men (GV-15), which were reversed to the sequence recorded in the *ZhēnJiūJùYīng*. In the DSG, the acupuncture sequence was disordered among these nine acupoints. In the RG, the acupoints to be stimulated were selected randomly. After inserted into these acupoints, the acupuncture needles were orderly scraped every 5 min until the rabbits stood up independently. The acupuncture method was the even reinforcing-reducing method. Locations of these acupoints and acupuncture methods were referred to “Xie’s Veterinary Acupuncture” [28].



### 5.3. Sample collection and data acquisition

Four mL blood was collected from the marginal ear vein before the rabbits were anesthetized and when they could stand up independently. The levels of blood glucose the hemorheology were tested immediately. The former were analyzed by automatic biochemical analyzer (IDEXX, Westbrook, Maine, USA), the latter were analyzed by the hemorheology analyzer (South990JK, Chongqing Nanfang numerical control equipment Co., Ltd) according to the manuals of instruments.

### 5.4. Statistical analysis

The experimental data were analyzed and processed by SPSS 22.0 software (SPSS Inc., Chicago, IL, USA), and the results were expressed as "mean  $\pm$  standard error of mean (mean  $\pm$  SEM)". The analysis of results was executed through independent sample *t*-test. When ( $P < 0.05$ ) was considered significant in statistics.

### CRediT authorship contribution statement

**Peiying Pang:** Investigation, Methodology, Writing – original draft. **Shen Zhuang:** Methodology, Writing – original draft, Writing – review & editing. **Jiaqi Liu:** Data curation, Formal analysis. **Li-jen Chang:** Methodology, Writing – review & editing. **Haoyan Yang:** Methodology, Investigation. **Xiaoyu Fan:** Investigation, Data curation. **Jie Mi:** Investigation, Data curation. **Yongjun Zhang:** Investigation. **Yunpeng Fan:** Supervision, Visualization. **Yingqiu Liu:** Resources, Software. **Weimin Zhang:** Conceptualization. **Wuren Ma:** Funding acquisition, Writing – review & editing, Conceptualization, Resources, Supervision.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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