

Effect of kallikrein on microcirculation of rats with pancreatic ischemia reperfusion injury (IRI)

Litao Liu¹, Jijun Yang^{2*}, Xinli Sun³, Xiaoshi Jin¹, Qian Sun¹,
Tianhao Xie¹, Yahan Liu¹ and Sining Ha¹

¹Department of General Surgery, Affiliated Hospital of Hebei University, Baoding, China

²Department of General Surgery, Anxin Hospital of Baoding City, Anxin, China

³Hebei University Medical College, Baoding, China

Abstract: The common pathway for pancreatitis onset is pancreatic ischemia reperfusion injury (IRI), which plays an especially significant role in the evolution process from acute edematous pancreatitis (AP) towards severe acute pancreatitis (SAP). This study explored the effect of Kallikrein (PK) on pancreatic ischemia reperfusion injury (IRI). Male Wistar rats were taken as study objects, and a SAP-IRI combined model was established through retrograde infusion of 5% sodium taurocholate in biliopancreatic duct combining 30 min splenic artery clipping; drug intervention was carried out by pumping PK into rat caudal vein. Pancreatic microcirculation blood flow, pancreatic micro vascular permeability, hemorheological change and levels of adherence factors CD18 and CD54 were determined respectively. PK can obviously improve pancreatic microcirculation blood flow volume and velocity of IRI rats and expand arteriole; expand diameter of pancreatic blood capillary so that perfusion state tends to be stable; decrease pancreatic micro vascular permeability, reduce rat whole blood viscosity, erythrocyte deformation index and rigidity index; SAP-IRI combination reduces expression levels of white cell adhesion factor CD18 and vascular endothelial cell adhesion cell CD54 in rats. In conclusion, PK is an effective method of improving SAP pancreatic IRI microcirculation.

Keywords: Kallikrein (PK), severe acute pancreatitis (SAP), ischemia reperfusion injury (IRI), pancreatic microcirculation

INTRODUCTION

Severe acute pancreatitis (SAP) is an extremely dangerous clinical emergency with a high fatality rate. Multiple factors have impacted pancreatic issues, inducing multiple inflammation-mediated waterfall-like cascade reactions and cytokine stress-induced disorders and causing systemic inflammatory response syndrome (SIRS) so as to break the balance with antagonistic compensatory anti-inflammatory response syndrome (CARS) and directly give rise to multiple organ failure (MODS) (Gukovsky *et al.*, 2012; Xu *et al.*, 2014; Li *et al.*, 2015).

The common pathway for pancreatitis onset is pancreatic ischemia reperfusion injury (IRI), which plays an especially significant role in evolution process from acute edematous pancreatitis (AP) towards severe acute pancreatitis (SAP). As antigen-activated white cells, damaged pancreatic tissues participate in generation and release of cytokines, thus causing waterfall-like cascade inflammatory reactions to the body, pancreatic microcirculation disorder and pancreatic tissue edema and exosmosis of pancreatic juice in a large quantity. Concrete manifestations are reduced pancreatic micro blood flow, increased micro vascular permeability, hemorheological change, infiltration of pancreatic tissue inflammatory

cells, etc. Preventing and mitigating SAP-IRI combination is of great importance to relieving necrosis of pancreatic tissues and preventing SIRS and MODS (Dabrowski *et al.*, 2014; Kang *et al.*, 2014; Xing *et al.*, 2015).

As a kind of activation factor, Kallikrein (PK) consists of 18 amino acids and 4 saccharides. It gradually degrades kininogen in human body so as to release a large quantity of plasmakinin which exerts an effect on expanding micro-vessel and blood capillary, meanwhile, this expands convergence between capillary networks, obviously improves microvascular permeability and increases blood flow volume. Besides, PK can inhibit conversion between angiotensins and relieve microvascular contraction effect; it causes reduced generation of capillary endothelial cell PGI₂ by improving blood coagulation time and inhibiting calcium ions so as to reduce platelet aggregation. In this way, PK can make plasminogen be activated into plasmin, reduce fibrous protein content and prevent microvascular thrombosis; moreover, it can regulate inflammatory reaction process of the body. As a vascular activation factor, PK has multiple vascular activities and has an obvious effect on improving microcirculation of limb peripheral tissues and eye ground, but its effect on pancreatic microcirculation has not been reported yet (Abdallah *et al.*, 2010; Nakamura *et al.*, 2011; Webb, 2011). By establishing the rat IRI model, this study implemented the intervention using the rat caudal venous

*Corresponding author: e-mail: yonglicn@yeah.net

pumping method so as to explore into the effect of PK on pancreatic microcirculation of IRI rats.

MATERIALS AND METHODS

Animals

Male Wistar rats of clean grade (3-4 months), weights ranging from 300 to 350g, were provided by Beijing Long'an Experimental Animal Breeding Center, and they could freely drink water and feed themselves. All experimental animals conformed to management standard of medical ethics. This study was performed in accordance with the *Guide for the Care and Use of Laboratory Animals of the National Institutes of Health* (Bethesda, MD, USA, Eighth Edition, 2010). The animal use protocol has been approved by the Institutional Animal Care and Use Committee (IACUC) of Affiliated Hospital of Hebei University.

Animal grouping

90 rats were randomly divided into 9 groups (A-G) with 10 rats in each group, including sham-operation group, IRI group and PK intervention group. All rats were executed 12h after modeling and drug taking. Rat pancreatic microcirculation blood flow and pancreatic microvascular permeability were detected in A-C groups; rat hemorheological change was measured in D-F groups; the expression levels of rat white cell adhesion factor CD18 and vascular endothelial cell adhesion cell CD54 were determined in H-G groups.

Establishment of experimental model

Establishment of IRI group model: intraperitoneal injection of 30mg/kg 3% pentobarbital sodium was implemented firstly, rats were fixed on operation panel after successful anesthesia, abdominal hairs were cut, and conventional sterilization and draping were conducted. Scalpel entered the abdomen layer by layer from 3cm median incision at the upper abdomen, dissociated in splenic artery, immediately clipped for 30 min and then loosened. The abdomen was temporarily closed after local ischemia at tail of pancreatic tissues and restoration of celiac viscera. The rats were put under fasting and 4h water deprivation treatments before modeling.

Establishment of PK intervention group model: after IRI rate modeling, caudal veins were soaked in 40-45°C warm water for 30s, No.5 needle was selected to be inserted at the position 2 cm from tail tip at 30° angle, and drug was given immediately after blood return with a reference to drug instructions. PK was dissolved in 5 ml NS by 2U/ea, and drug was continuously pumped into caudal veins for continuous 12 h. Establishment of sham-operation group model: pancreatic tissues were physically flapped after laparotomy and the action was repeated for 3 times.

Effect of PK on rat pancreatic microcirculation blood flow

Conventional laparotomy was implemented for rats in the groups after modeling and drug administration, Preflux 4001 two-pathway laser Doppler flowmeter was used to determine various indexes of pancreatic microcirculation blood flow, probe caliber was 0.25 mm and wavelength was 780 nm. The probe slightly contacted surface of pancreatic tissues, determination was conducted at pancreas body and pancreas tail, respectively, hematoma tissues and pancreatic aorta were avoided, and arithmetic mean value was taken as the final result. Concrete detection indexes included pancreatic microvascular blood flow volume, blood flow velocity, arteriole, venule diameter, blood capillary diameter, density, perfusion, etc.

Effect of PK on rat pancreatic microvascular permeability

Improved methods from Keiji et al. were used for detection. After detection of pancreatic microcirculation blood flow in rats, 1% Evan's blue dye was injected in femoral vein, dosage was 2ml/kg, pancreatic tissues were taken out after 30 min, after weighing of wet weight, 150 mg tissues were placed in a 5ml test tube and formamide was added according to 0.03/mg. 1ml leach liquor was taken after 24h, spectrophotometer was used to detect concentration of Evan's blue dye, and leakage of Evan's blue dye was successively calculated; residual pancreatic tissues were cut into pieces and placed in 160°C electrically heated drying oven. Weighing was implemented 24h later and the weight of 150mg pancreatic tissues was calculated according to ratio of wet weight to dry weight; microvascular permeability was finally expressed by Evan's blue dye leakage/dry weight of pancreatic tissues (ug/g).

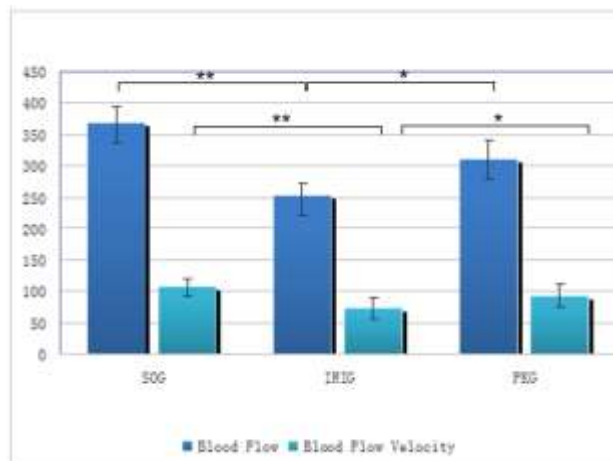


Fig. 1: Compared with the sham-operation group, the blood flow and blood flow velocity in IRI group decreased with significant intergroup difference, ** $P < 0.01$. Compared with the IRI group, blood flow and blood flow velocity of the PK treatment group increased significantly, * $P < 0.05$. SOG: sham-operation group, IRIg: IRI group, PKg: PK intervention group

Effect of PK on rat hemorheological change

BV-100 hemorheology instrument was used to detect rat hemorheological change. Conventional laparotomy was implemented 12 h after rat modeling in the groups. 5 ml blood was collected from abdominal aorta and placed in anticoagulant tube, it was shaken well and placed in BV-100 hemorheology tester and sent for detection. Detection indexes included whole blood viscosity, plasma viscosity, red cell aggregation index and red cell deformability index.

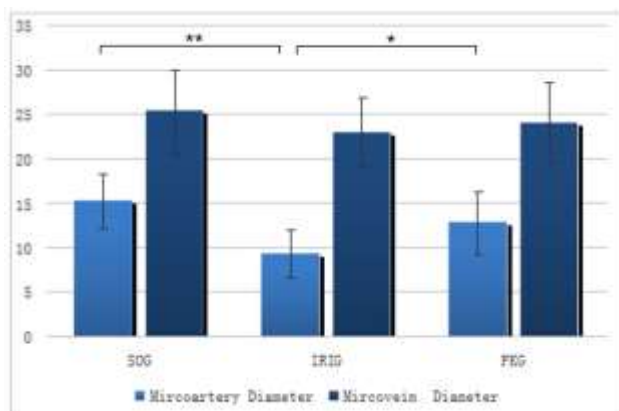


Fig. 2: Compared with the sham-operation group, the microarteriole diameter of the IRI group decreased significantly, the difference between the two groups, $**P<0.01$. Compared with the IRI group, the arteriole diameter of the PK treatment group increased significantly, the difference between the two groups, $*P<0.05$. Compared with the sham-operation group, the venule diameter of the IRI group decreased not significantly, the difference between the two groups, $P>0.05$. Compared with the IRI group, the venule diameter of the PK treatment group increased not significantly, $P>0.05$. SOG: sham-operation group, IRIG: IRI group, PKG: PK intervention group.

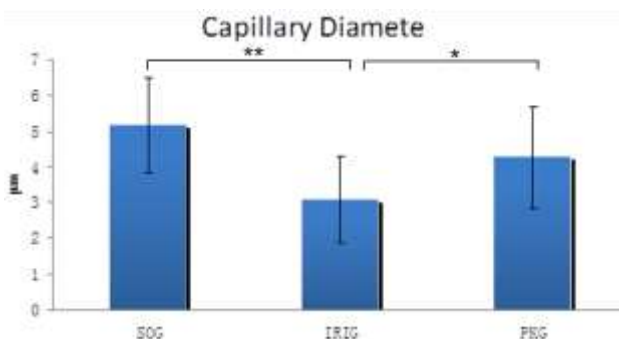


Fig. 3: Compared with the sham-operation group, the capillary diameter of the IRI group decreased significantly, the difference between the two groups was significant, $**P<0.05$. Compared with the IRI group, the capillary diameter of the PK treatment group increased significantly, $*P<0.05$. SOG: sham-operation group, IRIG: IRI group, PKG: PK intervention group.

Effect of PK on expression levels of rat white cell adhesion factor CD18 and vascular endothelial cell adhesion factor CD54

Conventional laparotomy was implemented 12 h after rat modeling in the groups. 5ml blood was collected from abdominal aorta, and the expression levels of CD18 and CD54 were detected through flow cytometry.

STATISTICAL ANALYSIS

SAS 8.0 software package was used in the statistical analysis, the results in the groups were expressed by $\bar{x}\pm s$, variance analysis was adopted for intergroup comparison of significant difference and $P<0.05$ meant that the difference had statistical significance.

RESULTS

Effect of PK on pancreatic microcirculation blood flow volume and velocity in IRI rats

Compared with the sham-operation group, pancreatic microcirculation blood flow volume decreased from 366.24 ± 29.15 to 251.36 ± 20.66 and pancreatic microcirculation blood flow velocity lowered from 105.64 ± 14.19 to 72.38 ± 16.74 in IRI group 12 h later after modeling. In PK treatment group, pancreatic microcirculation blood flow volume rose from 251.36 ± 20.66 to 309.47 ± 31.25 and flow velocity rose from 72.38 ± 16.74 to 92.44 ± 18.38 , so there were intergroup differences ($P<0.05$) (fig. 1).

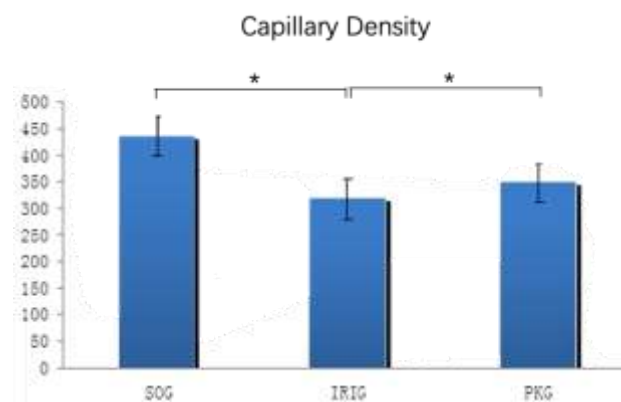


Fig. 4: Compared with the sham-operation group, the capillary density of the IRI group decreased significantly, the difference between the two groups was significant, $*P<0.05$. Compared with the IRI group, the capillary density of the PK treatment group increased significantly, $*P<0.05$. SOG: sham-operation group, IRIG: IRI group, PKG: PK intervention group.

Effect of PK on pancreatic arteriole and venule diameter in IRI rats

Compared with the blank control group, pancreatic arteriole diameter decreased from 15.22 ± 3.14 μm to 9.26 ± 2.66 μm 12 h after modeling in IRI group, and there

was intergroup difference ($P < 0.01$); pancreatic venule diameter decreased from $25.35 \pm 4.67 \mu\text{m}$ to $22.96 \pm 3.88 \mu\text{m}$ without intergroup difference ($P > 0.05$). 12h after modeling in PK treatment group, pancreatic arteriole diameter rose from $9.26 \pm 2.66 \mu\text{m}$ to $12.78 \pm 3.65 \mu\text{m}$ with intergroup difference ($P < 0.05$); pancreatic venule diameter rose from $22.96 \pm 3.88 \mu\text{m}$ to $24.02 \pm 4.53 \mu\text{m}$ without intergroup difference ($P > 0.05$) (fig. 2).

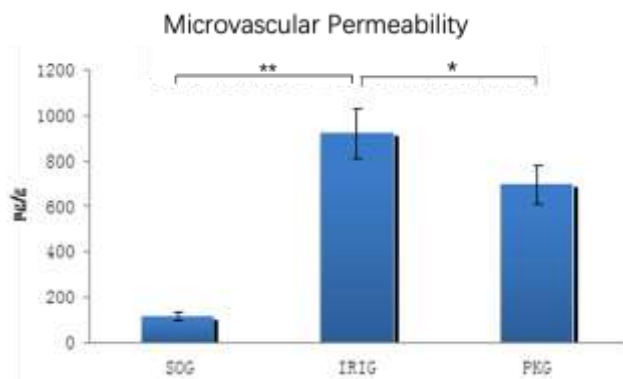


Fig. 5: Compared with the sham-operation group, the pancreatic microvascular permeability of the IRI group increased significantly, the difference between the two groups was significant, $**P < 0.01$. Compared with the IRI group, the pancreatic microvascular permeability of the PK treatment group significantly decreased, $*P < 0.05$. SOG: sham-operation group, IRIG: IRI group, PKG: PK intervention group.

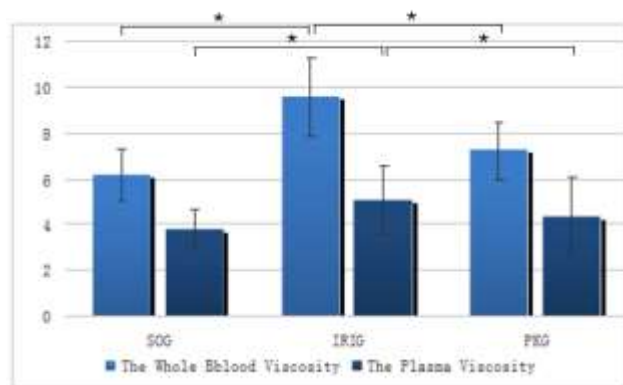


Fig. 6: Compared with the sham-operation group, the whole blood and plasma viscosity of the IRI group increased significantly, the difference between the two groups was significant, $*P < 0.05$. Compared with the IRI group, the whole blood and plasma viscosity of the PK treatment group decreased significantly, $*P < 0.05$. SOG: sham-operation group, IRIG: IRI group, PKG: PK intervention group.

Effect of PK on pancreatic blood capillary diameter, density and perfusion in IRI rats

Compared with the blank control group, in IRI group 12h after modeling, pancreatic blood capillaries became thin, decreasing from $5.15 \pm 1.34 \mu\text{m}$ to $3.09 \pm 1.23 \mu\text{m}$ and blood

capillary density reduced from 435.16 ± 35.89 to 317.36 ± 39.34 indicating significant differences between two groups ($P < 0.01$); blood capillary perfusion form changed from stable state to intermittent irregular state. 12h after modeling in PK treatment group, pancreatic blood capillary diameter became thickened, increasing from $3.09 \pm 1.23 \mu\text{m}$ to $4.27 \pm 1.43 \mu\text{m}$ and blood capillary density increased from 317.36 ± 39.34 to 347.66 ± 35.56 ($P < 0.05$); although blood capillary perfusion form turned good somehow, it's still under intermittent unstable state (figs. 3, 4).

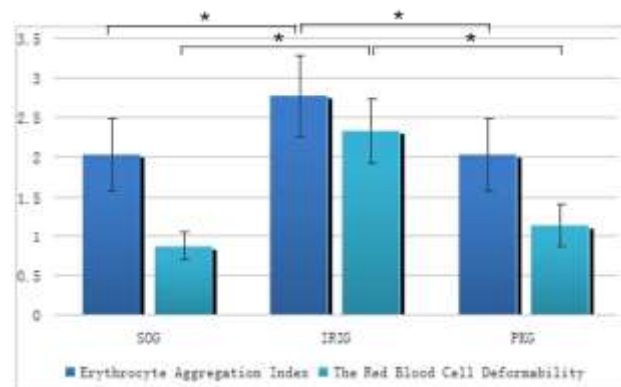


Fig. 7: Compared with the sham-operation group, the erythrocyte aggregation index and red blood cell deformability of the IRI group increased significantly, the difference between the two groups was significant, $*P < 0.05$. Compared with the IRI group, the erythrocyte aggregation index and red blood cell deformability of the PK treatment group decreased significantly, $*P < 0.05$. SOG: sham-operation group, IRIG: IRI group, PKG: PK intervention group.

Effect of PK on pancreatic microvascular permeability in IRI rats

Compared with the sham-operation group, in IRI group 12h after modeling, pancreatic microvascular permeability was obviously enhanced, rising rapidly from $115.48 \pm 16.46 \mu\text{g/g}$ to $923.41 \pm 108.31 \mu\text{g/g}$ with significant intergroup difference ($P < 0.01$). Compared with the IRI group, pancreatic microvascular permeability in PK treatment group obviously decreased ($695.45 \pm 86.39 \mu\text{g/g}$), showing statistical significance of the intergroup difference ($P < 0.05$) (fig. 5).

Effect of PK on blood viscosity in SAP-RI combined rats

Compared with the sham-operation group, both whole blood viscosity and plasma viscosity obviously increased in IRI group 12h after rat modeling from 6.14 ± 1.14 and 3.78 ± 0.85 to 9.56 ± 1.68 and 5.05 ± 1.52 respectively ($P < 0.05$). Whole blood viscosity and plasma viscosity decreased from 9.56 ± 1.68 and 5.05 ± 1.52 to 7.23 ± 1.25 and 4.34 ± 1.73 respectively 12h after modeling in PK treatment group, so intergroup differences had statistical significances ($P < 0.05$) (fig. 6).

Effect of PK on red cell aggregation and deformability in SAP-IRI combined rats

Compared with the sham-operation group, red cell aggregation index and equation k value of erythrocyte sedimentation rate increased in IRI group 12h after rat modeling from 2.03 ± 0.45 and 3.88 ± 1.23 to 2.77 ± 0.51 and 6.67 ± 1.68 respectively with intergroup differences showing statistical significance ($P < 0.05$), and Those of PK treatment group decreased from 2.77 ± 0.51 and 6.67 ± 1.68 to 2.03 ± 0.76 and 4.62 ± 1.02 respectively, and intergroup differences showed statistical significance ($P < 0.05$).

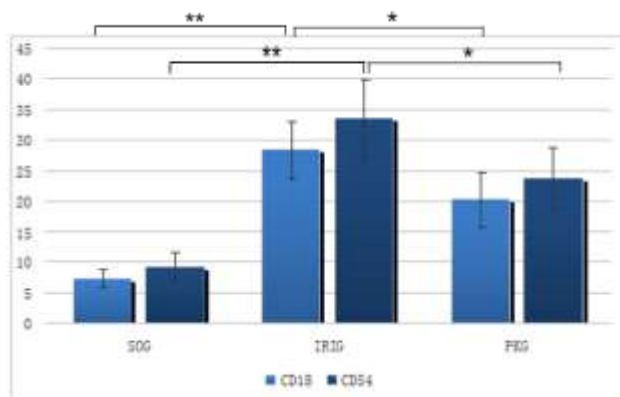


Fig. 8: Compared with the sham-operation group, CD18 and CD54 expression of the IRI group increased significantly, the difference between the two groups was significant, $**P < 0.01$. Compared with the IRI group, CD18 and CD54 expression the PK treatment group decreased significantly, $*P < 0.05$. SOG: sham-operation group, IRIG: IRI group, PKG: PK intervention group.

Compared with the sham-operation group, red cell deformability index and red cell rigidity index in IRI group 12h after rat modeling increased from 0.87 ± 0.17 and 2.35 ± 0.46 to 2.33 ± 0.41 and 4.92 ± 0.66 respectively with intergroup comparison showing significant differences ($P < 0.05$), and those in PK treatment group decreased from 2.33 ± 0.41 and 4.92 ± 0.66 to 1.13 ± 0.27 and 3.58 ± 0.87 respectively and intergroup comparison presented significant differences ($P < 0.05$) (fig. 7).

Effect of PK on CD18 and CD54 expression levels in IRI rat serums

Compared with the sham-operation group, CD18 and CD54 expression levels in rat serums in IRI group 12h after rat modeling increased from 7.26 ± 1.47 and 9.15 ± 2.35 to 28.33 ± 4.67 and 33.38 ± 6.55 respectively ($P < 0.01$), and those in PK treatment group decreased from 28.33 ± 4.67 and 33.38 ± 6.55 to 20.23 ± 4.57 and 23.67 ± 5.11 respectively, and intergroup differences had statistical significances ($P < 0.05$) (fig. 8).

DISCUSSION

In pancreatic ischemia reperfusion injury, microcirculatory disturbance is generally manifested at three aspects: microvascular blood flow volume and velocity, arteriole and venule diameters and change of blood capillary diameter, density and perfusion state (Cai *et al.*, 2012; Li *et al.*, 2012; Köksoy *et al.*, 2013; Sha *et al.*, 2013). It's verified in this experiment that 12h after modeling of pancreatic ischemia reperfusion injury rats, pancreatic blood flow volume and flow velocity decreased, pancreatic arteriole obviously became thin, pancreatic blood capillary diameter decreased with reduction of distribution density, and perfusion state became intermittent unstable, meaning that blood supply to pancreatic tissues reduced and pancreatic tissues would easily suffer from avascular necrosis. It's verified in the experiment that blood flow volume and velocity after PK intervention gradually increased, arteriole was thickened, pancreatic blood capillary diameter increased with rising distribution density, and perfusion state tended to be stable, indicating that it could improve pancreatic microcirculation blood flow and contributed to avascular necrosis of pancreatic tissues.

In pancreatic ischemia reperfusion injury, multiple inflammatory media in the whole body were excited, so were waterfall-like reactions. Connection between endothelial cells was separated, capillary endothelial void was enlarged, microvascular permeability was strengthened, a large quantity of body fluid and protein molecules flew out, pancreatic and peripheral edema and exudation rapidly appeared, so the disease was aggravated rapidly (Wang *et al.*, 2014; Wu and Liao, 2016).

Through a verification, 12 h after modeling, pancreatic microvascular leakage of rats obviously increased at a high speed with large increasing amplitude. PK obviously reduced pancreatic microvascular permeability and improved pancreatic edema and peripheral exudation in SAP, possibly because PK could protect capillary endothelium and keep structural completeness of endothelial cells.

In pancreatic ischemia reperfusion injury, microcirculation hemorheological change includes three aspects—increasing blood viscosity, strengthened red cell aggregation and weakened red cell deformability. Hemorheological change interacts with insufficient blood supply to pancreatic microcirculation and strengthens microvascular permeability, which will continuously aggravate the disease and gradually form a vicious circle (Kinnala *et al.*, 2001; Vournar and Menger, 2003). It's verified in the experiment that 12 h after model establishment, blood viscosity and red cell aggregation were strengthened while red cell deformability was weakened. But the situation in PK treatment group was

rightly on the contrary, and this would contribute to improvement of blood supply to pancreatic microcirculation and increase of blood flow volume. Moreover, this was helpful to improve pancreatic blood and oxygen supply, relieve necrosis of pancreatic tissues and prevent microvascular thrombosis.

In pancreatic IRI, white cells interact with vascular endothelial cells under the effect of cytokines. This process is mainly about interaction between CD18 and CD54. This interaction between white cells and vascular endothelial cells aggravated, a large quantity of activated white cells directly cause mechanical capillary blocking, strengthened venule resistance and exacerbated microcirculation disturbance (Kiris *et al.*, 2009). It's verified in this experiment that both CD18 and CD54 expression levels increased in IRI rats, accompanied by enhanced adhesion function between vascular endothelia cells and neutrophil granulocytes. After PK intervention, CD18 and CD54 expression levels obviously decreased, which would exert great effects on mitigating pancreatic tissue inflammation degree of rats and relieving local and systemic inflammatory response syndrome. In conclusion, as a drug with multiple vascular activities, Kallikrein has an obvious effect on improving microcirculation of pancreatic IRI rats.

REFERENCES

Abdallah RT, Keum JS, El-Shewy HM, Lee MH, Wang B, Gooz M, Luttrell DK, Luttrell LM and Jaffa AA (2010). Plasma kallikrein promotes epidermal growth factor receptor transactivation and signaling in vascular smooth muscle through direct activation of protease-activated receptors. *J. Biol. Chem.*, **285**(45): 206-215.

Cai Z, Knorr D and Smetanska I (2012). Enhanced anthocyanins and resveratrol production in *Vitis vinifera* cell suspension culture by indanoyl-isoleucine, N-linolenoyl-L-glutamine and insect saliva. *Enzyme Microb. Technol.*, **50**(1): 29-34.

Dabrowski A, Osada J, Dabrowska MI, Wereszczynska-Siemiakowska U and Siemiakowski A (2014). Increased expression of the intercellular adhesion molecule-1 (ICAM-1) on peripheral blood neutrophils in acute pancreatitis. *Adv. Med. Sci.*, **59**(1): 102-107.

Gukovsky I, Pandol SJ, Mareninova OA, Shalbueva N, Jia W and Gukovskaya AS (2012). Impaired autophagy and organellar dysfunction in pancreatitis. *J. Gastroenterol. Hepatol.*, **27**(Suppl 2): 27-32.

Kang R, Lotze MT, Zeh HJ, Billiar TR and Tang D (2014). Cell death and DAMPs in acute pancreatitis. *Mol. Med.*, **20**(1): 466-477.

Kinnala PJ, Kuttala KT, Gronroos JM, Havia TV, Nevalainen TJ and Niinikoski JH (2001). Pancreatic tissue perfusion in experimental acute pancreatitis. *Eur. J. Surg.*, **16**(9): 689-694.

Kiris I, Tekin I, Yilmaz N, Sutcu R, Karahan N and Ocal A (2009). Iloprost down regulates expression of adhesion molecules and reduces renal injury induced by abdominal aortic ischemia-reperfusion. *Ann. Vasc. Surg.*, **23**(2): 212-223.

Köksoy FN, Yankol Y, Şen Oran E, Ozkan Gürdal S, Yüksel M, Akyildiz İğdem A, Yildirim Yazgan N and Soybir GR (2013). Preventive effects of enoxaparin and hesperidin in cerulein-induced acute pancreatitis in rats. *Turk. J. Gastroenterol.*, **24**(6): 495-501.

Li S, Chen X, Wu T, Zhang M, Zhang X and Ji Z (2012). Role of heparin on serum VEGF levels and local VEGF contents in reducing the severity of experimental severe acute pancreatitis in rats. *Scand. J. Gastroenterol.*, **47**(2): 237-244.

Li H, Liu J, Wang W, Zhang Z, Li D, Lin K, Chen Z and Lin W (2015). Matrix Metalloproteinase P and Vasodilator-Stimulated Phosphoprotein Related to Acute Kidney Injury in Severe Acute Pancreatitis Rats. *Dig. Dis. Sci.*, **60**(12): 3647-3655.

Nakamura S, Morimoto N, Tsuruma K, Izuta H, Yasuda Y, Kato N, Ikeda T, Shimazawa M and Hara H (2011). Tissue kallikrein inhibits retinal neovascularization via the cleavage of vascular endothelial growth factor-165. *Arterioscler. Thromb. Vasc. Biol.*, **31**(5): 1041-1048.

Sha H, Ma Q, Jha RK, Wu Z, Qingyuan Z, Wang Z, Ma Z, Luo X and Liu C (2013). Resveratrol Suppresses Microcirculatory Disturbance in a Rat Model of Severe Acute Pancreatitis. *Cell Biochem. Biophys.*, **67**(3): 1059-1065.

Vournar B and Menger MD (2003). Microcirculatory dysfunction in acute pancreatitis. A new concept of pathogenesis involving vasomotion-associated arteriolar constriction and dilation. *Pancreatology*, **3**(3): 181-190.

Wang W, Ji M, Zhou YH and Li CL (2014). Discussion of early peritoneal drainage for severe acute pancreatitis. *J. Clin. Surg.*, **22**(5): 341-343.

Webb JG (2011). The kallikrein/kinin system in ocular function. *J. Ocul. Pharmacol. Ther.*, **27**(6): 539-543.

Wu TS and Liao LJ (2016). Percutaneous catheter drainage for acute severe pancreatitis complicated with peripancreatic necrosis and infection. *Chinese Journal of General Surgery*, **25**(3): 333-338.

Xing M, Ni JB, Wan R, Tang MC, Hu YL, Yu G, Yin GJ, Chen CY, Fan YT, Xiao WQ, Zhao Y, Wang XP and Hu GY (2015). Tetraspanin CD9 is involved in pancreatic damage during cerulein-induced acute pancreatitis in mice. *Dig. Dis.*, **16**(1): 43-51.

Xu B, Bai B, Sha S, Yu P, An Y, Wang S, Kong X, Liu C, Wei N, Feng Q and Zhao Q (2014). Interleukin-1 β induces autophagy by affecting calcium homeostasis and trypsinogen activation in pancreatic acinar cells. *Int. J. Clin. Exp. Pathol.*, **7**(7): 3620-3631.