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• ORIGINAL RESEARCH •

Effects of extract F of red-rooted Salvia on mucosal lesions of gastric corpus and antrum induced by hemorrhagic shock-reperfusion in rats

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Abstract

AIM **To compare the effects of extract F of red-rooted Salvia (EFRRS) on mucosal lesions of gastric corpus and antrum induced by hemorrhagic shock and reperfusion in rats.**

METHODS **The rats were subject to hemorrhagic shock and followed by reperfusion, and were divided randomly into two groups. Group 1 received saline, and group 2 received EFRRS intravenously. The index of gastric mucosal lesions (IGML) was expressed as the percentage of lesional area in the corpus or antrum. The degree of gastric mucosal lesions (DGML) was catalogued grade 0, 1, 2 and 3. The concentrations of prostaglandins (PGs) were measured by radioimmunoassay. The concentration of MDA was measured according to the procedures of Asakawa. The activity of SOD was measured by the biochemical way. The growth rates or inhibitory rates of above-mentioned parametes were calculated.**

RESULTS **As compared with IGML (%), grade 3 damage (%) and MDA content (nmol/g tissue) of gastric antrum which were respectively 7.96±0.59 , 34.86±4.96 and 156.98±16.12, those of gastric corpus which were respectively 23.18±6.82, 58.44±9.07 and 230.56±19.37 increased markedly ($P<0.01$), whereas the grade 0 damage, grade 1 damage, the concentrat ions of PGE_2 and PGI_2 (pg/mg tissue), the ratio of PGI_2/TXA_2 and the activity of SOD (U/g tissue) of corpus which were respectively 3.01±1.01, 8.35±1.95, 540.48±182.78, 714.38±123.74, 17.38±5.93 and 134.29±13.35 were markedly lower than those of antrum which were respectively 13.92±2.25, 26.78±6.06, 2218.56±433.12, 2531.76±492.35, 43.46±8.51 and 187.45±17.67 ($P<0.01$) after hemorrhagic shock and reperfusion. After intravenous EFRRS, the growth rates (%) of grade 0 damage, grade 1 damage, the concentrations of PGE_2 and PGI_2, the ratio of PGI_2/TXA_2 and the activity of SOD of corpus which were respectively 632.56, 308.62, 40.75, 74.75, 92.29 and 122.25 were higher than those in antrum which were respectively 104.89, 58.40, 11.12, 56.58, 30.65 and 82.64, whereas the inhibitory rates (%) of IGML, grade 3 damage and MDA content of gastric corpus were 82.93, 65.32 and 59.09, being higher than those of gastric antrum which were 76.64, 53.18 and 42.37.**

CONCLUSION **After hemorrhagic shock-reperfusion, the gastric mucosal lesions in the corpus were more severe than those in the antrum, which were related not only to the different distribution of endogenous PGs in the mucosa, but also to the different ability of anti-oxidation of the mucosa. The protective effect of EFRRS on the gastric mucosa in the corpus was more evident than that in the antrum, which was related to higher growth degree of PGs contents and anti-oxitative ability in gastric corpus after administratio n of EFRRS.**

Subject headings plant extracts/pharmacology; gastric mucosa/pathology; shock hemorrhagic; reperfusion; hydroxyl radical

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INTRODUCTION

More and more stress has been put on gastric mucosal reperfusional injury. Though scholars both at home and abroad have performed plenty of researches on it, there has been no satisfying method or drug yet[1-5]. Red-rooted Salvia is the traditional Chinese medicine for accelerating blood circulation and ameliorating congestion, and its pharmacological effect is very extensive. Resources of red-rooted Salvia in China is sufficient. It has been evidenced that the proportion of red-rooted Salvia dissolving in water can treat acute or chronic gastric mucosal lesions, and has protective effect on gastric mucosa. Extract F of red-rooted Salvia (EFRRS) is extracted from the proportion of red-rooted Salvia dissolving in water[6-11]. Because Prostaglandins (PGs) and oxygen free radical (OFR) play important roles in reper fusional injury[12-18], the present experiment was AIMed at studying the endogen ous PGs and the anti-oxidation of the gastric corpus and the antrum, and comparing their ability to resist the lesions induced by hemorrhagic shock-reperfusi on in rats and the protective effect of EFRRS on the gastric corpus and the antrum.

METERIALS AND METHODS

Drug

EFRRS was extracted from red-rooted Salvia solution provided by Chemical Assay Center of China Medical University using column chromatography.

Animal models

Male Wistar rats, weighing 260 g-300 g, were fasted overnight. The rats were anesthetized intraperitoneally with 5 mg·100g^{-1} of 20% Urethane. Tracheostomy was performed and PE-250 tubing was inserted into the trachea to maintain an open airway. Then open the abdomen and lavage the gastric lumen gently with warm saline. The right carotid artery was cannulated using a polyethylene tube to monitor the blood pressure. The femoral artery was canulated for withdrawing the blood and reinfused the shed blood. After the blood pressure was stabilized, normal saline or EFRRS (1 g·100gw·t^{-1}) was administered for 25 min via a tail vein (0.03 mL·min^{-1}). 1 mL of 0.1 mol/L HCl per 100 g body wt was then instilled into the stomach via the gastric tube, five min after the intragastric instillation of HCL, blood was withdrawn from the femoral artery. The mean arterial blood pressure fell to 2.67 kPa-4.0 kPa and was maintained at that level for 20 min. The shed blood was then reinfused, and 20 min later the rats were sacrificed[19]. Rats were allocated into two groups. Group 1 (n = 9) received NS via the tail vein, and group 2 (n = 7) received EFRRS (1 g·100gwt^{-1}) via the tail vein.

Index of gastric mucosal lesions (IGML) and inhibitory rate (IR) of IGML

The corpus and antrum lesional areas were measured in square millimeters. IGML was expressed as the percentage of lesional area in the corpus or antrum[20]. IR was calculated by the following formula.

$$IR=\frac{\text{Difference of mean value of lesional areas between the two groups}}{\text{Mean value of lesional area in group 1}}\times 100\%$$

Depth of gastric mucosal lesions (DGML) , growth rate(GR) and IR of DGML

After meaursing the lesional areas, the samples for light microscopy (LM) and scanning electron microscopy (SEM) were taken from the proximal anterior wall of the corpus or the middle of the antrum. The samples analyzed by LM were evaluated as follows[21]. The damage was graded as 0, 1, 2 and 3. Grade 0 was defined as normal intact surface mucous cells with intact gastric pits and glands. Grade 1: Surface mucous cells were vacuolated with pyknotic nuclei. Some exfoliation was present. Grade 2: In addition to the above changes, the cells lining the gastric pits were also disrupted and exfoliated. Grade 3: Cell destruction extended into the gastric glands (Figures 1-6). Samples analyzed by SEM were evaluated as follows[22]. Grade 0: The mucosa showed closely packed, polygonal surface mucous cells and narrow openings to the gastric pits. Grade 1: Surface cells were flattened with irregular shape, and gaps between individual cells. Grade 2: The basal lamina was exposed and was largely devoid of surface mucous cells, but still showed continuity, wide openings to the gastric pits were visible. The picture resembled that of a honeycomb. Grade 3: Most of the basal lamina were disrupted, and only a portion being still intact. Regular surface cells were no longer present (Figures 7-12). A close correlation between LM and SEM grading was found (r = 0.846, P<0.01). The percentage of damage of each grade was calculated in each group. The METHODS to calculate the GR or IR of DGML were the same as that of IR of the lesional area.

PGs contents and GRs of PGs

Prostaglandin E_2 (PGE_2), 6-keto-$PGF_{1\alpha}$ (6-keto-$PGF_{1\alpha}$: 6-keto is the metabolite of PGI_2), and TXB_2 (metabolite of TXA_2) boxes were provided by Biochemistry Laboratory of Liberal Army General Hospital, and their concentrations were assayed by using radiommunoassay. GRs of PGs were calculated in the same way as that of IR of the lesional area.

MDA content and IR of MDA

Malondialdehyde (MDA) is the final metabolism product of OFR. It can be measured by the way of Asakawa[23]. IR of MDA was calculated in the same way as that of IR of lesional area.

SOD activity and GR of SOD

Superoxide dimutase (SOD) was measured according to the biochemical method[24]. GR of SOD was calculated in the same way as that of IR of lesional area.

In all experiments, the date was represented by the mean value ± standard error, and analyzed by paired t test. P value of <0.05 was considered significant.

RESULTS

Comparison of IGML and its IRs between the gastric corpus and antrum

The results are shown in Table 1. After hemorrhagic shock-reperfusion, IGML in the corpus was much higher than that in the antrum (P<0.01). As compared with that in the corpus, IR in the antrum was lower after administratio n of EFRRS.

Table 1 IGML and its IR in gastric corpus and antrum (%, $\bar{x}\pm s$)

	IGML	IR
Group 1 (n = 9)		
Corpus	23.18±6.82	
Antrum	7.96±0.59[b]	
Group 2 (n = 7)		
Corpus	4.42±1.39[a]	82.93
Antrum	1.62±0.37[a]	76.64

[b]P<0.01, *vs* corpus; [a]P<0.01, *vs* group 1.

Comparison of DGML, and its IRs and GRs between the gastric corpus and antrum

The results are shown in Table 2. As compared with those in the corpus, grade 0 and 1 damages in the antrum were much increased (P<0.01), and grade 3 damage markedly decreased (P<0.01) after hemorrhagic shock-reperfusion. After administration of EFRRS, the GR of grade 0 and 1 damage and the IR of grade 3 damage in the antrum were much less than those in the corpus.

Comparison of the concentrations of PGE_2, 6-keto and TXB_2, the ratio of 6-keto/TXB_2 and their GRs between the gastric corpus and antrum

In Table 3, higher PGE_2 and 6-keto levels and 6-keto/TXB_2 ratio were found in the antrum compared with those in the corpus after hemorrhagic shock-reperfusion (P<0.01), and the GRs of PGE_2, 6-keto and 6-keto/TXB_2 in the corpus were higher than those in the antrum after administration of EFRRS.

Table 2 DGML and its IR or GR in the gastric corpus and antrum (%, $\bar{x}\pm s$)

	DGML							
	0	GR	1	GR	2	IR	3	IR
Group 1 (n = 7)								
Corpus	3.01±1.01		8.35±1.95		31.32±4.49		58.44±9.07	
Antrum	13.92±2.25[b]		26.78±6.06[b]		25.98±8.32		34.86±4.96[b]	
Group 2 (n = 6)								
Corpus	22.05±5.96[a]	632.56	34.12±8.12[a]	308.62	25.96±10.04	17.11	20.32±6.95[a]	65.32
Antrum	28.52±8.12[a]	104.89	42.42±8.58[a]	58.40	14.03±3.13[a]	45.98	16.32±4.05[a]	53.18

[b]P<0.01, *vs* corpus; [a]P<0.01, *vs* group 1.

Table 3 PGs contents (pg/mg tissue), and their GRs in the gastric corpus and antrum (%, $\bar{x}\pm s$)

Group	PGE_2	GR	6-keto	GR	TXB_2	6-Keto/TXB_2	GR
Group 1 (n = 6)							
Corpus	540.48±182.78		714.38±123.74		58.28±6.74	17.38±5.93	
Antrum	2218.56±433.12[b]		2531.76±492.35[b]		62.49±9.51	43.46±8.51[b]	
Group 2 (n = 6)							
Corpus	759.77±192.00[aa]	40.75	1248.37±158.54[a]	74.75	45.37±7.54[aa]	33.42±9.24[a]	92.29
Antrum	2465.17±480.36	11.12	2698.31±526.71	56.58	50.02±7.50[a]	56.78±5.45[a]	30.65

[b]P<0.01, *vs* corpus; [a]P<0.01, *vs* group 1; [aa]P<0.05, *vs* group 1.

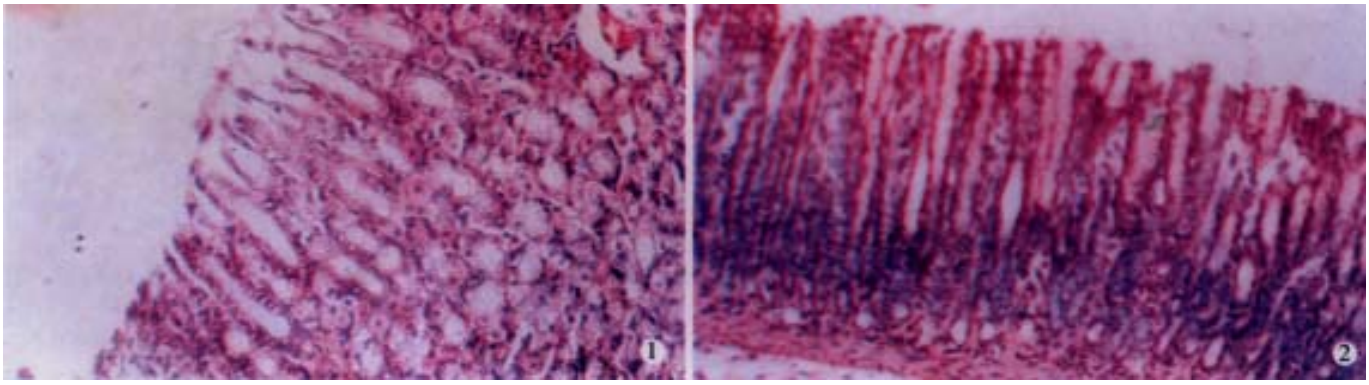
Comparison of MDA content, IR of MDA, SOD activity and GR of SOD between the gastric corpus and antrum

In Table 4, higher SOD activity and lower MDA level were found in the antrum com pared with those in the corpus after hemorrhagic shock-reperfusion (P<0 .01), and the GR of SOD and IR of MDA were higher in corpus than those in antrum after administration of EFRRS.

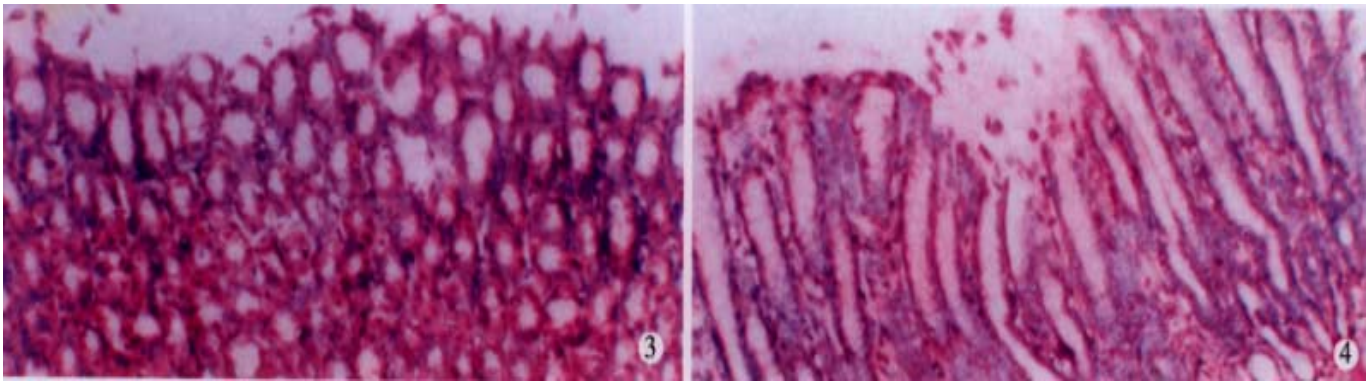
Table 4 MDA content (nmol/g tissue), SOD activity (U/g tissue), IR of MDA and GR of SOD in the gastric corpus and antrum (%, $\bar{x}\pm s$)

Group	MDA	IR	SOD	GR
Group 1 (n = 6)				
Corpus	230.56±19.37		134.29±13.35	
Antrum	156.98±16.12[b]		187.45±17.67[b]	
Group 2 (n = 6)				
Corpus	94.32±11.32[a]	59.09	298.47±20.12[a]	122.25
Antrum	90.46±12.45[a]	42.37	342.35±26.58[a]	82.64

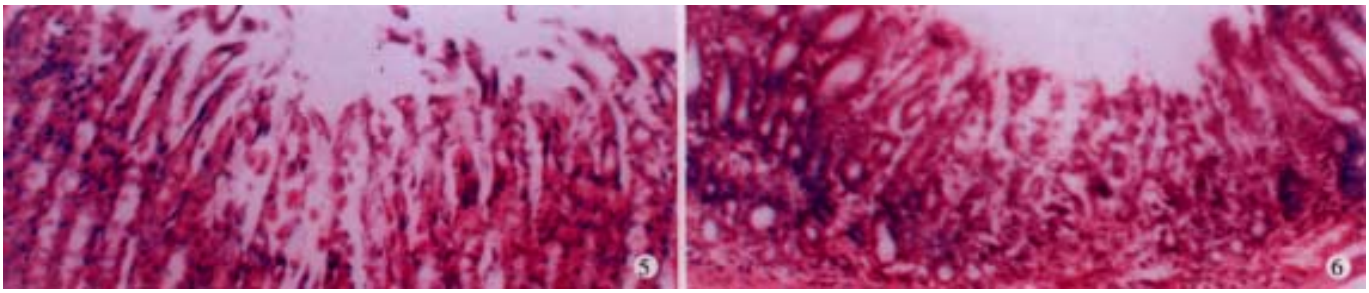
[b]P<0.01, *vs* corpus; [a]P<0.01, *vs* group 1.



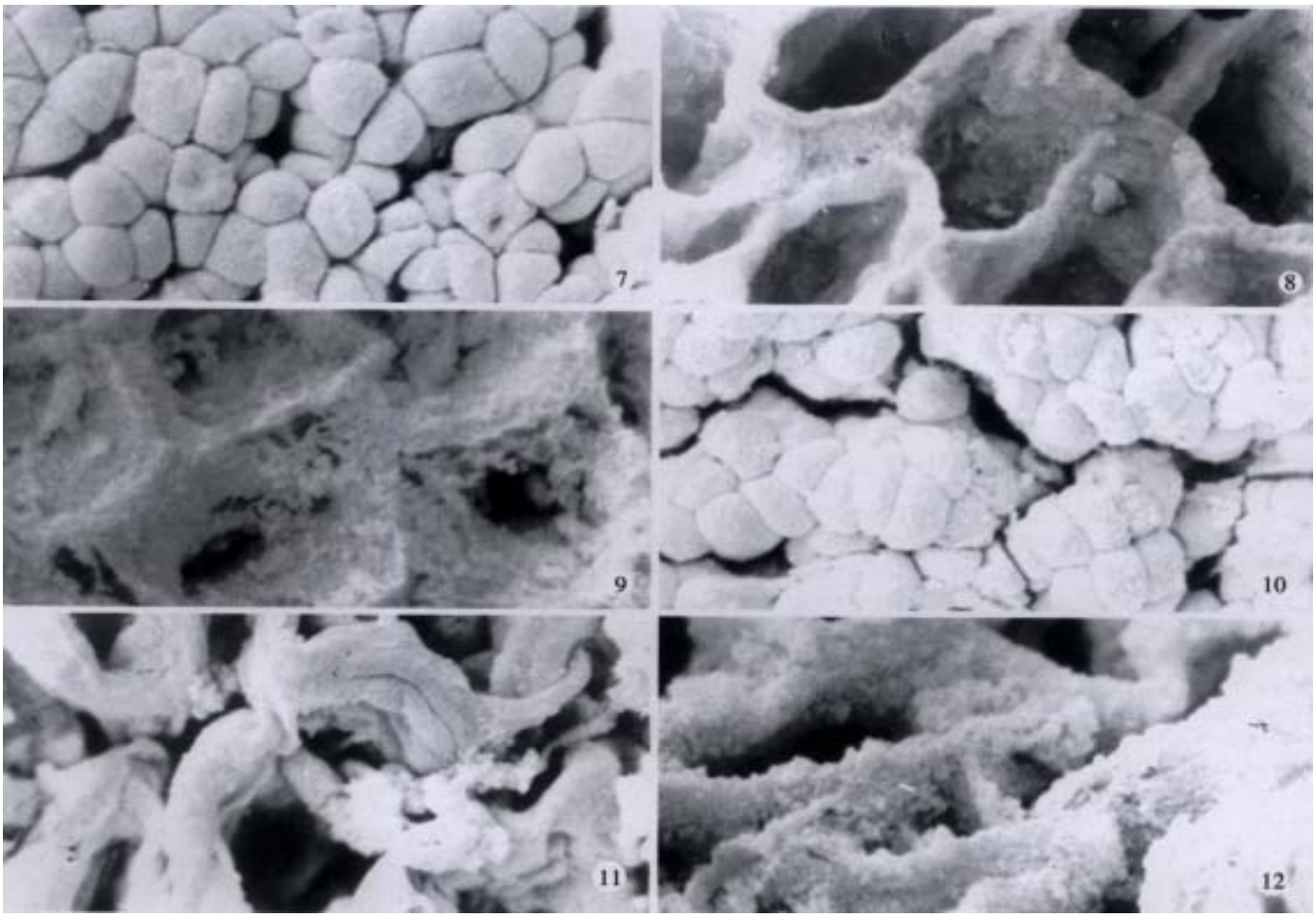
Figures 1, 2 Grade 1 damage in gastric corpus and antr um. LM×330.
In grade 1 damage, surface mucous cells were damaged.



Figures 3, 4 Grade 2 damage in gastric corpus and antrum. LM×330
In grade 2 damage, the cells kining the gastric pits were also disrupted.



Figures 5, 6 Grade 3 damage in gastric corpus and antrum. LM×330
In grade 3 damage, cell destruction extended into the gastric glands.



Figures 7, 8, 9 Grade 1, 2 and 3 damage in gastric corpus. SEM×1500
Figures 10, 11, 12 Grade 1, 2 and 3 damage in gastric antrum. SEM×1500
In grade 1 damage, surface cells were of irregular shape, and gaps between individual cells were present. In grade 2 damage, the basal lamina was exposed, but still showed continuity. Wide openings to the gastric pits were visible. In grade 3 damage, most of the basal lamina was disrupted, Regular surface cells were no longer present.

DISCUSSION

Reperfusion after hemorrhagic shock can lead to multiple organ damage, *i.e.* reperfusional injury. The gastric lesions include stress ulcer, hemorrhage, necrosis, or perforation[25-28]. The present study showed that the area and depth of gastric mucosal lesions caused by hemorrhagic shock-reperfusion in the gastric corpus of rats were more severe than those in the antrum. This indicated that there were differences in resistance in gastric mucosa of the corpus and the antrum, which was probably related to differences in gastric mucosal blood flow, energy metabolism and the capacity to dispose the influxing hydrogen ion, but most propably was related with the different distribution of endogenous PGs and the different ability of anti-oxidation[29-33]. The present study also showed that the protective role of EFRRS was different in the gastric corpus and the antrum, EFRRS possessed more powerful capability to reduce the area of lesions and to lighten the extent of lesions in corpus than those in the antrum, indicating EFRRS had potential protective effect on the corpus mucosa, which was related to the higher changes of PGs and OFR in the corpus caused by EFRRS.

It was generally thought that gastric mucosa was affected by both injury factors as gastric acid and pepsin and protective factors as PGs and gastric mucus. Large quantities of PGs were

found in the gastric mucosa. Numerous studies have doc umented that PGs possessed potent cytoprotective action. PGE_2 could obviously inhibit the secretion of basal gastric acid and acid stimulated by histamine, p entagastrin and food in dogs and humans. In addition, PGE_2 could increase the gastric mucus layer. PGE_2 and PGI_2 could dilate the blood vessel, increase the blood flow and carbohydrate secretion, and enhance the resistibility of gastric mucosa to injury. PGs could also lengthen the life span of epithelia and thick en the mucosa layer[34-37]. In many physiological and pathophysiological conditions, PGI_2 has protective effect on gastric mucosa. On the contrary, TXA_2 may aggravate the gastric mucosal injury[38,39]. The present findings showed the PGE_2 and PGI_2 contents and PGI_2/TXA_2 ratio in the antrum were markedly higher than those in the corpus after hemorrhagic shock-reperfusion, showing gastric antrum was more resistant than gastric corpus. Arakawa[40] found PGE_2 levels in the gastric corpus were significantly lower than that in the antrum, and drug like indomethacin could easily damage the mucosa of gastric corpus. He thought that the concentration of endogenous PGE_2 decided the defensive ability of gastric mucosa. The present study also showed that PGE_2 and 6-keto levels and 6-keto/TXB_2 ratio in the antrum and the corpus both increased after administration of EFRRS, but the GRs of PGE_2, 6-keto and 6-keto/TXB_2 in corpus were higher than t hose in antrum, demonstrating the reinforcement of defensive ability of gastric corpus was more powerful after administration of EFRRS.

OFR played an important role in reperfusional injury. OFR caused lipid peroxid ation (LPO) of polyunsaturated fatty acid of biomembrane, which resulted in the impairment of metabolism and function of cells, even the death of cells. Plenty of OFRs could lead to irreversible damage of gastric mucosa, because they could cause intracellular calcium overload besides of extensive LPO of tissues and cells[41-47]. OFR was produced by the system of enzyme and no-enzyme. Malondialdehyde (MDA) is the metabolite of LPO of OFR, and may reflect the degree of cells attacked by OFR, therefore MDA is usually an marker to monitor OFR. Superoxide dismutase (SOD) can clear superoxide anion,and may reflect the ability of scavenging system of free radical. Under normal conditions, OFR could be promptly cleared by the body. Only when the production of OFR markedly increased, or the ability of scavenging OFR much decreased, tissues were injured[48,49]. The study showed that there were higher SOD activity and lower MDA level in the antrum compared with those in corpus after hemorrhagic shock-reperfusion, so that the ability of anti-oxidation was more powerful in gastric antrum, and the reperfusional injury was easier in gastric corpus. This study also showed that the activity of SOD and the concentration of MDA decreased in the antrum and the corpus after administration of EFRRS, but the GR of SOD and IR of MDA in corpus were higher than those in antrum, demonstrating reinforcement of anti-oxidation of gastric corpus was more powerful after administration of EFRRS. The increase of SOD could accelerate the clearance of OFR to protect cell from the attact of OFR, while the decrease of OFR made cells produce more SOD, and clear more OFRs to form good cycle possessing the role of protective gastric mucosa.

It had been demonstrated in our previous studies[50-54], that EFRRS could increase the PGs contents, decrease the production of OFRs, and had calcium block effect, which resulted in some effects against gastric mucosal lesions induced by hemorrhagic shock-reperfusion. The present study discussed the mechanisms that the gastric injury in the corpus was easier after hemorrhagic shock-reperfusion, and the causes that the protective effects of EFRRS against gastric mucosal injury was moer powerful in the corpus through both PGs contents and OFR system. This made the researches of reperfusional injury of gastric mucosa and the protective effects of EFRRS perform more profoundly and detailedly.

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