



Effects of different periods of gastric ischemia on liver as a remote organ¹

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Abstract

Purpose: To evaluate the hepatic changes associated with gastric ischemia.

Methods: Thirty male rabbits were studied, distributed in 3 groups (n=10). Group 1: ligation and section of the gastric vasculature and removal of the liver after three hours; Group 2: ligation and section of the gastric vasculature and removal of the liver after 6 hours; Group 3: ligation and section of the gastric vasculature and removal of the liver after 12 hours. Blood samples were collected immediately before surgery and after the determined time of ischemia in each group to evaluate the hepatic function. After the death of the rabbits, the liver was removed for macro and microscopic study.

Results: An increase in aminotransferases and bilirubin occurred in groups 2 and 3. Total protein and albumin diminished in all of the animals. All of the rabbits from groups 2 and 3 presented hepatocellular necrosis.

Conclusion: The devascularization of the stomach for a period of above three hours is associated with hepatic morphological and functional disorders.

Key words: Stomach. Ischemia. Inflammation. Liver. Rabbits.

■ Introduction

Gastric ischemia is caused by reduction or interruption of blood flow to the stomach, due to mechanical and functional factors. It may be a result of esophagogastroplasties and gastric resections, used in the treatment of esophageal cancer, megaesophagus and severe caustic esophagitis. The other is when the stomach is used in retrosternal position to preserve the digestive tube when an obstructed esophagus cannot be removed. In both instances, the vitality of the stomach is preserved only by right gastroepiploic vessels, the last branch and affluents of the gastroduodenal vessels¹⁻⁴.

Gastric volvulus is a common disorder in dogs. In some occasions a delayed surgical treatment may lead to complete vascular obstruction due to their torsion with consequent gastric necrosis. Besides, gastric ischemia may be a consequence of the desvascularization of the organ in the treatment of portal hypertension, and also after splenectomy surgeries, venous thrombosis and phlebitis, coagulopathies, sepsis and shock¹⁻⁴.

This event is rarely diagnosed², and if the gastric blood flow is not reestablished immediately, irreversible disorders can occur, culminating in a catastrophic complete gastric necrosis and systemic remote injuries. Gastric necrosis unleashes a local inflammatory process that can be associated with disturbances in other organs and systems², giving rise to the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), which affects vital organs such as liver.

The liver plays an important role in the defense of the organism during SIRS, and is responsible for the modulation of the inflammatory process, through filtering, as well as the inactivation and destruction of bacteria, endotoxins, vasoactive substances and other inflammatory mediators⁵. Once stimulated, the

liver produces and releases a large quantity of cytotoxins, bioactive lipids, and acute-phase proteins, which promote hepatocellular lesions⁵. The etiopathogenesis of the liver morphological and functional disorders secondary to organ ischemia and SIRS continue to challenge scientific comprehension⁶⁻⁸. Gastric ischemia may occur in many clinical situations and liver injury may be a severe consequence that represents an important cause of death in critically ill patients.

In this way, the knowledge about liver engagement on conditions of gastric ischemia is important for the treatment, and, therefore, for the prognoses of these patients. Because of that, we aimed to investigate the repercussion of gastric ischemia on liver function and morphology, once it is an important event in Intensive Care Unit and, nevertheless, there is a lack of literature in this area.

This work seeks to verify if gastric ischemia does in fact have repercussions on hepatic morphology and functions.

■ Methods

This experiment was conducted according to the technical guidelines for animal experimentation, according to Brazilian Law 11.794, and was approved by the Research Ethics Committee in Animal Experimentation (CETEA) from the Universidade Federal de Minas Gerais (UFMG) under the Protocol nr. 007/2008.

This experiment studied 30 white New Zealand male rabbits, weighing between 2.5 kg and 3.0 kg. At the beginning of the procedure, 3 ml of blood were collected from all of the animals, by auricular venous puncture. The hepatic functions were examined by means of alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGT), total proteins

(TP), albumin, direct and indirect bilirubins. The rabbits were anesthetized with intramuscular 2% xylazine hydrochloride, at a dose of 10 mg/kg, associated with 10% ketamine hydrochloride, at a dose of 60 mg/kg. When necessary, one fourth of the initial dose of anesthesia was also applied. The same surgical procedure was performed on all of the animals. After median laparotomy, all of the perigastric arterial and venous blood vessels were ligated and sectioned. The abdominal cavity was closed and the rabbits were distributed randomly in three groups (n=10):

Group 1: animals submitted to gastric devascularization and removal of the liver after three hours;

Group 2: animals submitted to gastric devascularization and removal of the liver after six hours;

Group 3: animals submitted to gastric devascularization and removal of the liver after twelve hours. Immediately before removing the liver, a new blood sample was collected in the auricular vein for the same exams carried out before surgery.

No action was done to prevent or treat the gastric and hepatic injuries provoked by the gastric devascularization. The rabbits were operated on again under an overdose of ketamine (100 mg/kg). The abdominal cavity was reopened and the liver was removed. The livers were evaluated macroscopically and three fragments were collected for microscopy. After fixation in 10% formaldehyde, the fragments were processed according to the histological routine and stained with hematoxylin and eosin (HE). Only one pathologist performed all blinded histological analyses.

Data were reported as mean \pm standard error from the mean. Comparison among the biochemical exams was performed through analysis of variance (ANOVA), followed by the Tukey test after verifying its normal distribution by the Kolmogorov Smirnov test.

The comparison between the pre- and post-operative values for each group was carried out by the Student's t test. To compare the microscopic changes, the Fisher exact test was applied. All of the results were considered significant for a probability of above 95% ($p < 0.05$).

■ Results

Macro and microscopic analyses

Stomach

Macroscopic examination of the stomach of all the animals in the three groups showed localized or diffuse changes indicative of hemorrhagic necrosis (Figures 1 and 2). The gastric fundus and body were most affected in all rabbits. In most animals the antral region was preserved, presenting only mild congestive changes of the mucosa in two animals each in groups 2 and 3. All animals of groups 1, 2 and 3 presented macroscopic lesions indicative of hemorrhagic necrosis of varying extension in the body and fundus, of greater intensity in groups 2 and 3 (6 and 12h) compared to group 1 (3h).

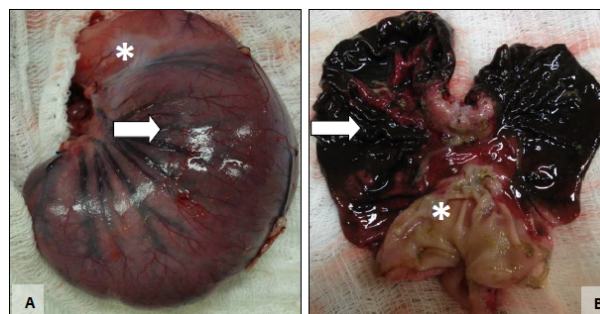


Figure 1 – Macroscopic aspect of the closed and opened stomach of the same rabbit after 6h of gastric ischemia. **A.** Outer surface of the stomach with signs of hemorrhagic necrosis of the body region (*arrow*) while the antropyloric region (*) is preserved. **B.** Diffuse hemorrhagic necrosis in the body and fundus regions (*arrow*), while the antral region (*) is preserved.

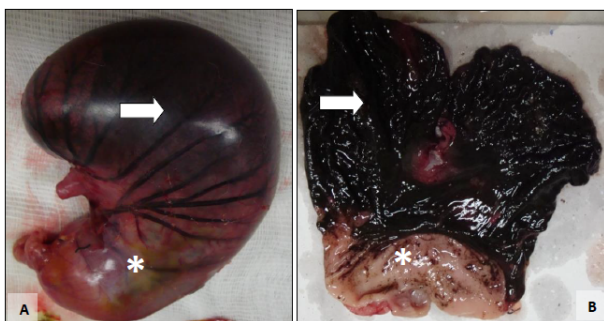


Figure 2 – Macroscopic aspect of the closed and opened stomach of the same rabbit after 12h of gastric ischemia. **A.** Outer surface of the stomach with signs of hemorrhagic necrosis of the body and fundus (arrow) while the antropyloric region (*) is preserved. **B.** Diffuse and marked hemorrhagic necrosis of the gastric mucosa in the body and fundus regions (arrow), while the antral region (*) is preserved.

Microscopic changes in stomach tissues became more conspicuous with increasing time of gastric ischemia. Edema and vessel congestion were observed in the mucosa, submucosa and muscle layers of the three gastric regions in all animals. Areas of mucosal necrosis of the body and fundus occurred in all animals after three hours of gastric ischemia and only two animals in this group presented necrosis of the muscle layer in the region of the gastric fundus.

Necrosis of the mucosa of the antropyloric region was observed in only one rabbit each in groups 2 and 3, and the muscle layer of this region was preserved in all animals of the three groups. Hemorrhagic necrosis of the mucosa of the gastric body and fundus was observed in all animals of groups 2 (6h) and 3 (12h). Four animals developed necrosis of the muscle layer in the gastric body and fundus after 6h of ischemia (group 2). After 12 h of ischemia (group 3), necrosis of the muscle layer

was observed in the gastric body of six animals and in the fundus of four animals.

Liver

Yellowish and whitish areas were observed in the hepatic parenchyma of two animals from group 1, six from group 2, and in all of the animals from group 3 (Figure 3).

The results obtained in the histological analysis are presented in Table 1. A difference among the groups as regards the microscopic changes was observed ($p=0.0010$). Extensive areas of vacuolar hydropic degeneration were found in all of the animals from groups 1 and 3 and in eight animals from group 2 (Figure 4A). Dilatation and congestion of blood vessels were found in all of the animals from groups 1 and 3, and in eight animals from group 2. Hepatocellular necrosis occurred in two animals from group 1 and in all of the rabbits from groups 2 and 3 (Figure 4 A-B). Leukocyte infiltration with predominance of polymorphs was observed in eight animals from group 3 (Figure 4B).

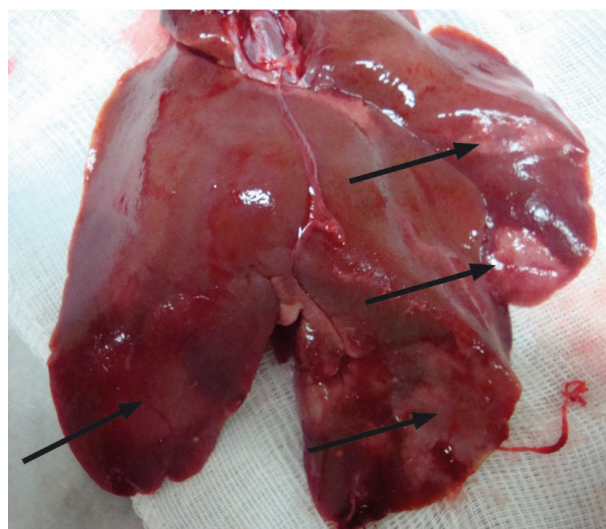


Figure 3 – Macroscopic aspect of a rabbit liver from group 3, showing whitish blotches (arrows) in the hepatic parenchyma.

Table 1 – Microscopic changes of liver in animals from Groups 1, 2 and 3, after determined periods of gastric ischemia.

GROUP/ MICROSCOPIC CHANGES	VACUOLAR HYDROPIC DEGENERATION n (%)	DILATATION OF BLOOD VESSELS n (%)	CONGESTION OF BLOOD VESSELS n (%)	HEPATOCELLULAR NECROSIS n (%)	LEUKOCYTE INFILTRATION n (%)
1	10 (100%)	10 (100%)	10 (100%)	2 (20%)	-
2	8 (80%)	8 (80%)	8 (80%)	10 (100%)	-
3	10 (100%)	10 (100%)	10 (100%)	10 (100%)	8 (80%)

Group 1 –gastric devascularization and removal of the liver after 3h.

Group 2 –gastric devascularization and removal of the liver after 6h.

Group 3 –gastric devascularization and removal of the liver after 12h.

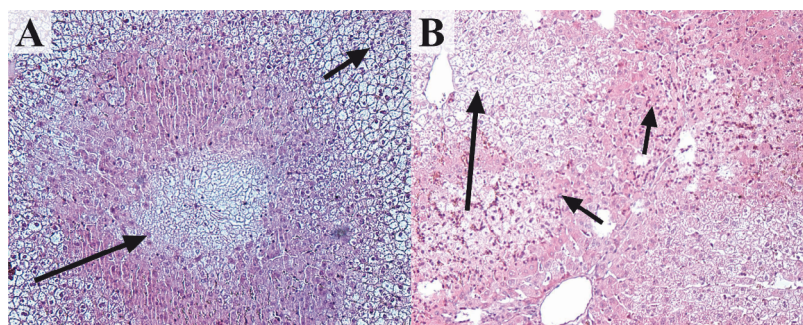


Figure 4 – Microscopic aspect of livers removed after gastric ischemia. A. Center lobule necrosis (*big arrow*) and vacuolar hydropic degeneration (*small arrow*) in a rabbit liver from group 1 (HE, x100). B. Areas of necrosis (*big arrow*) and leukocytes infiltration (*small arrows*) in a rabbit liver from group 3 (HE, x100).

Biochemical analyses

Table 2 shows the ALP, AST, ALT, GGT, TP and bilirubins values dosed in the animals from groups 1, 2, and 3. Comparing the pre- and post-gastric ischemia in each group, an increase in ALT in group 2 ($p = 0.0444$) and in group 3 ($p = 0.0154$) was identified. In group 1, the values of this enzyme did not differ ($p = 0.085$). No variation was observed in the values of AST in Group 1 and Group 2 ($p > 0,05$), but they were higher after gastric ischemia in Group 3 ($p = 0,0198$). A reduction in TP was observed in Group 1 ($p = 0.0014$), Group 2 ($p = 0.0063$), and Group 3 ($p = 0.0038$). The albumin values

diminished after gastric ischemia in Group 1 ($p = 0.0018$), Group 2 ($p = 0.0158$) and group 3 ($p = 0.0162$). The values of direct bilirubin diminished after gastric ischemia in group 1 ($p = 0.0098$) and increased in group 3 ($p = 0.0190$), remaining unchanged in group 2 ($p = 0.1396$). The values of indirect bilirubin increased after gastric ischemia in Group 2 ($p = 0.0494$), but remained unchanged in Group 1 ($p = 0.4796$) and Group 3 ($p = 0.1345$). No variation was observed in the ALP and GGT values after gastric ischemia in the three groups ($p > 0.05$), although there was great increases of these values in some animals of Group 3.

Table 2 – Values (mean \pm standard error from the mean) of ALT, AST, ALP, GGT, TP, albumin, direct and indirect bilirubin, of animals from groups 1, 2 and 3, obtained before and after determined periods of gastric ischemia.

VARIABLES	GROUPS	PREOPERATIVE	POST-ISCHEMIA	PRE- AND POST-VARIATION
ALT (IU/l)	1	135.8 \pm 23.2 A	158.8 \pm 19.8 A	23.00 a
	2	115.6 \pm 16.0 A	151.0 \pm 46.2 B	35.40 a
	3	96.8 \pm 20.0 A	135.0 \pm 45.6 B	-61.80 b
AST (IU/l)	1	32.4 \pm 12.5 A	20.2 \pm 12.5 A	-12.20 a
	2	40.2 \pm 6.3 A	138.0 \pm 264.0 A	93.80 a
	3	44.8 \pm 10.6 A	776.2 \pm 320.4 B	731.40 a
ALP (IU/l)	1	99.4 \pm 23.6 A	104.8 \pm 25.9 A	5.40 a
	2	141.6 \pm 44.2 A	138.0 \pm 21.5 A	-3.60 a
	3	146.0 \pm 41.6 A	290.0 \pm 194.2 A	144.00 a
GGT (IU/l)	1	5.9 \pm 4.8 A	6.4 \pm 3.6 A	0.50 a
	2	5.4 \pm 2.2 A	5.9 \pm 2.0 A	0.54 a
	3	5.2 \pm 2.9 A	17.6 \pm 13.4 A	12.26 a
TP (g/dl)	1	8.6 \pm 0.8 A	6.8 \pm 0.3 B	-1.60 a
	2	7.3 \pm 0.5 A	6.4 \pm 0.3 B	-1.00 a
	3	7.0 \pm 0.5 A	5.6 \pm 0.4 B	-1.40 a
ALBUMIN (g/dl)	1	4.2 \pm 0.2 A	3.3 \pm 0.4 B	-0.90 a
	2	3.7 \pm 0.2 A	2.5 \pm 0.3 B	-1.22 a
	3	3.7 \pm 0.9 A	2.4 \pm 0.5 B	-1.28 a
DIRECT BILIRUBIN (mg/dl)	1	0.26 \pm 0.1 A	0.2 \pm 0.1 B	-0.05 a
	2	0.5 \pm 0.3 A	0.6 \pm 0.4 A	0.10 ab
	3	0.2 \pm 0.03 A	0.3 \pm 0.1 B	0.16 b
INDIRECT BILIRUBIN (mg/dl)	1	0.5 \pm 0.2 A	0.5 \pm 0.3 A	-0.01 a
	2	1.0 \pm 0.8 A	1.3 \pm 0.6 B	0.03 a
	3	0.9 \pm 0.4 A	1.9 \pm 1.5 A	1.06 a

Group 1 –gastric devascularization and removal of the liver after 3h. Group 2–gastric devascularization and removal of the liver after 6h. Group 3 –gastric devascularization and removal of the liver after 12h .ALT – alanine aminotransferase. AST – aspartate aminotransferase. ALP – alkaline phosphatase. GGT – gamaglutamiltranspeptidase. TP – total proteins. a, b – Same column: equal letter p > 0.05, and different letters p < 0.05. A, B – Same line: equal letter p > 0.05, and different letters p < 0.05

■ Discussion

The effects of gastric devascularization on the vitality of the stomach have been evaluated in few experimental studies^{3,4}. In humans, partial stomach devascularization is used in the treatment of hypertension of gastric varices, acute hemorrhagic lesions of the gastroduodenal mucosa and also can

be observed in cases of venous thrombosis, phlebitis and coagulopathies are predisposing factors of ischemia⁴.

In this study, devascularization was performed in the entire wall of the stomach, including all veins and arteries. The results obtained showed that the model of gastric ischemia was effective in all animals, as confirmed by macro- and microscopic

examination, which revealed varied degrees of necrosis of the gastric wall. Gastric ischemia, even when induced for a relatively short period of time, may cause severe and irreversible injuries to one or more different tissues of the stomach.

As observed, the gastric fundus and body were the regions more sensitive to ischemia, whereas the antrum was preserved in practically all animals. Since all the vessels of the greater and lesser curvatures were sectioned, the most likely explanation for the preservation of the antropyloric region is based on two possibilities. The first refers to the rich vascular anastomosis present in the gastroduodenal interface. These anastomosis derive from small branches of the gastroduodenal artery, which derives from the hepatic artery and are largely responsible for the formation of the vascular plexuses present in the submucosa of the more distal regions of the stomach. Submucosal microvessels originating from the duodenum probably provide supplementary blood irrigation to the gastric antrum, leading to a greater resistance to ischemia.

Although there was a greater resistance of antrum region to ischemia, it was possible to confirm that desvascularization of stomach, even for a short period of time, result in a severe hemorrhagic necrosis of the gastric fundus and body wall, which was confirmed in the macro and microscopic studies.

The present work studied the repercussions of gastric ischemia upon the liver. The model of necrosis used here was chosen due to the systemic complications resulting from gastric ischemia, a subject which is scarce in the literature. The desvascularization of the stomach was carried out near the stomach wall, taking care not to affect the vascularization of neighboring organs, which can interfere in post-operative results.

Gastric ischemia, such as the gut ischemia, unleashes a distributive shock due

to the increase in the vascular permeability and reduction in aorta blood flow⁹ and a local inflammatory process which extends to other organs and can be prolonged, giving rise to the onset of MODS¹⁰. Liver failure is a common complication in critical diseases and contributes to the worsening of patient prognosis¹⁰⁻¹⁵. The liver plays an important role in the immune, endocrine, and metabolic control, and is frequently damaged in medical conditions of shock, sepsis and systemic inflammation. Changes in perfusion and hepatic cellular homeostasis stemming from these situations interfere in their functions and determine local and systemic deleterious effects⁷. The present work showed that the desvascularization of stomach resulted in liver damage. Based on the results of this study, it is worth to suppose that ischemia of the stomach is associated with hepatic dysfunction, which is defined as an increase in the circulating levels of aminotransferases and bilirubins¹¹. Since the increase in ALT, AST and bilirubins was not related to other comorbidities that could interfere in the results, it is possible to presume that the liver damage was secondary to gastric ischemia. The increase of direct bilirubin observed in Group 3 was probably caused by the vacuolization occurred in these animals, which may result in obstruction of biliary capillaries. In the other hand, the increased values of indirect bilirubin observed in Group 2 is commonly caused by hemolysis and hepatic dysfunction, which results from deformation of red blood cells and hypoxemia during systemic inflammation (SIRS)¹¹. Although the values of inflammatory mediators were not measured in this work, it is possible to suggest, based on literature and on the results of this study, that gastric ischemia unleashes a local and systemic inflammatory process. The reduction in the albumin values in the animals from the three groups reinforces the SIRS hypothesis, in which an increase in protein consumption

occurs^{5,11}. During SIRS, the albumin values can diminish in up to 70%, due to the vasodilation and hepatic prioritization for the acute-phase proteins^{8,12}. No increase was observed in the values of other hepatic markers, probably due to the short period of observation of the animals. A pilot study showed that the rabbits died between 12 and 24 hours after ligation and sectioning of the gastric vasculature. For this reason, this study favored to evaluate the animals over a shorter period of time, in an attempt to verify the initial changes taking place in the liver. The first signs of liver failure result from the hypoperfusion of splanchnic organs¹², which leads to an increase in the circulating values of hepatic markers, such as aminotransferases and bilirubins¹¹. By contrast, secondary hepatic dysfunction, which is more severe than primary one, is characterized by structural and functional lesions, and results from the direct action of bacteria, endotoxins and inflammatory molecules, which unleash or perpetuate the systemic inflammation and organ dysfunction¹¹. Gastric ischemia causes a distributive shock, with a reduction in the splanchnic perfusion, which compromises the proper functions of the organ^{12,16}. Diverse mechanisms are involved in the pathogenesis of this disorder, including the deformation of red blood cells, as well as an increase in both vascular permeability and the apoptosis of endothelial cells. Change in the vasomotor tone is also observed, with an opening of the arteriovenous derivations, as well as an increase in platelet and leukocyte aggregation, due to the greater expression of adhesion molecules on the surface of the endothelial cells¹⁷. The activation of coagulation cascade results in deposit of fibrin and formation of microthrombi^{17,18}. All of these mechanisms act together, causing tissue hypoxia, as well as the degeneration and death of hepatocytes¹¹, which may better explain the morphological changes in the present study, characterized

by vacuolar hydropic degeneration and hepatocellular necrosis. Trauma, shock, and systemic inflammation result in the activation of the immune system, promoting a greater production and release of inflammatory mediators, such as interleukins (IL) 1, 6, and 10; inflammatory proteins; and tumor necrosis factor (TNF). These mediators act directly in the hepatic parenchyma, causing the degeneration and death of hepatocytes¹⁹. In addition, IL1 and TNF, associated with the vascular changes and platelets and leukocytes aggregation may be related to the hepatic cells necrosis, which contributes to accelerated hepatic dysfunction^{14,15,20,21}. Kupffer cells, macrophages present in the liver, are highlighted the main causes of direct lesions to this organ^{15,21}. These are the first line of defense against microorganisms that cross the intestinal mucosa and reach the blood vessels⁶. These cells possess a large amount of inflammatory mediators, such as TNF, IL1, E2 prostaglandin, superoxides, and nitric oxide (NO)^{21,22}, which are released in response to inflammation, infection, and changes in hepatic oxygenation⁸. These products provoke hepatic morphological and functional changes¹¹, worsening hypoperfusion lesions²³. Hepatic endothelial cells (HEC) can also contribute to the formation of hepatic damage during the systemic inflammatory response. Although they consist of a barrier between the sinusoidal capillaries and the hepatic parenchyma, once activated by the inflammatory mediators, the HEC release IL8 and the platelets aggregation factor (PAF), which stimulates the adherence of the platelets and leukocytes to the hepatic parenchyma^{6,14,23}, perpetuating the hepatocellular lesion process^{11,23-26}. This fact can be explained by the leukocyte infiltration observed in the rabbits' livers after 12 hours of gastric ischemia. Previous literature has shown hepatic morphological and functional effects secondary to SIRS and ischemia of

other organs. Singer *et al.*¹⁷ observed platelet and leukocyte adhesion in rat livers two hours after the induction of sepsis. Dourado *et al.*²⁷ observed an increase in the levels of AST, ALT and inflammatory cytokines after gut ischemia/reperfusion. Brøchner *et al.*²⁸ reported liver failure coupled with the presence of leukocyte infiltration in mice livers after the induction of renal ischemia. In a similar study, Seifi *et al.*²⁹ reported liver failure after renal ischemia and reperfusion (I/R), while Kadkhodae *et al.*¹⁹ verified hepatic dysfunction associated with leukocyte infiltrate, as well as congestion, degeneration and necrosis in rat livers after 60 minutes of renal I/R. In another model of systemic inflammation, Mohammad *et al.*³⁰ induced ischemia of the posterior limbs by occlusion of femoral artery for two hours, followed by reperfusion for 24 hours. This procedure led to an increase in ALT and AST, sinusoidal congestion, enlarged sinusoids, cytoplasmic vacuolation and necrosis. The results of the present study are in accordance with the data from literature, once hepatic dysfunction, degeneration and hepatocellular necrosis, associated with leukocyte infiltrate in the parenchyma after 12 hours of gastric ischemia, were observed.

These results demonstrated that gastric ischemia caused changes in liver morphology and function. With three hours ischemia, the magnitude of these changes was less than those with 12 hours. These findings confirm the importance of prompt diagnoses and treatment in medical conditions of gastric ischemia, to prevent remote lesions. This study was the first in the literature to indicate hepatic lesions resulting from gastric ischemia and necrosis.

■ Conclusion

Gastric ischemia and necrosis is associated with liver structure and functions damages.

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