Gastric mucosal function in portal hypertensive gastropathy secondary to schistosomal hepatic fibrosis: effect of sclerotherapy

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وظيفة البطانة المخاطية للمعدة في حالات اعتلال المعدة بسبب ارتفاع الضغط البابي الناجم عن التليف الكبدي البلهارسي : تأثير العلاج التصلبي

سمير الديب وحسن غنّام وطارق ثابت وأسامة سالم ونبيلة متولي

خلاصة : تم تقييم وظيفة البطانة المخاطية للمعدة في حالات اعتلال المعدة بسبب ارتفاع الضغط البابي الناجم عن التليف الكبدي البلهارسي . فتكونت مجموعة الدراسة الأولى من عشرين مريضا ليس بهم نزف ، ولكن عشرة منهم كان بهم اعتلال معدي بسبب ارتفاع الضغط البابي . وتكونت المجموعة الثانية من عشرين مريضا ينزفون . ولقد وجد أن الحموضة الحرة والحموضة الإجمالية والناتج الحمضي الأساسي وببسينوجين المصل الأول وجريان الدم بالبطانة المخاطية للمعدة والغاسترين كانت جميعها أقل في المجموعة الثانية بفارق يُعتدّ به . بينما كان غاسترين المصل وتلوين سوماتوستاتين أعلى بفارق يُعتدّ به . ولم تلاحظ أية تغيرات مرضية بالأنسجة بين المجموعتين . وانتهت الدراسة إلى أن النزف الناجم عن تليف الكبد البلهارسي يؤدي إلى نقص الحموضة وفرط غاسترين الدم ونقص ببسينوجين الدم . كما أن جريان الدم التقديري بالبطانة المخاطية للمعدة يميز المصابين باعتلال المعدة بسبب ارتفاع الضغط البابي والمرضى النازفين .

ABSTRACT Gastric mucosal function in portal hypertensive gastropathy secondary to schistosomal hepatic fibrosis (SHF) was evaluated. Group I comprised 20 patients with no bleeding: 10 had portal hypertensive gastropathy (PHG). Group II comprised 20 patients with bleeding. Free acidity, total acidity, basal acid output, serum pepsinogen I, gastric mucosal blood flow (GMBF) and gastrin were significantly lower in group II, whereas serum gastrin and somatostatin staining were significantly higher. No histopathological changes were noted between both groups. In conclusion, bleeding caused by SHF results in hypoacidity, hypergastrinaemia and hypopepsinogenaemia. Estimated GMBF distinguishes patients with PHG and those who are bleeders.

La fonction de la muqueuse gastrique dans la gastropathie d'hypertension portale secondaire à une fibrose hépatique due à la schistosomiase: effet de la sclérothérapie

RESUME La fonction de la muqueuse gastrique dans une gastropathie d'hypertension portale secondaire à une fibrose hépatique due à la schistosomiase a été évaluée. Le groupe I comprenait 20 patients n'ayant pas d'hémorragies digestives; 10 avaient une gastropathie d'hypertension portale. Le groupe II comprenait 20 malades qui avaient des hémorragies digestives. L'acidité gastrique totale et sous forme libre, le débit acide basal, le pepsinogène sérique de type I, le débit sanguin au niveau de la muqueuse gastrique et la gastrine étaient nettement plus faibles dans le groupe II, tandis que la gastrinémie et la coloration de la somatostatine étaient considérablement plus élevées. Aucune modification histopathologique n'a été notée entre les deux groupes. En conclusion, le saignement causé par la fibrose hépatique entraîne une hypoacidité, une hypergastrinémie et une hypopepsinogénémie. Le débit sanguin estimé distingue les patients présentant une gastropathie liée à l'hypertension portale de ceux qui font des hémorragies.

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Introduction

Hepatic schistosomiasis is the most frequent cause of portal hypertension worldwide [*1*]. Oesophageal varices are frequent and dangerous sequelae of portal hypertension. Sclerotherapy is the key to managing bleeding oesophageal varices [2].

Gastric mucosal lesions are common in individuals with portal hypertension and can be an important cause of blood loss, which is generally slow and insidious but can be massive and occasionally fatal [*3*]. Reports of hypergastrinaemia and hypopepsinogenaemia in individuals with portal hypertensive vascular ectasia exist [*4*].

This study examined gastric secretory, hormonal and mucosal changes in individuals with portal hypertensive gastropathy (PHG) due to schistosomal hepatic fibrosis (SHF) before and after sclerotherapy.

Subjects and methods

Forty patients with a history of schistosomal infestation, confirmed histopathologically by percutaneous liver biopsy, were studied. Only patients who were negative for hepatitis B and/or C were included. None of the studied patients had received proton pump inhibitors, H_2 blockers, antacids, sucralfate or beta-blockers. They were divided into the following two groups:

- Group I (non-bleeders): Twenty patients with schistosomal hepatic fibrosis (mean age 27.28 ± 11.13 years) who had no history of prior bleeding. They were further subdivided into:
  - Subgroup Ia (no PHG): Ten patients with schistosomal hepatic fibrosis with no endoscopic evidence of portal hypertensive gastropathy;
  - Subgroup Ib (PHG): Ten patients with schistosomal hepatic fibrosis, with endoscopic evidence of portal hypertensive gastropathy.
- Group II (PHG-bleeders): Twenty patients with schistosomal hepatic fibrosis with a previous history of haematemesis and/or melena (mean age 33.215 ± 13.41 years). All 20 patients had endoscopic evidence of portal hypertensive gastropathy and had oesophageal varices with or without oesophagogastric extensions; none had fundal varices. These patients were assessed both before and after sclerotherapy when complete eradication of the varices was believed to have been achieved.

A complete medical evaluation and the following investigations were undertaken:

- percutaneous liver biopsy to confirm the presence of schistosomal hepatic fibrosis;
- percutaneous intrasplenic portal pressure measurement [*5*];
- gastric acid secretory study [*6*] to include determination of the basal free and total acid output;
- measurement of serum gastrin [*7*] and pepsinogen I [*8*] levels by radioimmunoassay;
- oesophagogastroduodenoscopy with mucosal biopsies for histopathological evaluation which included:
  - estimate of gastric mucosal blood flow through morphometric analysis of the gastric mucosa [*9*]. The morphometric unit consists of a combination of size and number of mucosal vessels [*10*] and is a semiquantitative measurement of vessel volume.
  - immunohistochemistry for the detection of gastrin and somatostatin [*11*] in the gastric mucosa.
- endoscopic sclerotherapy until eradication of all oesophageal varices.

Results

There were no significant differences between the two study groups regarding any of the routine laboratory investigations. However, the serum albumin was significantly lower in group II (3.18 ± 0.37 mg/dl) than in group I as a whole (3.97 ± 0.51 mg/dl); subgroup Ia (4.2 ± 0.49 mg/dl) and subgroup Ib (3.75 ± 0.45 mg/dl) ($P < 0.05$). Prothrombin activity was also significantly lower in group II (63.60 ± 8.81%) than in group I (76.35 ± 5.98%), subgroup Ia (77.20 ± 7.47%) and subgroup Ib (75.50 ± 4.28%) ($P < 0.05$).

Gastric secretory functions

Gastric residue free acidity was significantly lower in group II (18.5 ± 4.23 mEq/l) than in group I (22.55 ± 2.5 mEq/l); subgroup Ia (22.8 ± 2.53 mEq/l) and subgroup Ib (22.3 ± 2.58 mEq/l) ($P < 0.05$). Gastric residue total acidity was also lower in group II (40.05 ± 4.88 mEq/l) than in group I (44.05 ± 3.78 mEq/l); subgroup Ia (43.5 ± 4.38 mEq/l) and subgroup Ib (44.6 ± 3.2 mEq/l) ($P < 0.05$).

Basal acid output free acidity was significantly lower in group II (18.65 ± 4.13 mEq/l) than in group I (22.25 ± 1.62 mEq/l); subgroup Ia (22.0 ± 1.7 mEq/l) and subgroup Ib (22.5 ± 1.62 mEq/l) ($P < 0.05$). Basal acid output total acidity was significantly lower in group II (40.4 ± 5.89 mEq/l) than in group I (44.7 ± 3.56 mEq/l); subgroup Ia (43.7 ± 3.47 mEq/l) and subgroup Ib (45.7 ± 3.53 mEq/l) ($P < 0.05$).

There was no significant difference for either gastric residue or basal acid output in group II subjects before and after sclerotherapy.

Serum gastrin

Serum gastrin was significantly higher in group II (121.10 ± 70.80 pg/ml) than in group I (48.9 ± 54.5 pg/ml); subgroup Ia (26.4 ± 17.28 pg/ml) and subgroup Ib (71.4 ± 69.74 pg/ml) but no significant difference was observed between subgroups Ia and Ib. There was no significant difference in the serum gastrin levels in group II subjects before (121.1 ± 70.86 pg/ml) and after (128.35 ± 36.7 pg/ml) sclerotherapy.

Serum pepsinogen I

Serum pepsinogen I levels were significantly lower in group II (22.75 ± 6.07 ng/ml) than in group I (34.25 ± 6.36 ng/ml); subgroup Ia (37.7 ± 5.31 ng/ml) and subgroup Ib (30.8 ± 5.53 ng/ml) but no significant difference was observed between subgroups Ia and Ib. There was no significant difference in serum pepsinogen I levels in group II subjects before (22.75 ± 6.07 ng/ml) and after (21.95 ± 4.33 ng/ml) sclerotherapy.

Oesophagogastroduodenoscopy

Oesophageal varices were present in 50% of subgroup Ia, 80% of subgroup Ib and in 100% of group II. Oesophageal varices were graded according to the Waldram classification. Oesophageal varices grade I were present in 3 cases (30%) of subgroup Ia, 2 cases (20%) of subgroup Ib and none of group II. Oesophageal varices grade II were present in 2 cases (20%) of subgroup Ia, 2 cases (20%) of subgroup Ib and 7 cases (35%) of group II. Grade III oesophageal varices were present in none of subgroup Ia, in 4 cases (40%) of subgroup Ib and 13 cases (65%) of group II. Red colour signs were present in 75% of group II and none of group I. Gastric junctional varices were present in none of group I but present in 3 cases (15%) of group II. Gastric erosions were present in 1 case (5%) of group I and in 3 (15%) of group II. As a selection parameter, mosaic pattern of gastric mu-

cosa was present in none of subgroup Ia and all patients of subgroup Ib and group II.

Histopathological findings

Gastric inflammation. Gastric mucosal inflammation was present in 60% of subgroup Ia, 80% of subgroup Ib and 60% of group II. Mild inflammation was present in 40% of subgroup Ia, 20% of subgroup Ib and 25% of group II. Moderate inflammation was present in 10% of subgroup Ia, 50% of subgroup Ib and 15% of group II. Severe inflammation was present in 10% of subgroup Ia, 10% of subgroup Ib and 20% of group II. There was no significant difference between any of the studied groups regarding the presence or severity of inflammation. After sclerotherapy, despite the development of eosinophilic infiltration in the gastric mucosa, no significant change in the presence or severity of gastric mucosal inflammation was evident (Figures 1 and 2).

Capillary ectasia. Capillary ectasia, defined as dilated capillaries, was found in 40% of subgroup Ia, 70% of subgroup Ib and 70% of group II ($P > 0.05$). After sclerotherapy, there was a slight insignificant reduction in the presence of capillary ectasia (60%) as compared to before sclerotherapy (70%) (Figures 3–8).

Estimation of gastric mucosal blood flow (GMBF)

The estimated GMBF was 601.6 ± 66.81 morphometric units in group I (648 ± 47.32 morphometric units in subgroup Ia, 554.30 ± 47.02 morphometric units in subgroup Ib) and 429 ± 81.35 morphometric units in group II. The GMBF was statistically significantly lower in group II compared to group I, subgroups Ia and Ib; it was also statistically significantly lower in subgroup Ib compared to subgroup Ia. After sclerotherapy, there was no change in the estimated GMBF (424 ± 79.78 morphometric units) in group II.

Estimation of portal venous pressure

Portal venous pressure (PVP) was 9.7 ± 3.95 mmHg in group I (6.7 ± 1.34 mmHg in subgroup Ia, 12.7 ± 3.33 mmHg in subgroup Ib) and 6.25 ± 3.19 mmHg in group II. These differences between groups and subgroups were statistically significant.

Immunohistopathological evaluation for gastrin and somatostatin

Gastrin. Gastrin was histochemically present in the gastric mucosa of 7 cases (70%) of subgroup Ia, 5 of which were strongly positive; 6 cases (60%) of subgroup Ib, 4 of which were strongly positive; and in 9 cases (45%) of group II, 3 of which were strongly positive. There was no statistically significant difference between any of the studied groups regarding the presence gastrin staining. After sclerotherapy, gastrin was present in 8 cases (40%) of group II, 2 of which were strongly positive. No significant difference existed between pre- and post-sclerotherapy studies.

Somatostatin. With regard to the presence of somatostatin in the gastric mucosa, there were no statistically significant differences between any of the studied groups and subgroups, nor between studies performed before and after sclerotherapy in group II (Figures 9–12). All histopathological findings are shown in Tables 1–3.

Discussion

The mosaic pattern of the gastric mucosa is said by some authors to be a sensitive and

specific sign for portal hypertension because it disappears after portosystemic shunt operations [*12*]. On the other hand, other authors deny this finding as endoscopic gastric biopsies obtained from areas showing mosaic patterns do not reveal any indent vascular abnormalities [*13*].

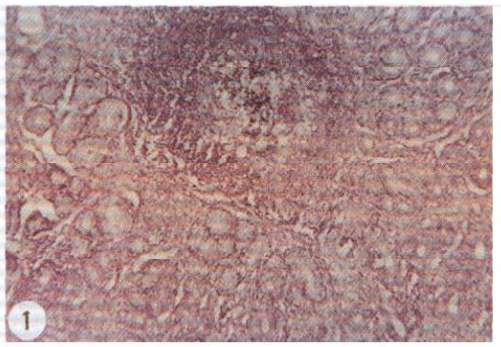
Fikry et al. [*14*] and Orloff et al. [*15*] have suggested that hyperacidity occurs in patients with cirrhosis secondary to an impairment of gastric secretagogue metabolism as a result of advanced liver disease. Our study (as well as others [*16*]), shows that gastric acid secretory function is significantly less in bleeders than in non-bleeders. Lam et al. [*16*] suggested that the hypoacidity seen in bleeders might be a consequence of excessive circulating amounts of acid inhibiting intestinal peptides, e.g. higher plasma levels of gastrointestinal inhibitory polypeptide, gastrin and glucagon. This was reported in patients with cirrhosis, secondary to either reduced liver inactivation through portosystemic shunts or diminished liver degradation due to hepatic insufficiency.

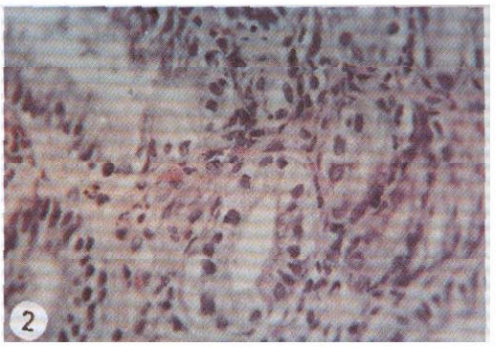
In this study, as well as others [*17*], sclerotherapy did not affect either free or total acidity. Bleeders had both hypergastrinaemia and hypopepsinogenaemia I. Quintero et al. [*18*] attributed this finding to the presence of atrophic gastritis in the fundic mucosa. In contrast, Lam et al. [*16*] reported hypergastrinaemia in people with cirrhosis, with no relationship between the fundic mucosal morphology and gastric acidity.

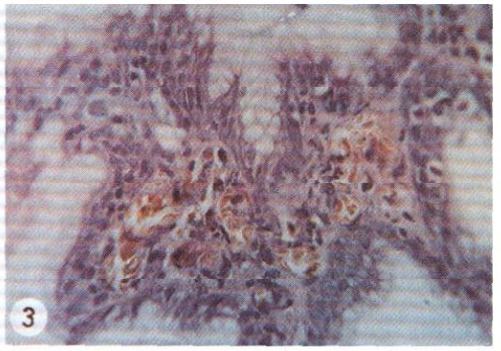
Although McCormack et al. [*19*] reported no relation between the presence of gastropathy and the degree of hepatic dysfunction, Sacchetti et al. [*20*] observed that severe liver dysfunction is associated with the presence and severity of gastropathy.

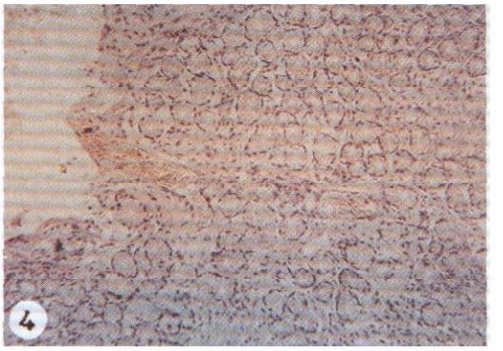
The macroscopic appearance of inflammatory gastritis is indistinguishable from that seen in mild congestive gastropathy [*21,22*] . However, McCormack et al. [*19*] were able to distinguish PHG from inflammatory gastritis by the presence of dilatation of the submucosal veins which are tortuous and show irregular foci of internal thickening. These vascular abnormalities correlate well with the gastric microcirculation as described by Hashizume et al. [*23*]; using silicon rubber casts, they were able to demonstrate increased numbers of arteriovenous communications in the submucosa together with dilated precapillaries, capillaries and veins. A morphometric analysis [*24*] has confirmed the capillary dilatation, while a recent ultrastructural study has shown that the presence of gastric red spots corresponds with extravasation of red blood cells through defective regions in the endothelium, as well as between interepithelial spaces [25]. Although Saperas et al. [*21*] found that the snare biopsy technique was ideal for obtaining good specimens in portal hypertension, such a procedure cannot be recommended for routine use. In contrast, however, both Corbishley et al. [*26*] and Foster et al. [22], using standard biopsy techniques, failed to distinguish between mucosal capillary dilatation due to PHG and in control subjects.

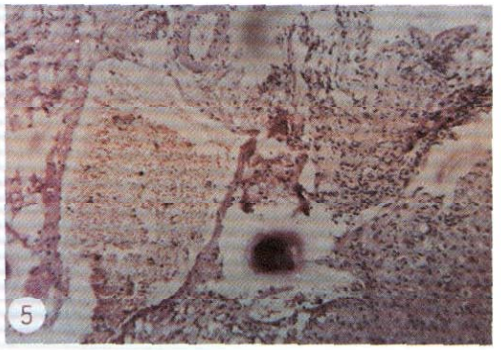
Manabe et al. [*27*] observed significant arteriovenous shunting in the gastric microcirculation, a finding confirmed indirectly by Sarfeh et al. [*28*] who reported impaired mucosal, but not serosal, oxygen tension in portal hypertensive rats. In addition, Sato et al. [*29*] estimated mucosal blood volume and oxygenation in patients with cirrhosis. They found that mucosal blood volume tended to increase in such patients; in contrast, the mucosal oxygenation level decreased significantly. In addition, cirrhotic patients with oesophageal varices showed a greater reduction in gastric mucosal oxy-











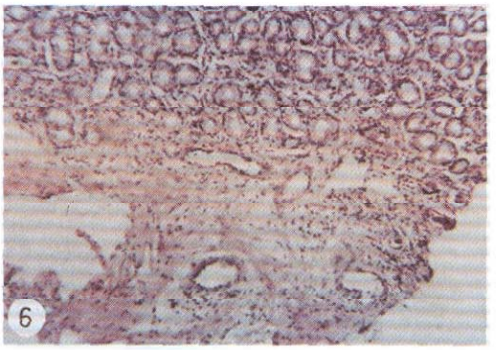


Figure 1 **Gastric mucosal endoscopic biopsy H & E (× 250), showing chronic inflammatory reaction with germinal centre formation**

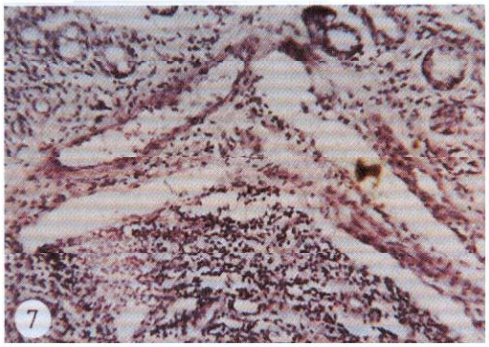
Figure 2 **Gastric mucosal endoscopic biopsy H & E (× 400), showing the appearance of eosinophils post-sclerotherapy**

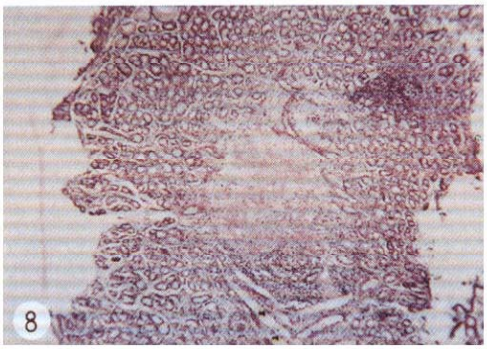
Figure 3 **Gastric mucosal endoscopic biopsy H & E (× 400), showing congested, dilated, small-sized blood vessels pre-sclerotherapy**

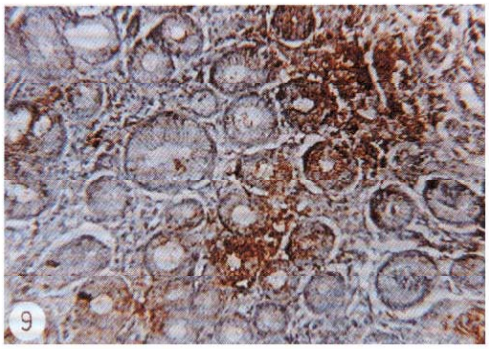
Figure 4 **Gastric mucosal endoscopic biopsy H & E (× 400), showing congested, dilated, medium-sized blood vessels pre-sclerotherapy**

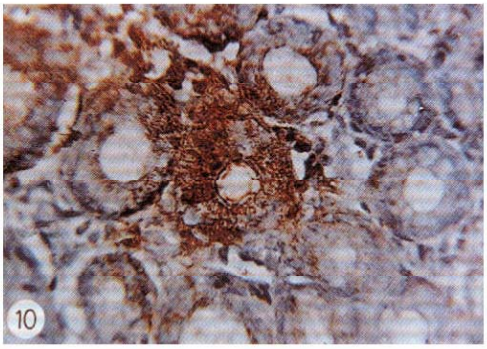
Figure 5 **Gastric mucosal endoscopic biopsy H & E (× 400), showing congested, dilated, large-sized blood vessels pre-sclerotherapy**

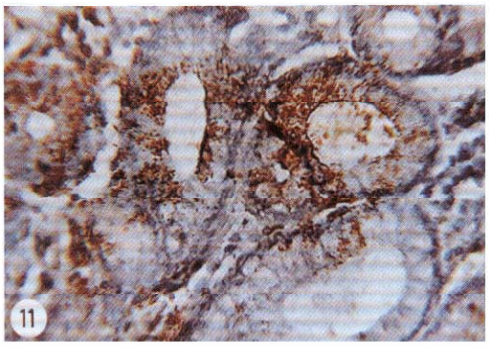
Figure 6 **Gastric mucosal endoscopic biopsy H & E (× 250), showing medium-sized, collapsed blood vessels post-sclerotherapy**











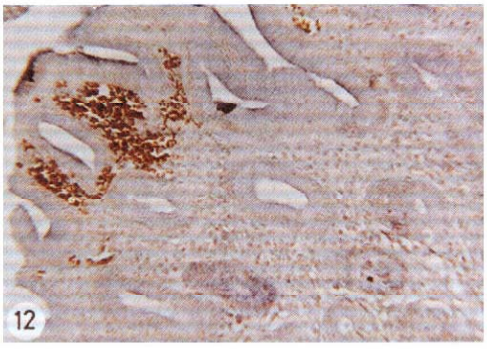


Figure 7 **Gastric mucosal endoscopic biopsy H & E (× 100), showing large-sized blood vessels in between mucosal glands. Glands are collapsed post-sclerotherapy**

Figure 8 **Higher power view of Figure7 H & E (× 400), showing collapsed post-sclerotherapy vessels surrounded by mild chronic inflammatory infiltrate**

Figure 9 **Gastric mucosa, antigastrin (× 250), showing patchy distribution of antigenic staining (about 50% = strongly positive)**

Figure 10 **Gastric mucosa, antigastrin (× 400), showing cytoplasmic membranous deposits and myoepithelial deposits in some glands**

Figure 11 **Gastric mucosa, antisomatostatin (× 400), showing cytoplasmic, membranous, intraluminal deposits**

Figure 12 **Gastric mucosa, antisomatostatin (× 250), showing negative staining of the gland in a group I patient, while blood vessels and red blood cells represent a positive internal control**

Table 1 **Histopathological findings in group I and II patients**

Histopathological findings	Group I						Group II				Significance				
	Ia (n = 10)		Ib (n = 10)		Total (n = 20)		before EVS (n = 20)		after EVS (n = 20)		Z_1 Group I vs II	Z_2 Group Ia vs 1b	Z_3 Group Ia vs II	Z_4 Group Ib vs II	Group II before vs after χ^2 value
	No.	%	No.	%	No.	%	No.	%	No.	%					
Gastric mucosal inflammation															
Mild	4	40	2	20	6	30	5	25	4	20	0.3541 ($P > 0.05$)	0.9759 ($P > 0.05$)	0.8425 ($P > 0.05$)	0.3052 ($P > 0.05$)	0.3232 NS
Moderate	1	10	5	50	6	30	3	15	4	20	1.1359 ($P > 0.05$)	1.9518 ($P > 0.05$)	0.3798 ($P > 0.05$)	2.0436 ($P > 0.05$)	0.3738 NS
Severe	1	10	1	10	2	10	4	20	6	30	0.8856 ($P > 0.05$)	0.000 ($P > 0.05$)	0.6928 ($P > 0.05$)	0.6928 ($P > 0.05$)	0.3738 NS
Capillary ectasia	4	40	7	70	11	55	14	70	12	60	$\chi^2 = 0.96000$		$\chi^2 = 2.8800$		1.1282 NS

EVS = endoscopic variceal sclerosis
NS = not significant

Table 2 **Gastric mucosal blood flow and portal venous pressure in group I and II patients**

Variable	Group I			Group II		t test	F test
	Ia (n = 10) $\chi \pm s$	Ib (n = 10) $\chi \pm s$	Total (n = 20) $\chi \pm s$	before EVS (n = 20) $\chi \pm s$	after EVS (n = 20) $\chi \pm s$		
Gastric mucosal blood flow (morphometric units)	648.90 ± 47.32	554.30 ± 47.02	601.60 ± 66.81	424.60 ± 79.78	429.75 ± 81.35	7.3011 ($P < 0.05$)	37.9490 ($P < 0.05$)
Portal venous pressure (mmHg)	6.70 ± 1.34	12.70 ± 3.33	9.70 ± 3.95	6.25 ± 3.19 ($P < 0.05$)	4.79 ± 2.96 ($P < 0.05$)	5.7684 ($P < 0.05$)	36.3509 ($P < 0.05$)

EVS = endoscopic variceal sclerosis

Table 3 Immunohistopathological study for antigastrin and antisomatostatin antibody in groups I and II patients

Variable	Group I				Group II					χ^2 test	χ^2 test	Fisher
	Ia (n = 10)		Ib (n = 10)		Total (n = 20)		before EVS (n = 20)		after EVS (n = 20)	Group (I, II)	Group (Ia, II) + (Ib, II)	exact test (group II before and after)
	No.	%	No.	%	No.	%	No.	%	No.	%	Value	Value	
Antigastrin antibody	7 (5)	70	6 (4)	60	13 (9)	65	9 (3)	45	8 (2)	40	0.90226 P = 0.34218	4.11028 P = 0.12808	P = 0.1280
Antisomatostatin antibody	2	20	6 (2)	60	8 (2)	40	11 (9)	55	10 (8)	50	1.61616 P = 0.20363	6.66667 P = 0.091821	P = 0.3438

EVS = endoscopic variceal sclerosis.

genation than those without. Cirrhotic patients with gastric lesions have significantly lower oxygenation levels than those without such lesions.

Although the total gastric blood flow is reported to be increased in patients with portal hypertension, the GMBF is generally lower in patients with portal hypertension than in controls [*30*], as seen in our study, regardless of the method employed in measurement [*9,27,28,30*]. GMBF, assessed morphometrically in the present study, as well as by Nishiwaki et al. [*10*], revealed that the GMBF is decreased in PHG bleeders, as compared to non-bleeders. Also, the GMBF is decreased in non-bleeders with PHG as compared to non-bleeders without PHG.

Immunohistopathologically, gastrin was detected less often in PHG-bleeders than in non-bleeders, with or without PHG. This finding suggests that the hypergastrinaemia reported to occur in cirrhosis is secondary to a reduced degradation as a result of portosystemic shunting and/or diminished hepatic degradation of the hormone and is not due to increased gastric mucosal production of the hormone. This also suggests that gastric lesions seen in patients with cirrhosis with PHG may be a result rather than a cause of hypergastrinaemia.

In addition, somatostatin staining was detected more often in PHG-bleeders than in non-bleeders. This may be due to a physiological response to suppress the increased levels of other gastrointestinal inhibitory peptides observed in patients with cirrhosis.

Our findings can be summarized as follows:

- Biochemically, SHF bleeders with PHG had significantly greater hypoacidity, hypergastrinaemia and hypopepsinogenaemia I than non-bleeders.

- Histopathologically, SHF bleeders with PHG did not have greater gastric mucosal inflammation and capillary ectasia than non-bleeders.
- Morphometrically, SHF bleeders with PHG had a significantly lower estimated GMBF, than non-bleeders, and a significantly lower estimated GMBF than those without PHG.
- Immunohistopathologically, SHF bleeders with PHG had more mucosal somatostatin and less gastrin than non-bleeders.
- SHF patients with PHG did not differ from those without PHG except for estimated GMBF, which was found to be significantly lower in patients with PHG than in those without PHG.
- Sclerotherapy did not affect any of the gastric parameters studied.

Conclusions

First, SHF bleeders with PHG constitute a new syndrome as they have significant hypoacidity, hypergastrinaemia and hypopepsinogenaemia I compared to non-bleeders, which may be secondary to either portosystemic shunting or hepatic dysfunction, but not to increased production. Second, GMBF is a specific sign for PHG, as well as bleeding, as it seems to be able to differentiate between SHF patients with PHG and those without PHG, as well as between SHF bleeders with PHG and non-bleeders. It seems that the lower the GMBF is, the more likely PHG will develop, and the more likely SHF patients with PHG will bleed. Third, sclerotherapy does not significantly alter any of the studied parameters of gastric functions.

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