Digestive Diseases and Sciences, Vol. 31, No. 2 (February 1986 Supplement), pp. 35S–41S

Hemodynamics of the Gastric Mucosa and Gastric Ulceration in Rats and in Patients with Gastric Ulcer

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The microcirculation is the fundamental nutrient supply and waste removal system of all tissues. Recent improvements in spectrophotometric technique have made possible the noninvasive assessment of oxygen supply and utilization in the gastric mucosa. The authors have utilized such methods to assess gastric mucosal hemodynamics. The technique permitted further clarification of the roles of the gastric microcirculation, mucosal oxygenation, and acid secretion in the pathogenesis of stress ulcers in the stomach of rats. Furthermore, it provided important information on the function of gastric mucosal hemodynamics in the healing of gastric ulcers in man. The technique is described along with the authors' correlation studies between spectrophotometric data and other techniques for measuring gastric blood flow (hydrogen gas clearance and aminopyrine clearance methods and direct electromagnetic flowmeter techniques) and the prevention of ulcerogenesis.

Despite intermittent exposure to a very low intraluminal pH, the integrity of the gastric mucosa is maintained under the usual physiological conditions, primarily because of a balance between aggressive factors (acid, pepsin, etc) and mucosal defense mechanisms.

Mucosal cellular function, the most important of these defense mechanisms, is maintained by the microcirculation, the fundamental nutrient supply and waste removal system of all tissues. Alterations in the mucosal microcirculation can result in decreased mucosal blood flow and/or decreased mucosal oxygenation, which in turn may produce hemorrhage and ulceration (Figure 1) (1–6).

Recent improvements in spectrophotometric techniques have made possible the noninvasive assessment of oxygen supply and utilization in the gastric mucosa during endoscopy (7, 8). Noninvasive spectrophotometric methods have permitted further clarification of the roles of the gastric microcirculation, mucosal oxygenation, and acid secretion in the pathogenesis of stress ulcers at different locations in rat stomach (6). Furthermore, these methods have provided important information on the function of gastric mucosal hemodynamics in the healing of gastric ulcers in man (9).

We have studied, by an *in vivo* microscopic technique (800X), the mechanisms by which hemorrhagic shock causes: (1) a significant change in the gastric microcirculation, (2) a severe reduction of mucosal oxygenation, and (3) acute gastric ulceration. This report will describe the technique and review the authors' correlation studies of spectrophotometric data with other techniques for measuring gastric blood flow (hydrogen gas clearance methods, aminopyrine clearance methods, and direct electromagnetic flowmeter techniques) and the mechanisms of protection against ulcerogenesis.

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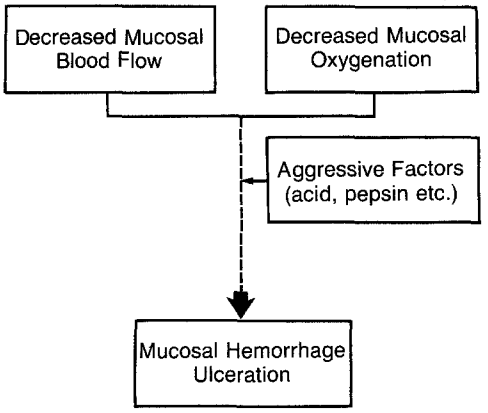

Fig 1. Mechanisms by which alterations in mucosal microcirculation can lead to ulceration.

SPECTROPHOTOMETRIC MUCOSAL PHOTOGRAPHY

Advances in the study of microcirculation in the gastric mucosa have, to a considerable degree, resulted from new methodological developments. One such achievement is organ reflectance spectrophotometry, which employs optoelectronics technology. With this technique, a beam of light emitting from the tips of optical fibers is directed toward the gastric mucosa and diffusely reflected by the mucosal surface. The reflected light is analyzed by a computer-equipped spectrophotometer.

The spectral pattern of the reflected light varies according to the color tone of the mucosa. Small differences in blood volume and oxygen saturation of hemoglobin can be spectrally distinguished. Reflectance spectrophotometry can thereby estimate not only the volume of blood flowing in the gastric microcirculation, but also the degree of oxygen saturation of hemoglobin.

Data obtained from animal studies or from ulcer patients can be processed by computer, and the mucosal blood flow graphically represented. Mucosal blood volume in a person in good health is represented by color variation ranging from red to light blue; a red color reflects greater blood volume, a blue color a lesser volume. In a patient with an active ulcer, the ulcer image appears entirely in dark blue, revealing the marked decrease in mucosal blood volume. In a patient with a healing ulcer, the red color is intensified, showing an increasing blood volume in the vicinity of the ulcer. In the scarring stage of an ulcer, the red color loses its intensity, whereas blood volume in the vicinity of an intractable ulcer remains low, as seen spectrophotometrically.

In order to demonstrate the spectrophotometric method, and to observe the role of gastric mucosal microcirculation and mucosal oxygenation in the pathogenesis of gastric ulcers, hemorrhagic shock was induced in a rat by means of a standard technique reported elsewhere (10), and followed by baseline determinations. With the unaided eye, we observed no precise color change, but upon examining the reflectance spectra, a simultaneous decrease in mucosal blood volume and in the degree of oxygen saturation was noted (Figure 2).

A reduction in the mucosal blood flow was also seen through the microscope. The flow had become sluggish, exhibiting a characteristic rouleau formation or "sludge phenomenon." In addition, retrograde flow from the collecting venules into the

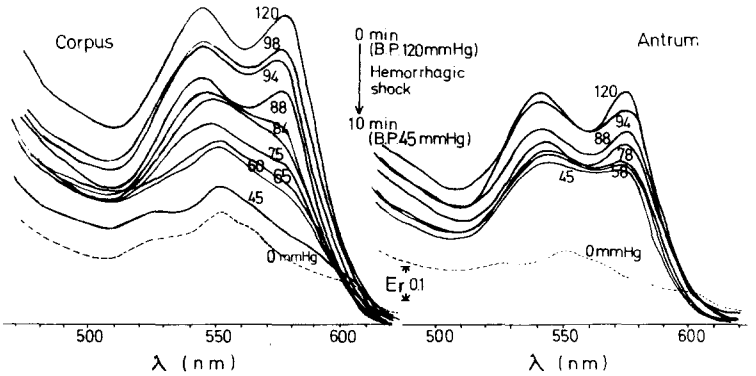

Fig 2. Sequential change in reflectance spectra of rat gastric mucosa during hemorrhagic shock. Spectra were taken at the various arterial blood pressures (BP) indicated. From Sato et al: Gastroenterology, 1979 (6); reproduced by permission of The American Gastroenterological Association.

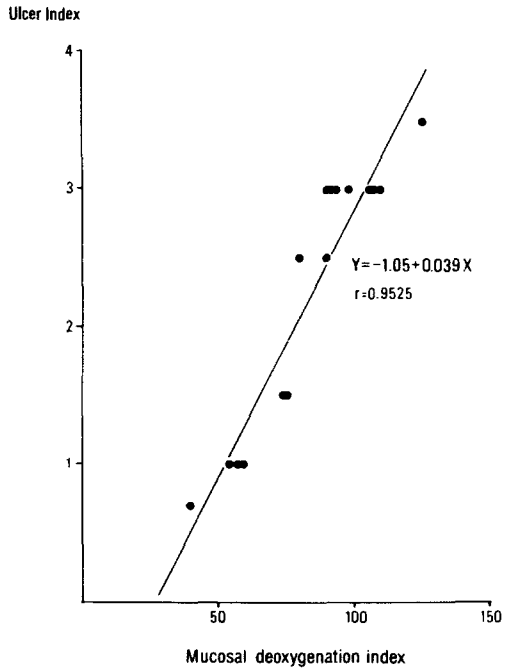

Fig 3. Relationship between the mucosal deoxygenation index and the ulcer index.

capillaries was observed. However, the presence of an ulcer was not clearly seen.

What, then, causes an ulcer to form? If blood is reinfused into the rat in hemorrhagic shock, the stagnant blood cells begin to flow again. When blood flow resumes under normovolemic conditions, mucosal hemorrhage appears and an ulcer forms.

This phenomenon may be explained in the following manner. Hemorrhagic shock reduces the mucosal blood volume, resulting in a decrease in mucosal oxygenation. The hypoxic mucosa is weakened and when normal blood flow resumes, the intravascular pressure increases abruptly, causing damage to the weakened vascular wall.

The mucosal oxygenation index can be derived from the spectrophotometrically determined blood volume and degree of oxygen saturation. A linear relationship exists between the mucosal deoxygenation index and the ulcer index (Figure 3), and mucosal deoxygenation is closely associated with the development of mucosal ulceration.

When pirenzepine, a selective M_1 antimuscarinic agent, is administered to the hypovolemic rat, the hemorrhagic shock-induced reduction of blood flow and decrease in oxygen saturation is significantly inhibited (10). Hemorrhage and ulceration are also prevented by this agent. Why does pirenzepine inhibit the reduction in blood flow?

Recently Nakamura et al (11) discovered parasympathetic nerve endings adjacent to mucosal capillaries that act on microfilaments in capillary endothelial cells. Hence, the following hypothesis can be presented. Stress stimulates the cholinergic nerves, promoting the release of acetylcholine. The microfilaments in capillary cells may produce contraction or increase the permeability of capillaries in response to changing concentrations of acetylcholine. These alterations can also affect mucosal oxygen saturation. It has been shown that pirenzepine inhibits ulcer formation to an extent greater than that predicted from the inhibition of reduced oxygen saturation (10). It appears that pirenzepine inhibits acid secretion in addition to its effect on mucosal oxygenation (10).

It is believed that ulcerogenesis is promoted by the reduction of mucosal blood flow and the decrease in oxygen delivery to the mucosa. This condition is aggravated by aggressive factors such as acid secretion, promoting mucosal hemorrhage and ulcer formation. Pretreatment with the H_2-receptor antagonists cimetidine and ranitidine, and the presumed gastrin-receptor antagonist proglumide, also produced a protective effect, inhibiting both the reduction of mucosal oxygenation induced by hemorrhagic shock and subsequent gastric ulcer formation (10).

CORRELATIVE SPECTROPHOTOMETRIC DATA

It has been shown experimentally that the reduction of mucosal blood flow varies with the magnitude of hemorrhage (12). This same study also demonstrated a close relationship between results derived from the hydrogen gas clearance method and the spectrophotometric method (Figure 4).

In another experiment, the effects of prostaglandin E_2 and intravenous indomethacin on mucosal blood volume (MBV), mucosal blood flow (MBF), gastric arterial flow (GAF), and oxygen saturation of hemoglobin (SO_2), were compared, using a stomach flap *in vivo* (13). The spectrophotometrically determined relationships among these parameters are seen in Figure 5. Prostaglandin E_2 increased MBV, MBF, and GAF, while indomethacin decreased these parameters. A significant linear correlation can be seen between the change of MBV and MBF and between MBV and GAF. A less significant correlation exists between MBV and oxygen saturation changes, indicating that changes in oxygen saturation are not always correlated with changes in MBV.

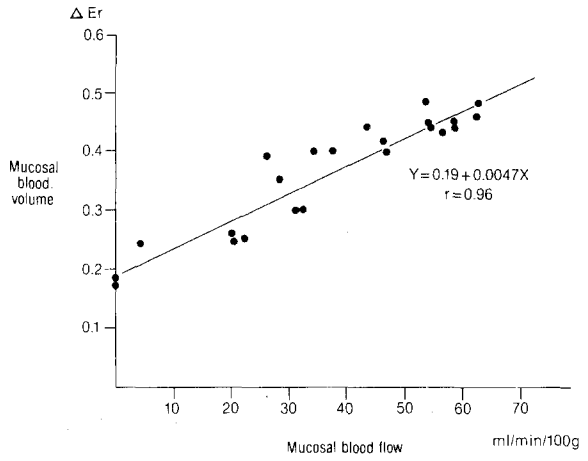

Fig 4. Correlation between spectrophotometrically determined gastric mucosal blood volume (Δ Er) and the mucosal blood flow as measured by the hydrogen gas clearance method.

The role of gastric mucosal hemodynamics in the pathogenesis of the gastric ulcer is seen more clearly in Figures 4 and 5. The effects of intragastric hydrochloric acid alone, hemorrhagic shock alone, and the two combined, on gastric mucosal damage and intraluminal bleeding is shown in Figure 6. Intragastric acid administration alone and blood removal alone caused minimal gastric lesions. However, the combination of 0.2 N HCl and blood removal caused significant gastric mucosal lesions and bleeding.

Figure 7 shows the effects of subcutaneous histamine alone, and histamine followed by hemorrhagic shock. Subcutaneous histamine alone and blood removal alone caused minimal gastric lesions. However, the combination of histamine 100 mg/kg subcutaneously and blood removal caused a significant increase in gastric mucosal lesions and intraluminal bleeding.

Administration of famotidine, an H_2-receptor antagonist, prior to histamine administration, significantly decreased gastric ulcer size (Figure 8). Famotidine protected the mucosa from bleeding. Even in the complete absence of acid secretion, in the presence of high doses of famotidine, the appearance of gastric lesions was correlated with the decrease in gastric MBV and deoxygenation.

DISCUSSION

The observations reported above suggest that stress ulceration is initiated by disturbance of the mucosal microcirculation and by mucosal deoxygenation and that acid secretion subsequently promotes mucosal lesions in hemorrhagic shock-induced gastric ulcers. It was also found that mu-

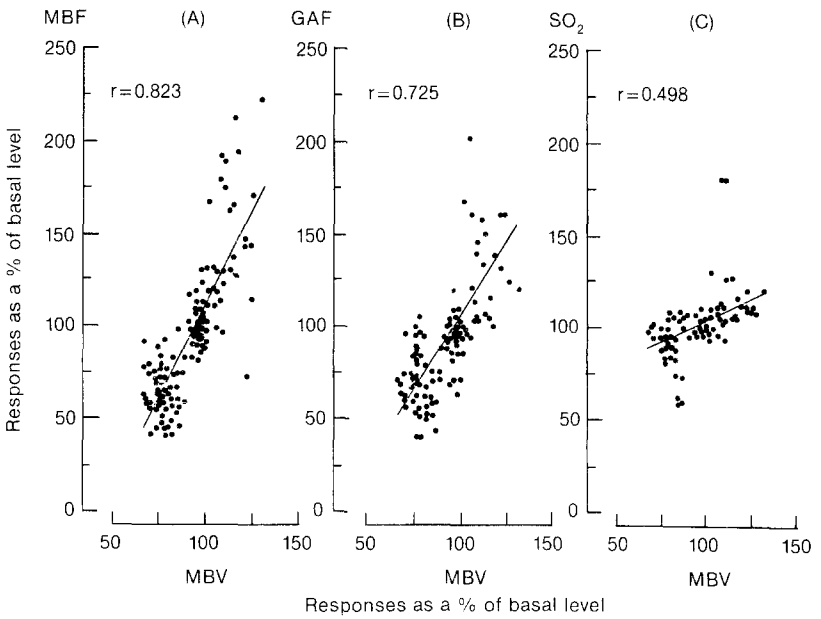

Fig 5. Spectrophotometrically determined relationships between estimated mucosal blood volume (MBV), and mucosal blood flow (MBF) measured by the aminopyrine clearance method (A); gastric arterial flow (GAF) measured by electromagnetic flow meter (B); and gastric mucosal hemoglobin saturation (SO_2) estimated spectrophotometrically (C) in dogs.

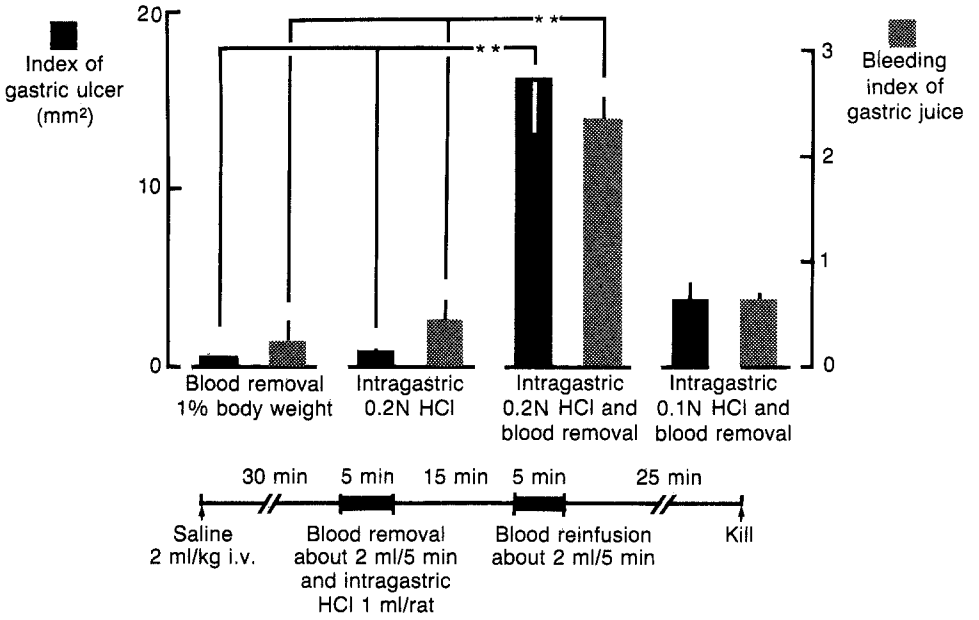

Fig 6. Effects of intragastric hydrochloric acid, hemorrhagic shock, and HCl plus hemorrhagic shock on gastric mucosal damage and bleeding in anesthetized rats ($N = 7$).**$P < 0.01$.

cosal blood volume in the whole stomach markedly alters the healing process of gastric ulcers and that increased mucosal blood volume at the ulcer margin, with less acid secretion, is important for the early healing of gastric ulcers in man.

If noninvasive spectrophotometric techniques are to be of value in the clinical determination of mucosal injury prior to ulcer formation, it will be necessary to measure mucosal blood flow at the precise site of ulcer occurrence. Although it is possible to localize the gastric mucosal ischemic site experimentally, a clinical correlation has not yet been demonstrated.

In addition to decreased mucosal blood flow and oxygen saturation, decreased prostaglandin (PG)

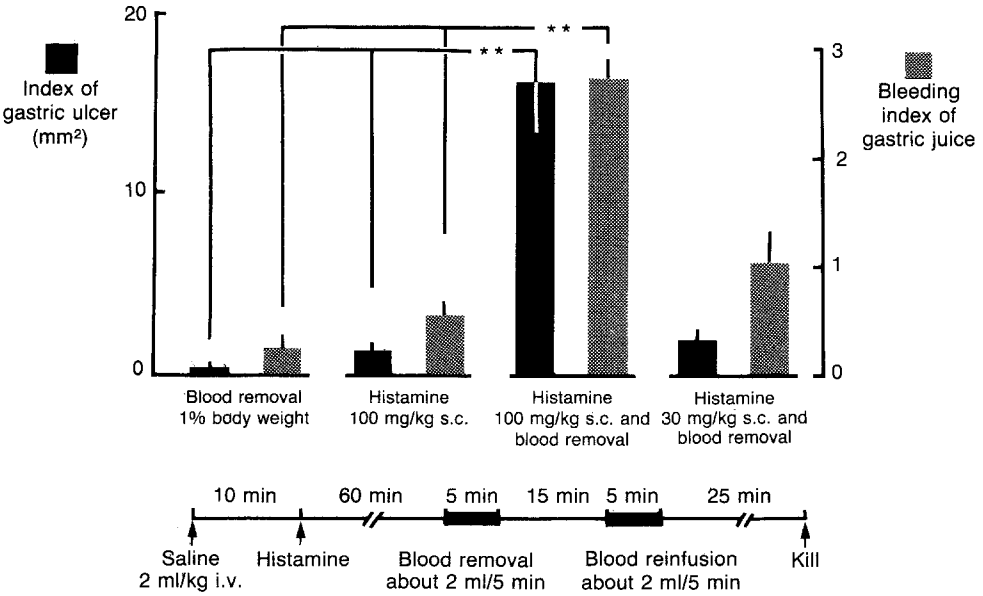

Fig 7. Effects of hemorrhagic shock, histamine, and histamine plus hemorrhagic shock on gastric mucosal damage and intraluminal bleeding in anesthetized rats ($N = 7$).**$P < 0.01$.

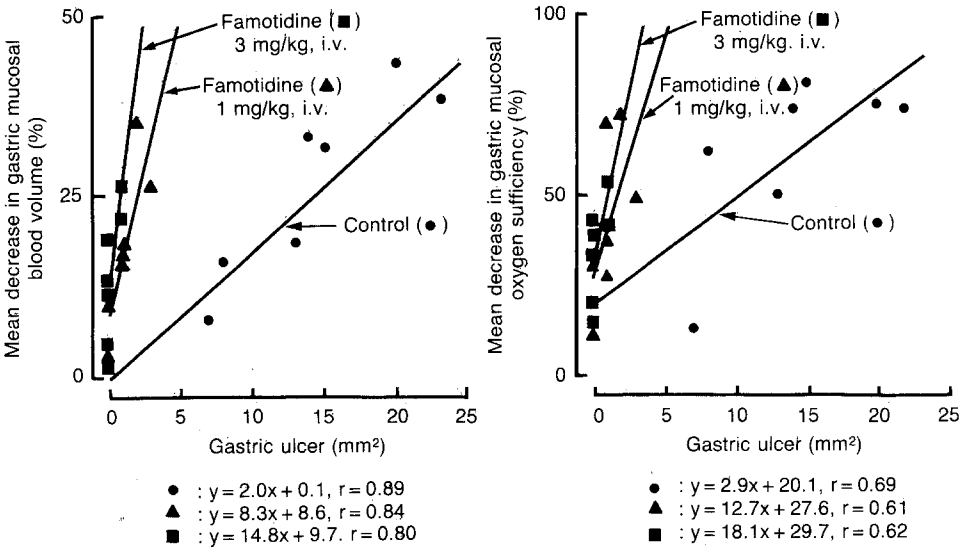

Fig 8. Relationship between gastric ulcer and decrease in gastric mucosal circulation following histamine administration and hemorrhagic shock in control rats and rats treated with the H_2-receptor antagonist famotidine (N = 7).

content has also been shown to play a significant role as an etiologic factor in mucosal injury prior to ulcer formation and hemorrhage. It is not yet known whether the alterations in microcirculation or the decrease in PG content are primarily responsible for mucosal damage. The authors are now examining the effect of misoprostol on the gastric mucosal blood volume amd oxygenation in healthy human subjects.

CONCLUSIONS

The following conclusions may be drawn from the above findings: (1) The gastric mucosal microcirculation, as demonstrated by noninvasive spectrophotometric methods, is altered by stress and hemorrhagic shock in rats. (2) Alterations in gastric mucosal microcirculation, particularly decreased blood flow and reduced oxygen saturation, produce changes that are ulcerogenic in the presence of acid secretion. (3) A correlation exists between gastric mucosal blood volume, as measured by spectrophotometry, and gastric mucosal blood flow, as measured by the hydrogen gas clearance method. (4) Prostaglandins increase mucosal blood volume and flow, and prostaglandin inhibitors decrease these parameters. (5) Hydrochloric acid alone and hemorrhagic shock alone produce minimal gastric mucosal lesions; however, the combination of these factors produces significant gastric mucosal lesions and bleeding. (6) Histamine alone and hemorrhagic shock alone produce a very slight gastric mucosal injury; however, the combination of these factors produces significant gastric mucosal lesions and bleeding. Famotidine, a potent H_2-receptor antagonist, can protect the gastric mucosa from histamine-induced bleeding.

There are still many unsolved problems regarding the role of mucosal hemodynamics in ulcerogenesis. However, the qualitative measurement of mucosal microcirculation is providing new information regarding the etiology and treatment of ulcer disease.

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