STIGMATA OF RECENT HAEMORRHAGE

Different implications of stigmata of recent haemorrhage in gastric and duodenal ulcers. CHI-SIN CHANG-CHIEN, CHENG-SYANG WU, PANG-CHI CHEN et al. Dig. Dis. Sci. 1988; 33: 400-4.

In this report, 193 patients with bleeding peptic ulcers were studied. The majority (n=141) had duodenal ulcers. Stigmata of recent haemorrhage were described as spurt, active oozing, fresh clot, black clot, protruding vessel and clear base without stigmata. Patients with continuous bleeding or those who rebled were categorized as unstable bleeders. A higher rate of unstable bleeders was found in gastric ulcer patients. Likewise, those patients with lesions over the lesser curvature of the stomach tended to have a significantly higher risk for continuous or recurrent bleeding than those ulcers found in other portions of the stomach. No such difference was found as far as location of the ulcer is concerned in patients with duodenal ulcer. Furthermore, they stated that spurt had the highest unstable bleeder rate, followed by active oozing, clots (fresh and black), and protruding vessel, in order of decreasing rates. They further commented that, although the bleeding gastric ulcer tended to have a higher unstable bleeder rate than the duodenal ulcer, a significant difference was observed only in ulcers with clots (fresh and black).

A protruding vessel in both gastric and duodenal ulcer patients did not predict rebleeding or subsequent surgery. Likewise, the incidence of unstable bleeders in patients with bleeding gastric ulcer or duodenal ulcer was not influenced by age.

In those patients with bleeding gastric ulcer, 11 cases had continuous bleeding and all underwent surgery. Five of the seven with rebleeding needed surgical intervention. For those patients with duodenal ulcer, all five cases with continuous bleeding underwent operation, and one of five cases with rebleeding had surgery. As such, the authors commented that patients with bleeding gastric ulcer required surgery more frequently than patients with duodenal ulcer.

Comment

Several reports have appeared since Foster et al. introduced the identification of stigmata of active or recent bleeding as a measure of prognostic significance in cases of upper gastrointestinal bleeding. Controversies abound regarding its implications or predictive importance as far as prognosis and rebleeding rate of peptic ulcer patients are concerned. Some authors have assigned great importance to stigmata of recent haemorrhage while others have questioned the prognostic significance of these stigmata. Chang-Chien et al. attempted to document such prognostic significance.

As stated in their methodology, all emergency endoscopies were carried out day or night, by the eight authors. Thus, it would be appropriate to ask how much inter-observer variability has been introduced regarding documentation of the different stigmata of recent haemorrhage. This could probably account for their different results compared with previous studies, especially in relation to the significance of a protruding vessel. In this present study, it is really surprising that none of the 19 patients with a protruding vessel rebled or subsequently required surgery. It might have been entirely different if these lesions had been photodocumented and thereafter reviewed and agreed upon by the authors.

The statement that spurters had the highest unstable bleeder rate is expected, since these are mostly, if not all, coming from arterial bleeders.
The authors commented further on the comparison of blood requirements between unstable and stable cases. However, this seems superfluous, considering their definition of unstable bleeders which comprised those who continued to bleed or those who rebled.

The apparent insignificant rate of rebleeding in those with spurt (five gastric ulcer, three duodenal ulcer) could only be due to the small number of patients in this subgroup, in addition to the surgical intervention performed on these cases which could have affected their course. This paper confirms the clinical suspicion that active bleeding, spurters or oozing, carry a bad prognosis and are likely to require intervention. However, one question that could be asked in this report, and probably in other papers which attempt to document the different stigmata of recent haemorrhage, is whether the endoscopic finding of active bleeding is simply fortuitous, since it is logical to think that all of these ‘bleeding peptic ulcers’ have bled at one point of their course, and certainly the timing of endoscopy will play a very important role in the documentation of such lesions.

To date, attempts at defining the implications of the different stigmata of recent haemorrhage in peptic ulcer lesions have provided more questions than answers. This could probably be explained by variation in interpretation of findings, different terms of description, different timing of endoscopy, and different combinations of subgroups of stigmata in arriving at a comparable prognostic grouping. Thus, a standardization of criteria needs to be established.

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DOES DIMINISHED VASCULAR RESPONSIVENESS TO NOREPINEPHRINE ACCOUNT FOR THE SYSTEMIC HYPOTENSION OF CIRRHOSIS?

Vascular reactivity to norepinephrine in rats with cirrhosis of the liver. Villamediana L. M., Dieguez G., Santos J. C. et al. Can. J. Physiol. Pharmacol. 1988; 66: 567–72.

The present experiments were designed to evaluate vascular reactivity to norepinephrine in a widely used animal model of cirrhosis, the carbon tetrachloride-induced cirrhotic rat when the animals were retaining sodium but before ascites formation. Vascular reactivity was assessed by measuring (i) the pressor response to increasing doses of intravenously injected boluses of norepinephrine in conscious rats; (ii) the pressor response to cumulative doses of intra-arterially injected norepinephrine into the perfused hindlimb; and (iii) the in vitro contractile response of arterial rings prepared from the femoral arteries of cirrhotic rats. In addition, the experimental animals were hypotensive with increases in the plasma norepinephrine concentrations and urinary excretion of its metabolites. Using these three experimental protocols, they could not find any evidence of refractoriness to norepinephrine in the cirrhotic rats compared with the sham-treated animals. Thus, they concluded that the peripheral vascular bed has a well-maintained
ability to constrict in response to norepinephrine, suggesting that the circulatory abnormalities in early experimental cirrhosis are not caused by refractoriness of the vascular smooth muscle to norepinephrine.

Comment

It is well documented that the sympathetic nervous system activity in patients suffering from cirrhosis is increased.1 Patients with cirrhosis tend to be hypotensive in the face of an elevated cardiac output. The basis for this hypotension is thought to be due to a fall in the total peripheral resistance with an inadequate compensatory increase in the cardiac output.2 The pathogenesis for the fall in total peripheral resistance is unclear, but the early studies of Laragh and his colleagues indicated that, in part, it may be due to refractoriness to endogenous vasoactive compounds, such as angiotensin II.3-5 These initial observations prompted additional investigations in cirrhotic subjects into the ability of the cardiovascular system to respond to numerous stimuli, such as changes in posture or infusions of other vasoactive compounds, such as norepinephrine. From such clinical studies, together with numerous observations made in experimental animal models of liver disease, the concept of diminished end-organ responsiveness or blunted vascular reactivity to norepinephrine developed and has now been implicated as a reason for the tendency to hypotension of cirrhotic patients.

One of the first descriptions of loss of responsiveness to norepinephrine in cirrhotic patients was made by Morandini and his colleagues.6-7 Their observations contrast with the earlier findings of Laragh's group, who found that pressor responsiveness to the amine was normal.4 Subsequent studies by Lunzer and his colleagues in 1973 and 1975 confirmed the findings that the vasculature of cirrhotic patients was refractory to endogenous as well as exogenous norepinephrine.5,6 Recently, Lenz et al. reported that the pressor response to norepinephrine in 11 patients with hepatic encephalopathy (nine of which had chronic liver disease) was enhanced.10

Despite the differences observed in the responsiveness to norepinephrine in the human cirrhotic patients, the results of experiments which assessed in vivo pressor and in vitro contractile responsiveness in the carbon tetrachloride-induced cirrhotic rats are quite equivocal (Tables 1, 2). It can be seen that, in this animal model of cirrhosis, none of investigators, including Villamediana and his colleagues, showed in vivo

| Table 1 | The summary of experiments that assessed in vivo pressor responsiveness to norepinephrine in the carbon tetrachloride-induced cirrhotic rat |
|--------|---------------------------------------------------------------------------------------------------------------------------------|
| Source | Rat | Responsiveness |
| Leehy et al.11 | Anaesthetized | Normal |
| Murray & Paller 12 | Conscious | Normal |
| Bomzon et al.13 | Conscious | Normal |
| Villamediana et al. | Conscious | Normal |

| Table 2 | The summary of experiments that assessed in vitro vascular responsiveness to norepinephrine in the carbon tetrachloride-induced cirrhotic rat |
|--------|---------------------------------------------------------------------------------------------------------------------------------|
| Source | Test site | Responsiveness |
| Kitano et al.14 | Arterial strip and portal vein | Normal |
| Leehy et al.11 | Arterial ring | Normal |
| Gali 15 | Portal vein | Potentiated |
| Lee et al.16 | Arterial ring | Potentiated |
| Bomzon et al.13 | Arterial ring | Normal |
| Villamediana et al. | Perfused hindlimb and arterial ring | Normal |
pressor and in vitro contractile refractoriness to norepinephrine.

To summarize at this stage, the results of this study are consistent with all the other animal studies. Furthermore, the animal studies are not in agreement with the clinical observations, which are at odds with each other. Therefore, do all these observations mean that diminished end-organ responsiveness to norepinephrine does not contribute to the reduction in total peripheral resistance? On the basis of the clinical findings, it indicates that the loss of pressor response to norepinephrine may be due to factors other than its effect on resistance vessels. These other factors include the heart, where attenuated positive inotropic and chronotropic responsiveness has been observed, and the lung as a potential source of inactivating norepinephrine following its intravenous injection. The influence of each of these factors on pressor responsiveness to norepinephrine in cirrhosis needs to be evaluated. It also goes without question that additional clinical studies need to be undertaken.

Methodological considerations need to be taken into account in the evaluation of diminished end-organ responsiveness to norepinephrine in liver disease. For example, the discrepancy between the in vivo pressor responses and the in vitro contractile reactivity may be in part explained by the differences in methodology associated with in vivo and in vitro techniques. In the latter situation, the vessel is isolated from its 'normal' environment and its reactivity assessed. Whilst this approach is acceptable, its major limitation is that it assumes that isolated vessels have a 'memory' which is recalled when exposed to norepinephrine. This drawback can be overcome if the hindquarter is perfused or the vessel bathed in 'abnormal' plasma instead of normal bathing media. In this instance, the cirrhotic rat hindquarters were perfused or the aortic ring was bathed in normal Krebs' solution.

Species differences may also account for the discrepancy between the clinical observations and those in this model of cirrhosis. In a recent review, we concluded that there was no appropriate animal model in which to study the cardiovascular complications of cirrhosis. The results of this study are applicable only to this model and similar studies should be done in the other animal models of cirrhosis and portal hypertension, namely, the chronic bile duct-ligated dog and rat.

Finally, cirrhosis is a chronic disease where the development of symptoms can take many years. One of the major advantages in the use of animal models, and in particular, the carbon tetrachloride rat, is that the development of symptoms is time-compressed. Villamediana and his colleagues undertook their study in cirrhotic rats who were retaining sodium but before ascites formation. Since the sodium balance can influence the end-organ response, it would be advantageous to know whether an intact responsiveness to norepinephrine was present in a more advanced state of cirrhosis. Such an observation would be beneficial in explaining the diversity of the clinical findings.

The contribution of the present paper is that it demonstrates comprehensively that the hypotension of sodium-retaining, non-ascitic cirrhotic rats is not associated with attenuated responses of the peripheral vasculature to norepinephrine. However, in view of the limited and conflicting clinical data, as well as the species, methodological and time considerations, the concept of diminished vascular responsiveness to norepinephrine in cirrhosis still remains to be proven.

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