

*Progress report*

## Bicarbonate ( $\text{HCO}_3$ ) delivery to the gastroduodenal mucosa by the blood: its importance for mucosal integrity

Recent results from our laboratory,<sup>1-3</sup> as well as data reported by others,<sup>4-9</sup> have shown that gastroduodenal blood flow functions not only provide  $\text{O}_2$ <sup>10</sup> and substrates, but also deliver  $\text{HCO}_3$  to the mucosa. This may be of particular relevance to the pathogenesis of stress ulceration. Sepsis and haemorrhagic shock are frequently associated with systemic acidosis and reduced arterial  $\text{HCO}_3$  concentration. The recent decline in the rate of severe bleeding from acute gastroduodenal lesions may in part be explained by the more aggressive approach to promptly correct any imbalance of the acid base status in these patients.<sup>11</sup>

It is clear that reduction of blood flow increases the susceptibility of the gastric and duodenal mucosa to the injurious actions of luminal acid.<sup>12,13</sup> In many experimental models gastric mucosal ulceration after luminal acid exposure alone can only be achieved when blood flow is artificially reduced.<sup>14,17</sup> Bile salt or aspirin injury is enhanced by concomitant reduction of blood flow.<sup>18-20</sup>

The gastric mucosa appears to be relatively resistant to changes in blood flow compared with the duodenum.<sup>15</sup> Thus a 60% reduction of baseline blood flow was necessary to produce damage in a model of hypotensive shock in the rat, whereas the duodenal mucosa ulcerated after relatively minor changes in blood flow. Conversely, increasing blood flow by intra-arterial infusion of isoproterenol decreased gastric mucosal damage caused by bile salts, haemorrhagic shock or aspirin in the dog.<sup>21,22</sup> The fact that sympathectomy attenuated the decrease in blood flow during haemorrhagic shock and also reduced gastric lesion formation is consistent with the protective role of blood  $\text{HCO}_3$ .<sup>23</sup> A direct effect on other protective mechanisms such as cellular  $\text{HCO}_3$  transport mechanisms may also be involved as this has been shown to be under sympathoadrenergic control in the isolated mucosa.<sup>24,25</sup> Similar arguments apply to the action of prostaglandins (PG) which effect both the vasculature as well as having direct effects on  $\text{HCO}_3$  transport by the mucosal cells. Whittle reported an increase in blood flow and associated protection against bile salt and indomethacin induced damage after iv administration of a variety of prostaglandin analogues. Direct infusion of  $\text{PGI}_2$  into the coeliac artery supplying an *in vivo* chambered gastric mucosal flap prevented taurocholate and macroscopic acid induced damage in indomethacin pretreated dogs, and this was associated with a large increase in mucosal blood flow.<sup>26</sup> A later report from the same laboratory, however, showed that surface cell damage was induced by taurocholate and acid alone emphasising the importance of microscopic evaluation in the assessment of damage.<sup>17,14</sup> We do not know whether increased blood flow protects against damage of the surface

epithelium because all the above studies only used macroscopic assessment of lesions.

Increased  $H^+$  back diffusion stimulates blood flow to the gastric and duodenal mucosa.<sup>13 27 28</sup> In the rabbit stomach this increase seemed to occur in apparently undamaged mucosa and was proposed to prevent tissue acidification.<sup>28</sup> Careful histological studies evaluating surface damage were, however, not done in these experiments. In the duodenum histologic damage to the villous tips was not prevented and a relative decline in blood flow was only seen when damage reached the base of the villi.<sup>13</sup> These findings suggest that at least in the duodenum an increase in mucosal blood flow is not protective for the superficial layer of the mucosa. Similar results were obtained by Cheung *et al*<sup>29</sup> who found that the increase in blood flow associated with increased  $H^+$  loss from the gastric lumen was correlated with the magnitude of gastric mucosal damage after aspirin, taurocholate, or ethanol. McGreevy<sup>30</sup> also found an increase in blood flow in areas of aspirin induced erosions compared with macroscopically undamaged mucosa.

The increase in blood flow after damage has occurred may be important in limiting the degree of mucosal acidosis by buffering and diluting back diffusing  $H^+$  and in facilitating rapid repair by creating an alkaline milieu underneath the layer of fibrin, mucus, and necrotic cells. Direct evidence for such a mechanism has recently been obtained by Kivilaakso<sup>8</sup> in the rat after taurocholate damage. Using subepithelial pH sensitive micro-electrodes, surface cell damage was associated with an intense alkalisation (after a transient drop in pH) that was blocked by haemorrhagic shock, suggesting outpouring of  $HCO_3^-$  rich fluid from subepithelial blood vessels in response to mucosal injury. Increase in  $HCO_3^-$  effusion may also be important for epithelial repair after damage of the amphibian isolated gastric mucosa with hypertonic NaCl and in the rabbit isolated duodenum after acid damage<sup>3 1-33</sup> as recovery depends on the presence of  $HCO_3^-$  in the serosal bathing solution.

Experiments using pH sensitive microelectrodes have shown that in the rabbit gastric mucosa reduction of blood flow by haemorrhagic shock or vasopressin was accompanied by a reduction of pH in the lamina propria that exceeded the fall in blood pH suggesting  $H^+$  back diffusion.<sup>6 28 34</sup> When submucosal pH dropped below 6.9 mucosal ulceration occurred. Ischaemia alone in the absence of luminal acid and associated fall in mucosal pH did not lead to macroscopic damage. These results indicated that mucosal acidosis may be more important in the development of mucosal lesions than the limitation in  $O_2$  supply. This hypothesis is further supported by the experimental findings that acid secreting stomachs were more resistant to injury by comparison with non-secreting preparations and had a lesser degree of intramural acidosis, presumably because of increased serosal  $HCO_3^-$  produced by the parietal cells.<sup>35</sup> Thus  $HCO_3^-$  is extruded across the basolateral membrane and readily available for buffering back-diffusing  $H^+$ . Microvascular architecture appropriate to accomplish the transport of  $HCO_3^-$  from the gastric glands to the surface cells has been shown.<sup>36</sup> Similar results showing that the secreting stomach is more resistant to injury have been obtained *in vitro*.<sup>37 38</sup>

Recent experiments in the frog gastric mucosa *in vitro* using pH-sensitive fluorescent dye have directly shown a profound alkalisation of the lamina propria upon onset of acid secretion.<sup>39</sup> Using the same technique to measure

pH actually within cells of rabbit gastric glands showed these cells to be sensitive to alteration of extracellular pH.<sup>40</sup> When the basolateral membrane was exposed to Ringers solutions of different pH, glands seemed to tightly regulate their intracellular pH over the range between extracellular pH 7.0 and pH 7.8. Outside this range the intracellular pH varied linearly with the pH outside. It is therefore to be expected that changes in pH in the lamina propria of the intact tissue below pH 7 cause intracellular acidosis with ensuing cell damage and death.

The combined effects of acidosis and low blood flow are certainly deleterious to the gastric mucosa. Prevention of acidosis can attenuate gastric mucosal injury. As early as 1948, Cummins and Grossman<sup>41</sup> showed that  $\text{HCO}_3$  infusions can prevent ulcer formation induced by continuous acid instillation into the stomach of dogs. Studies *in vitro* and *in vivo* have further confirmed the concept that nutrient  $\text{HCO}_3$  is essential for the gastric mucosa to withstand luminal acid.<sup>2 7 17 38 42 43</sup> This buffer species cannot be substituted by other buffers because phosphate, HEPES, MES or TES *in vitro*, and TRIS and phosphate *in vivo* were without effect.<sup>2 43</sup> In a study of acute gastric lesion formation in the rat, however, it was clearly shown that preventing the fall in gastric mucosal blood flow during hemorrhagic hypotension using intra-arterial  $\text{PGI}_2$  did not prevent gross mucosal ulceration, but correction of the accompanying acidosis by infusion of  $\text{HCO}_3$  inhibited the development of haemorrhagic lesions despite low blood flow.<sup>2</sup> These results indicated that it is the availability of  $\text{HCO}_3$  that is the critical factor in the development of lesions even in states of reduced blood flow rather than the limited  $\text{O}_2$  supply or flow *per se*.

There are no data available on the dependence of gastric  $\text{HCO}_3$  secretion in the lumen on blood flow, but experiments in our laboratory have clearly shown that changes in blood flow are directly related to changes in alkaline secretion from the duodenal mucosa.<sup>1</sup> When arterial  $\text{HCO}_3$  concentration was also considered and bicarbonate availability ( $[\text{HCO}_3]$  art x blood flow) was plotted against alkaline secretion, the fitted curve demonstrated a saturable process. Thus alkaline secretion was independent of  $\text{HCO}_3$  delivery to the mucosa above 4 mmol/cm<sup>2</sup>/min, but extremely sensitive to a reduction below this value (Fig. 1). Because alkaline secretion in this model is also an important determinant of acid induced injury and directly correlated to the extent of damage, it seems reasonable to conclude from these data that at least in the duodenum,  $\text{HCO}_3$  availability is of primary importance for the mucosa to withstand luminal acid.<sup>3</sup> Similarly, when  $\text{HCO}_3$  delivery to the rat gastric fundus during haemorrhagic shock and  $\text{PGI}_2$  and/or  $\text{HCO}_3$  infusions (data calculated from ref. 2) are plotted against the percentage of stomachs ulcerated a linear correlation is found (Fig. 2), suggesting that  $\text{HCO}_3$  delivery to the gastric mucosa is also a critical factor in the development of lesions. The mechanism of action of nutrient bicarbonate in the stomach is less clear, however, than in the duodenum where luminal buffering by alkaline secretion is the single most important factor in the defence against luminal acid.<sup>3 44</sup>

$\text{HCO}_3$  secretion from the gastric mucosa is relatively small, amounting to <5% of maximal acid secretion. Under basal conditions, acidification of the lumen down to pH 2 causes a two to three fold increase of luminal  $\text{HCO}_3$  appearance which can completely account for the  $\text{H}^+$  disappearance measured under these conditions.<sup>44-47</sup> The concentration of acid used in

these experiments<sup>47</sup> was rather small, however (10 mmol/l HCl), and the rate of H<sup>+</sup> loss in this model (dog Heidenhain pouch) is linearly dependent on luminal H<sup>+</sup> concentration up to 150 mmol/l.

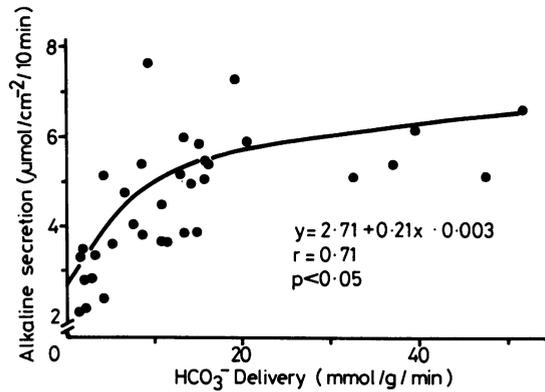


Fig. 1 Correlation of alkaline secretion and HCO<sub>3</sub><sup>-</sup> delivery in rabbit duodenum. Mucosal blood flow determined with radioactive microspheres. Alteration of blood flow and arterial HCO<sub>3</sub><sup>-</sup> concentration with iv infusion of vasopressin, HCO<sub>3</sub><sup>-</sup> and NH<sub>4</sub>Cl.

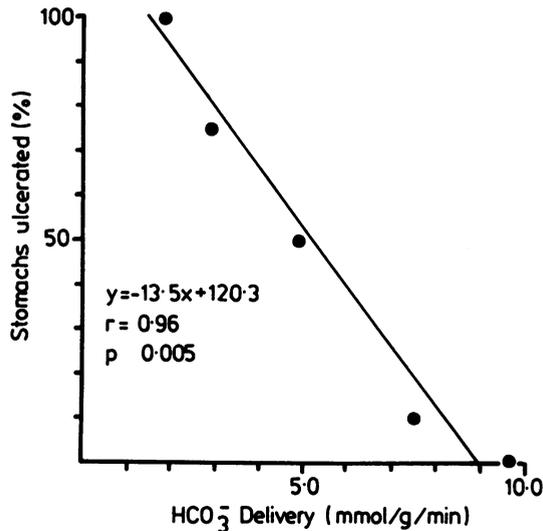


Fig. 2 Dependence of gastric mucosal damage (expressed as per cent of stomachs ulcerated) on HCO<sub>3</sub><sup>-</sup> delivery by blood flow (mucosal blood flow determined with radioactive microspheres) in stomachs of rats subjected to haemorrhagic shock with and without infusion of PGI<sub>2</sub> and HCO<sub>3</sub><sup>-</sup> (points represent means of each experimental group, ref 2).

The essential remaining question is where and when HCO<sub>3</sub><sup>-</sup> acts to prevent damage and facilitate repair. The pre-epithelial 'mucus bicarbonate' barrier may not be of primary importance in the stomach because the gradient measured with microelectrodes readily dissipated at luminal pH 1.5 or less,

values frequently encountered in the *in vivo* situation.<sup>40-49-52</sup> Also luminal stirring and shear forces are likely to reduce surface unstirred layers even further in the intact stomach.<sup>53-54</sup> The actual thickness of the adherent mucus gel varies enormously and may be as thin as 5  $\mu\text{m}$ .<sup>55</sup>

There are several recent data indicating that the permeability of the apical plasma membrane to  $\text{H}^+$  is low and this, together with efficient mechanisms to regulate intracellular pH, would mean that complete neutralisation of  $\text{H}^+$  at the cell surface is unnecessary.<sup>56-57</sup> Nutrient  $\text{HCO}_3$  is intimately involved in these pH regulatory mechanisms.<sup>40-56-58</sup>

Basal  $\text{HCO}_3$  secretion in the stomach is low and stimulation by luminal acid, sham feeding or prostaglandin only increases measurable alkali output by a small amount (two to three fold).<sup>59-62</sup> Increases in secretory rate in the duodenum are much greater.<sup>63-65</sup> In the stomach damage to the surface epithelium is associated with a comparatively large flux of alkali from the interstitium into the lumen. Such an increase in passive  $\text{HCO}_3$  effusion has been shown to occur after damage in variety of models.<sup>9-33-59-66-68</sup> Thus  $\text{HCO}_3$  in conjunction with a thick layer of mucus and necrotic debris probably acts to limit damage by facilitating rapid repair of minor disruption of the epithelial cell layer that occurs during everyday life.<sup>32-68-69-70</sup>

In summary,  $\text{HCO}_3$  delivery to the gastroduodenal mucosa is necessary to maintain its structural and morphological integrity. In the stomach the main function of  $\text{HCO}_3$  probably lies in its role in intracellular pH-regulation and in passive effusion after even minor injury. In the duodenum transepithelial secretion of  $\text{HCO}_3$  and intraluminal buffering is the predominant defence mechanism against luminal acid.

M STARLINGER AND R SCHIESSEL

*Ist Surgical University Clinic of Vienna,  
Vienna, Austria.*

Address for correspondence: M Starlinger, Chirurgische Klinik u Poliklinik, Calwerstr 7, D-7400 Tübingen, West Germany.

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