Effect of Proximal Gastric Vagotomy on Calculated Gastric HCO₃⁻ and Nonparietal Volume Secretion in Man
Studies during Basal Conditions and Gastrin-17 Infusion

Mark Feldman, A. John Blair III, and Charles T. Richardson
Departments of Internal Medicine and Surgery, Veterans Administration Medical Center and University of Texas
Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas 75216

Abstract

We calculated gastric HCO₃⁻ and H⁺ secretion, as well as nonparietal and parietal volume secretion, in 15 duodenal ulcer patients who had previously undergone successful proximal gastric vagotomy, 15 unoperated duodenal ulcer patients, and 15 normal control subjects. Basal HCO₃⁻ secretion was not significantly altered after vagotomy, while basal H⁺ secretion, parietal volume and nonparietal volume secretion were reduced significantly. Intravenous gastrin-17 infusion increased H⁺, parietal volume and nonparietal volume secretion significantly in all three groups. In contrast, gastrin-17 infusion reduced gastric HCO₃⁻ secretion by ~50% in both unoperated ulcer patients and normal subjects (P < 0.05). Gastrin-17 infusion did not inhibit gastric HCO₃⁻ secretion after vagotomy. In fact, mean gastric HCO₃⁻ secretion increased to a nearly significant extent in response to gastrin (P = 0.06). These findings indicate that gastrin inhibits gastric HCO₃⁻ secretion in humans and that the gastrin-induced reduction in gastric HCO₃⁻ secretion is dependent upon intact vagal innervation to the oxyntic mucosa.

Methods

Studies were approved by a Human Studies Subcommittee and informed written consent was obtained in each case.

Patients and subjects. Patients who had previously had PGV for DU were identified on a computerized printout. 30 patients agreed to undergo a sham feeding test and, in 15, completeness of PGV was documented using previously described criteria (3). Ages of these 15 patients (12 of whom were male) averaged 54±3 yr and weights averaged 72.3±3.0 kg. 15 unoperated DU patients (12 male) who were attending an outpatient gastroenterology clinic volunteered to serve as controls in these studies, and as did 15 healthy volunteers (12 male) who were primarily students and hospital employees. Ages of DU patients and healthy controls averaged 49±3 and 31±2 yr, respectively, and their weights averaged 75.7±3.6 and 71.5±3.5 kg, respectively. Antisecretory medications were discontinued by patients receiving them at least 48 h before experiments.

Intubation and study protocol. After an overnight fast, a nasogastric tube (AN 10, Andersen Products Inc., Oyster Bay, NY) was positioned in the dependent portion of the stomach under fluoroscopic control. Residual gastric secretions were manually evacuated and then secretions were collected by aspiration in 15-min aliquots using a Stedman pump (American Cystoscope Makers, Inc., Stamford, CT). After a 30-min basal period during which 0.15 M NaCl was infused intravenously through an indwelling venous catheter, a solution of G-17 dissolved in 0.15 M NaCl and containing 1% human albumin was infused intravenously in doses of 7, 22.1, 70, 221, and 700 pmol/kg·h (IMED infusion pump 922, IMED Corp., San Diego, CA). Each G-17 dose was infused over a 45-min period in a stepwise fashion as described previously (3). At the end of the 700 pmol/kg·h G-17 infusion, the infusion was stopped and gastric secretion was measured for an additional 30 min.

The volume of each 15-min sample of gastric juice was measured to the nearest ml and was multiplied by 4 to express results in milliliters per hour. The hydrogen ion concentration of gastric juice and the osmolality of gastric juice and plasma were determined as described previously (7). Plasma osmolality averaged 292±2, 293±1, and 291±2 mosmol/kg in PGV patients, DU patients, and normal subjects, respectively. Gastric HCO₃⁻ and H⁺ secretion rates (in millimoles per hour), as well as nonparietal and parietal volume secretion rates (in milliliters per hour), were then calculated from gastric juice volume, hydrogen ion concentration, osmolality, and plasma osmolality as described previously (7). Saliva was aspirated using a dental suction catheter throughout these experiments.

Statistics. Results are expressed as mean±SEM. Differences in mean values among groups were analyzed by two-tailed group t tests. Changes from basal secretion rates during G-17 infusion within groups were tested by analysis of variance. P values <0.05 were considered significant. Effective doses of G-17 necessary to produce 50% of peak acid output (ED₅₀) were calculated as described previously (8).

Results

Measured gastric volume, acidity, and osmolality. The time course of the experiments and mean results for gastric juice volume in milliliters per hour, acidity in millimoles per liter, and osmolality in milliosmoles per kilogram for each 15-min period
are shown in Fig. 1. Mean gastric juice volume output basally and during intravenous G-17 infusion was lowest in PGV patients, intermediate in normal subjects, and highest in DU patients (Fig. 1, top). As indicated in Table I, mean volume output in PGV patients was significantly lower than in DU patients and in normal subjects, whereas volume output in DU patients was significantly higher than in normal subjects. As shown in Fig. 1 B and Table I, mean gastric acidity was significantly lower in PGV patients than in unoperated controls and normal subjects; results in DU patients and normal subjects were comparable, although DU patients had a slightly lower mean gastric acidity than normal controls at higher doses of G-17. Gastric juice osmolality was significantly lower in PGV patients than in DU patients and normal subjects (Fig. 1 C, and Table I), while osmolality was not significantly different in DU patients and normal subjects. As shown in Fig. 1, when G-17 infusion was discontinued mean gastric juice volume, acidity, and osmolality decreased.

**Calculated HCO₃⁻ secretion.** As shown in Fig. 2, in both normal subjects and unoperated DU patients, there was a significant dose-related decrease in gastric HCO₃⁻ secretion during intravenous G-17 infusion, with maximal inhibition of ~ 50% occurring with G-17 doses of 70 pmol/kg·h and higher. After cessation of 700 pmol/kg·h G-17 infusion, HCO₃⁻ secretion rates over the ensuing 30 min returned toward basal rates (data not shown). In contrast to results in unoperated DU patients and normal controls, G-17 infusion did not inhibit gastric HCO₃⁻ secretion in PGV patients (Fig. 2). In fact, mean HCO₃⁻ secretion during G-17 infusion was higher than basal and this increase approached significance (P = 0.06). Mean (±SE) HCO₃⁻ secretion during G-17 infusion in PGV patients was significantly higher than in normal subjects at G-17 doses of 22.1 to 700 pmol/kg·h and in DU patients at doses of 221 and 700 pmol/kg·h (Fig. 2).

**Calculated H⁺ secretion.** As indicated in Fig. 3, mean basal H⁺ secretion of 3.3±0.7 mmol/h in PGV patients was lower

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**Figure 1.** Mean gastric juice volume (A), gastric juice acidity ([H⁺]; B), and gastric juice osmolality (C) in 15 normal subjects (NL), 15 patients with duodenal ulcer (DU), and 15 DU patients who had been treated by (PGV). Basal secretion was measured for two 15-min periods and then G-17 was infused for the next fifteen, 15-min periods (periods 3–17) (arrows), after which G-17 infusion was stopped and secretion measured for two final 15-min periods (periods 18 and 19). Statistical comparisons among groups are made in Table I.
than in normal control individuals (6.1±1.2 mmol/h; P = 0.06) and DU patients (11.1±2.6 mmol/h, P < 0.001). As anticipated, H⁺ secretion increased significantly and in a dose-related fashion during G-17 infusion in all three groups. For each G-17 dose, H⁺ secretion was significantly lower in PGV patients than in normal subjects (P < 0.05) or DU patients (P < 0.001). The calculated ED₅₀ to G-17 was significantly higher in PGV patients than in unoperated DU patients and normal controls (Table II). Thus, the rightward shift in the G-17 dose-response curve for H⁺ secretion in PGV patients was statistically significant. H⁺ secretion was significantly higher in DU patients than in normal controls for each dose of G-17.

Calculated nonparietal and parietal volume secretion. As shown in Fig. 4, basal nonparietal volume secretion in PGV patients and normal controls was similar and significantly lower than in DU patients (29.1±4.1 and 24.8±3.2 ml/h vs. 50.1±6.6 ml/h, P < 0.02). In all three groups, nonparietal volume secretion increased significantly above basal rates during G-17 infusion. Throughout G-17 infusion, nonparietal volume secretion in PGV patients was comparable to that of normal subjects and 20–30 ml/h below nonparietal secretory rates of DU patients (P < 0.02 for each G-17 dose, PGV patients or normal subjects versus DU patients). Curves for parietal volume secretion (not shown) were similar to H⁺ secretion curves previously shown in Fig. 3.

**Table I. Comparison of Mean±SE Gastric Juice Volume, Acidity, and Osmolality in 15 Patients after PGV, 15 Unoperated DU Patients and 15 NL Subjects**

<table>
<thead>
<tr>
<th>G-17 Dose (pmol/kg·h)</th>
<th>0 (Basal)</th>
<th>7</th>
<th>22.1</th>
<th>70</th>
<th>221</th>
<th>700</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume (ml/h)</strong></td>
<td></td>
<td></td>
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<tr>
<td>PGV</td>
<td>50±8*</td>
<td>70±6**</td>
<td>106±10***</td>
<td>144±16***</td>
<td>184±12***</td>
<td>198±16***</td>
</tr>
<tr>
<td>DU</td>
<td>120±22a</td>
<td>172±18a</td>
<td>254±22a</td>
<td>316±26a</td>
<td>326±28a</td>
<td>336±30a</td>
</tr>
<tr>
<td>NL</td>
<td>64±10</td>
<td>104±10</td>
<td>156±14</td>
<td>224±22</td>
<td>234±12</td>
<td>240±20</td>
</tr>
<tr>
<td><strong>Acidity (mmol/liter)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PGV</td>
<td>24.6±4.8**</td>
<td>35.0±6.5**</td>
<td>69.3±8.5**</td>
<td>96.6±7.4**</td>
<td>102.6±5.0**</td>
<td>103.8±4.5**</td>
</tr>
<tr>
<td>DU</td>
<td>57.4±8.1</td>
<td>92.1±5.9</td>
<td>111.0±4.7</td>
<td>122.2±3.5</td>
<td>120.1±3.1f</td>
<td>120.7±3.5</td>
</tr>
<tr>
<td>NL</td>
<td>56.5±8.1</td>
<td>92.3±7.8</td>
<td>114.9±5.9</td>
<td>124.9±3.0</td>
<td>130.1±3.3</td>
<td>128.9±3.0</td>
</tr>
<tr>
<td><strong>Osmolality (mosmol/kg)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PGV</td>
<td>220±6*</td>
<td>233±7**</td>
<td>251±5**</td>
<td>263±8**</td>
<td>271±7**</td>
<td>269±5**</td>
</tr>
<tr>
<td>DU</td>
<td>250±7</td>
<td>277±5</td>
<td>286±6</td>
<td>297±5</td>
<td>298±5</td>
<td>298±6</td>
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<tr>
<td>NL</td>
<td>229±10</td>
<td>267±8</td>
<td>286±7</td>
<td>298±4</td>
<td>301±5</td>
<td>301±5</td>
</tr>
</tbody>
</table>

Gastric volume during G-17 infusion was expressed as the last 30 min of each G-17 dose, multiplied by 2. Acidity and osmolality for 30 min basal period (0 dose) represent average values; during G-17 infusion the last 15-min period of each G-17 dose was used. * P < 0.05, PGV vs. DU by two-tailed group t test. ** P < 0.05, PGV vs. NL by two-tailed group t test.  * P < 0.05, DU vs. NL by two-tailed group t test.

![Figure 2. Mean (±SE) HCO₃⁻ secretion basally and during the last two 15-min periods of each G-17 dose in 15 NL subjects, 15 DU patients, and 15 DU patients after PGV. *Significant (P < 0.05) differences between PGV patients and DU patients; †significant differences between PGV patients and normal subjects. None of the differences between DU patients and NL subjects was significant.](image1)

![Figure 3. Mean (±SE) H⁺ secretion basally and during the last two 15-min periods of each G-17 dose in 15 NL subjects, 15 DU patients, and 15 DU patients after PGV. *Significant (P < 0.05) differences between PGV and DU patients, between PGV patients and NL subjects; †between DU patients and NL subjects.](image2)

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infusion was significantly greater than in both nonvagotomized control groups. Ratios were not significantly different in DU patients and normal subjects, except that DU patients reached a steady ratio of ~ 28% with the two highest G-17 doses, while normal subjects achieved a ratio of ~ 22% (P < 0.05).

### Discussion

We previously reported in normal subjects and DU patients that mean steady state gastric HCO$_3^-$ secretion during a 2- or 3-h intravenous infusion of a single, submaximal dose of pentagastrin was lower than basal HCO$_3^-$ secretion; however, the reduction in gastric HCO$_3^-$ secretion during pentagastrin infusion did not reach statistical significance (7, 9). The present study examined the effect of gastrin on gastric HCO$_3^-$ secretion in considerably more detail, using a wide range of doses of synthetic human gastrin heptadecapeptide I (G-17). In both normal subjects and DU patients, G-17 inhibited gastric HCO$_3^-$ secretion significantly, and in a dose-related fashion, with a maximal inhibition of HCO$_3^-$ secretion of ~ 50% of basal HCO$_3^-$ secretion. In both groups there was a prompt increase in HCO$_3^-$ secretion after cessation of G-17 infusion as serum gastrin concentrations fell toward basal levels (3, 10). We have recently shown in these same 15 normal subjects and 15 DU patients that steady state serum gastrin concentrations during infusion of 7, 22.1, and 70 pmol/kg·h G-17 are within the physiologic range (10). Thus, when gastric H$^+$ secretion is stimulated by physiologic or supraphysiologic amounts of gastrin, gastric HCO$_3^-$ secretion is inhibited in parallel. Because gastric HCO$_3^-$ neutralizes acid under normal conditions, inhibition of gastric HCO$_3^-$ secretion probably contributes to the large increase in gastric acidity that occurs during G-17 infusion in normal subjects and nonvagotomized DU patients (Fig. 1 B). That gastric HCO$_3^-$ secretion was significantly reduced by G-17 is even more interesting since G-17 also increased H$^+$ secretion in our studies and since H$^+$ within the gastric lumen is known to augment, rather than reduce, gastric HCO$_3^-$ secretion (11–13).

An unexpected finding in this study was that G-17 infusion did not inhibit gastric HCO$_3^-$ secretion after PGV. In fact, mean gastric HCO$_3^-$ secretion increased during G-17 infusion in patients with PGV and this increase was very nearly statistically significant (P = 0.06). Normal or even enhanced gastric HCO$_3^-$ secretion coupled with reduced H$^+$ secretion led to reduced gastric luminal acidity and osmolarity after PGV (Fig. 1 B and C). We can only speculate why G-17 did not reduce gastric HCO$_3^-$ secretion after PGV. It is possible that the amount of HCO$_3^-$ that refluxed into the stomach from the duodenum increased after PGV, but this seems unlikely since the pylorus remained intact after this operation and bile staining of gastric samples did not occur with increased frequency in PGV patients compared with DU patients or normal controls. Gastric HCO$_3^-$ secretion arises from both the fundus and antrum of the stomach (14). Thus, it is possible that gastrin may effect gastric HCO$_3^-$ secretion differently in these two regions. For example, gastrin may inhibit the output from fundic HCO$_3^-$-secreting surface cells to maximize H$^+$ secretion into the lumen. If a substantial portion of gastric HCO$_3^-$ secretion originates from the fundus rather than the antrum (14), total gastric HCO$_3^-$ secretion

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**Table II. Comparison of Mean±SE Effective Dose of Gastrin-17 Necessary to Produce 50% of Peak Acid Output (ED$_{50}$) in 15 Patients after PGV, 15 Unoperated DU Patients, and 15 NL Subjects**

<table>
<thead>
<tr>
<th></th>
<th>ED$_{50}$ (pmol/kg·h)</th>
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<tbody>
<tr>
<td>PGV</td>
<td>61.3±31.3*</td>
</tr>
<tr>
<td>DU</td>
<td>11.0±2.2</td>
</tr>
<tr>
<td>NL</td>
<td>24.0±8.1</td>
</tr>
</tbody>
</table>

* P < 0.001 vs. DU and < 0.05 vs. normal by group t test. Because of the large intersubject variation in calculated ED$_{50}$, especially in the PGV group, data were normalized by using log ED$_{50}$ before performing t tests.
would be inhibited in normal humans or DU patients by G-17 as H⁺ is stimulated. After PGV, however, gastrin-induced inhibition of fundic HCO₃⁻ secretion may be absent due to denervation of the fundus by PGV. Since the antrum is not denervated after PGV and continues to secrete HCO₃⁻, the net result would be no inhibition of total gastric HCO₃⁻ secretion during G-17 infusion after PGV.

If the above hypotheses regarding regional differences in HCO₃⁻ secretory responses to G-17 are correct, it would suggest that gastrin’s inhibitory effect on gastric HCO₃⁻ secretion may be indirect and dependent upon intact vagal innervation to the proximal stomach. Of interest, in vitro studies in amphibians, using chambered preparations of stomach stripped of muscle layers and submucosal tissue, have found no direct inhibitory effect of either 10⁻⁸ M pentagastrin or 10⁻⁹ M G-17 on fundic or antral gastric HCO₃⁻ secretion, respectively (15, 16). Assuming that inter-species differences are not the explanation for differing effects of gastrin on gastric HCO₃⁻ secretion in these in vitro studies and our present study, the findings taken together suggest that the inhibitory effect of gastrin on gastric HCO₃⁻ secretion in vivo is an indirect one, perhaps mediated via the vagus nerves. It would be of interest to compare in vivo effects of gastrin on gastric HCO₃⁻ secretion in the fundus and antrum separately, for example in animals with vagally innervated fundic and antral pouches. Moreover, by also studying animals with vagally denervated fundic pouches, it may be possible to confirm the importance of vagus nerves in mediating fundic inhibition of gastric HCO₃⁻ secretion. Konturek et al. recently reported that a large dose of G-17 (500 pmol/kg h i.v.) did not inhibit gastric HCO₃⁻ secretion in vivo in ranitidine-treated dogs with vagally denervated fundic pouches or in dogs with vagally denervated antral pouches (17), agreeing with our present findings in humans after PGV.

Several peptide hormones including pancreatic glucagon (18), neurotensin (19), and peptide YY (20) have recently been reported to inhibit net gastric acid output only in individuals or animals with intact vagal innervation of the oxyntic mucosa. (Net gastric acid output refers to H⁺ secretion minus HCO₃⁻ secretion. A decrease in net gastric acid output can be due to a decrease in H⁺ secretion, an increase in HCO₃⁻ secretion, or both.) It is possible that some of the reduction in net gastric acid output induced by these peptides is due to a vagally dependent stimulation of gastric HCO₃⁻ secretion. In support of this hypothesis, both glucagon and neurotensin have been shown to augment gastric HCO₃⁻ secretion (16, 17). Thus, it is conceivable that some peptide hormones such as glucagon and neurotensin that inhibit H⁺ secretion also augment fundic HCO₃⁻ secretion, while peptide hormones such as gastrin, which stimulate H⁺ secretion inhibit fundic HCO₃⁻ secretion. Furthermore, these hormone-induced reciprocal changes in HCO₃⁻ secretion (relative to effects of these peptides on H⁺ secretion) may be mediated by the vagus nerves.

As anticipated, PGV led to a marked decrease in H⁺ (parietal) secretion, both basally and during G-17 infusion, with a significant rightward shift in the G-17 dose response curve. This extends our previous observations in vagotomized patients in which only net gastric acid output was reported (3). Lower net gastric output during G-17 infusion after PGV is thus due to both significantly lower H⁺ secretion and significantly higher HCO₃⁻ secretion. PGV also decreased nonparietal volume secretion significantly, indicating that cells and glands that contribute to nonparietal volume secretion in the proximal stomach are under vagal control. Since atropine also decreases nonparietal volume secretion (5), this fluid may be under vagal-cholinergic regulation. Of interest, nonparietal volume hypersecretion in DU patients was reduced to normal rates after PGV, both basally and during G-17 infusion, whereas parietal volume hypersecretion was reduced to well below normal rates after PGV. This may be because parietal hypersecretion in DU patients arises entirely from the proximal stomach, which is denervated after PGV, whereas nonparietal volume hypersecretion in DU patients may arise from both the proximal stomach and the nondenervated distal stomach. Thus, PGV may have markedly reduced fundic nonparietal volume hypersecretion without altering antral nonparietal volume hypersecretion. The net results of these events in DU patients after PGV would be a decrease in total nonparietal secretion to near normal rates and also an increased ratio of nonparietal to parietal volume secretion basally and during G-17 infusion. Assuming that patients with hypergastrinemia due to gastrinoma (Zollinger-Ellison syndrome) behave like our normal subjects and DU patients during intravenous G-17 infusion, our findings suggest that PGV, an operation that is clinically efficacious in patients with gastrinoma (21), should increase the ratio of nonparietal to parietal volume secretion and also the ratio of HCO₃⁻ to H⁺ secretion at any given, elevated serum gastrin concentration (Fig. 5).

While inhibiting gastric HCO₃⁻ secretion in normal subjects and DU patients, G-17 caused a dose-related increase in nonparietal volume secretion, agreeing with our earlier study using a single, submaximal dose of pentagastrin (9). Because of the opposite effects of G-17 on gastric nonparietal volume secretion and gastric HCO₃⁻ secretion in both normal subjects and DU patients (Figs. 2 and 4), it seems likely that conventional two-component models of gastric secretion (22, 23) are overly simplified. Although the acidic component almost certainly derives only from parietal cells, the alkaline, nonparietal component probably arises from several different kinds of cells. Current evidence suggests that surface epithelial cells are most responsible for gastric HCO₃⁻ secretion, via a volume-independent chloride/bicarbonate exchange mechanism (14), whereas nonparietal volume secretion may arise primarily from other, more deeply positioned cells within gastric glands (e.g., chief cells, mucous neck cells). Thus, G-17 may indirectly inhibit HCO₃⁻ secretion by surface epithelial cells via a vagal-dependent mechanism and at the same time stimulate fluid secretion from chief cells, mucous neck cells, or some other cells.

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