Gastric Bicarbonate Secretion in Humans

EFFECT OF PENTAGASTRIN, BETHANECHOL,
AND 11,16,16-TRIMETHYL PROSTAGLANDIN E₂

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A B S T R A C T Although the stomach is mainly known for its ability to secrete hydrochloric acid, there is increasing evidence that the gastric mucosa also secretes bicarbonate. A simple method for simultaneous measurement of gastric HCO₃⁻ secretion and H⁺ secretion was developed from a two-component model of gastric secretion. The method, which is based upon gastric juice volume, H⁺ concentration, and osmolality, was validated both in vitro and in vivo. In 14 healthy human beings, basal gastric HCO₃⁻ secretion averaged 2.6 mmol/h (range, 0.7–8.7 mmol/h). Basal HCO₃⁻ secretion was ~50% of basal H⁺ secretion and there was a significant correlation between basal HCO₃⁻ and H⁺ secretion in individual subjects (r = 0.79). HCO₃⁻ was secreted in basal nonparietal secretion at a concentration of ~90 mmol/liter. Intravenous pentagastrin infusion markedly stimulated H⁺ secretion but did not increase HCO₃⁻ secretion. During pentagastrin infusion, the cholinergic agonist, bethanechol, significantly augmented H⁺ secretion (from 20.2 to 24.7 mmol/h) and increased HCO₃⁻ secretion (from 2.2 to 4.2 mmol/h). A prostaglandin E₂ analogue significantly reduced H⁺ secretion and increased HCO₃⁻ secretion during pentagastrin infusion. The reduction in net gastric juice H⁺ output following prostaglandin E₂ was due more to H⁺ secretory inhibition than to HCO₃⁻ secretory stimulation. We conclude that the healthy human stomach actively secretes HCO₃⁻ and that gastric HCO₃⁻ secretion can be influenced by cholinergic stimulation and by prostaglandin E₂.

INTRODUCTION

Although bicarbonate secretion probably plays an important role in protecting the gastric epithelium from damage by luminal acid and pepsin (1), there is limited information on the amount of bicarbonate secreted by the stomach (2). Attempts to quantitate gastric HCO₃⁻ secretion have been hampered by concomitant H⁺ secretion, which converts HCO₃⁻ to CO₂. One approach to this problem has been to use agents that reduce H⁺ secretion, such as cimetidine (3). For quantitative purposes, it is assumed that the antisecretory agent blocks H⁺ secretion completely and that the antisecretory agent has no effect per se on HCO₃⁻ secretion. However, it is uncertain whether either of these assumptions is valid (2). A second method to avoid concomitant H⁺ secretion has been to measure the secretion from antral mucosa in vitro (4) or an antral pouch in vivo (5). These methods assume that no acid-secreting parietal cells are present in the antral preparation, an assumption which sometimes may not be true (5). Moreover, these techniques are not readily applicable to humans. A third approach has been to study gastric HCO₃⁻ secretion in patients with achlorhydria (6). It is uncertain, however, whether alkaline secretion rates in these patients with atrophic fundic gastritis are representative of HCO₃⁻ secretion rates in healthy individuals whose stomachs secrete H⁺.

A fourth method for estimating gastric HCO₃⁻ secretion is to measure the volume, H⁺ concentration, and chloride concentration of gastric juice and use a mathematical, two-component model of gastric secretion (7–10). However, the equations derived from a two-component model of gastric secretion have never been validated as a method for measuring gastric HCO₃⁻ secretion.

The present studies had two major purposes. First, equations were derived from a two-component model of gastric secretion to calculate gastric HCO₃⁻ and H⁺ secretion, nonparietal and parietal volume secretion, and the HCO₃⁻ concentration of nonparietal secretion utilizing measurements of gastric juice volume, H⁺
concentration, and osmolality. Experiments designed to validate these derived equations were then carried out in vitro and in vivo. A second purpose was to utilize this method to calculate \( \text{HCO}_3^- \) and \( \text{H}^+ \) secretion rates, nonparietal and parietal flow rates, and the \( \text{HCO}_3^- \) concentration of nonparietal secretion in healthy humans. Subjects were studied basally, during intravenous pentagastrin infusion, during intravenous infusion of betahanechol (a cholinergic agonist), and after oral ingestion of a prostaglandin \( \text{E}_2 \) analogue.

**METHODS**

Studies were approved by a Human Research Studies Committee. Informed written consent was obtained from each subject.

**Subjects and intubation.** 14 healthy subjects (nine men and five women) participated in these studies. Their ages averaged 35 yr (range, 19–51 yr). Basal and peak acid output to 6 \( \mu \text{g} / \text{kg} \) pentagastrin s.c. averaged 2.4±0.6 and 31.2±2.2 mmol/h, respectively. After an overnight fast, patients swallowed a nasogastric tube (H. W. Anderson Products, Inc., Oyster Bay, NY) which was positioned fluoroscopically in the gastric antrum. Gastric juice was collected by a Stedman pump which applied suction for 48 out of every 60 s (American Cystoscope Makers, Inc., Stamford, CT). The subjects were trained not to swallow their saliva and to collect saliva through two dental suction catheters.

Preliminary studies in three subjects indicated that simultaneous aspiration of alkaline duodenal juice through a second, nasoduodenal Anderson tube (that had been passed through the other nostril and positioned fluoroscopically in the second part of the duodenum) did not alter gastric juice volume, \( \text{H}^+ \) concentration, osmolality, calculated nonparietal volume secretion, or gastric bicarbonate secretion (compared with the use of a single nasogastric tube in the same subjects). For this reason and for patient comfort, only a single nasogastric tube was employed. Visible bile staining of gastric juice was seldom present. When gastric juice was noted to contain bile, the specimen was discarded and an additional 15-min collection performed. In a few instances, it was necessary to withdraw the nasogastric tube a few centimeters to obtain bile-free specimens because presumably, the tip of the tube had advanced past the pylorus after initial fluoroscopic placement.

**Measurements.** All measurements were made at room temperature. Volumes of test solutions (in vitro studies) or gastric juice samples (in vivo studies) were measured in a graduated cylinder to the nearest 0.5 ml. The osmolality of each test solution, gastric juice sample, or venous plasma sample was measured in duplicate by freezing point depression (Advanced Digmatic Osmometer, model 3DH, Advanced Instruments, Inc., Needham Heights, MA) and expressed in milliosmoles per kilogram. Hydrogen ion concentration, [\( \text{H}^+ \)]

\[ \text{[H}^+] \text{=} \text{measured by water titration to pH 7.00} \]

with 0.1 N NaOH or by the glass electrode method of Moore and Scarlata (11) or by both methods. In 28 test solutions analyzed by both methods, the results were closely correlated (\( r = 0.996, \text{slope} = 0.979 \)). Likewise, in 210 gastric juice specimens, there was a close correlation between [\( \text{H}^+ \)] with the two methods (\( r = 0.972, \text{slope} = 1.042 \)). Unless otherwise stated, values for [\( \text{H}^+ \)] used in calculations were derived by the glass electrode method (11).

**Equations.** Two basic equations were used:

- measured acid output
  \[
  = \text{acid secreted} - \text{acid neutralized, and (1)}
  \]
- measured osmolar output
  \[
  = \text{osmoles secreted} - \text{osmoles neutralized. (2)}
  \]

Under usual circumstances, acid secretion (AS) exceeds bicarbonate secretion (BS). Thus, the amount of acid neutralized by bicarbonate equals the amount of bicarbonate secreted, and from Eq. 1:

\[
\text{measured acid output} = AO = AS - BS. \tag{3}
\]

It is apparent that
\[
\text{AO} = V_{\text{GJ}}[\text{H}_2\text{CO}_3] \tag{4}
\]

and that
\[
\text{AS} = V_{\text{P}}[\text{H}^+]. \tag{5}
\]

where \( V_{\text{GJ}} \) is the volume of gastric juice sample, \([\text{H}_2\text{CO}_3] \) is the hydrogen ion concentration of gastric juice sample, \( V_{\text{P}} \) is the volume of parietal (acid) secretion, and \([\text{H}^+] \) is the hydrogen ion concentration of parietal secretion. Thus, substituting Eqs. 4 and 5 into Eq. 3:

\[
V_{\text{GJ}}[\text{H}_2\text{CO}_3] = V_{\text{P}}[\text{H}^+] - BS. \tag{6}
\]

From references 7, 10, 12, and 13 and from data that will be presented below, it is reasonable to assume that \([\text{H}_2\text{CO}_3] = 160 \text{ mmol/liter} \). Also, from the two-component model:

\[
V_{\text{GJ}} = V_{\text{P}} + V_{\text{NP}}. \text{ or } \tag{7}
V_{\text{P}} = V_{\text{GJ}} - V_{\text{NP}}.
\]

After substituting Eq. 7 into Eq. 6 and solving for \( V_{\text{NP}} \), we obtain:

\[
V_{\text{NP}} = V_{\text{GJ}}(160 - [\text{H}_2\text{CO}_3]) - BS \tag{8}
\]

From Eq. 2, it can be determined that

\[
V_{\text{GJ}}\text{OSM}_{\text{GJ}} = (V_{\text{P}}\text{OSM}_P + V_{\text{NP}}\text{OSM}_{\text{NP}}) - 2\text{ BS, } \tag{9}
\]

where \( \text{OSM}_{\text{GJ}} \) is the osmolality of gastric juice sample, \( \text{OSM}_P \) is the osmolality of pure parietal secretion, and \( \text{OSM}_{\text{NP}} \) is the osmolality of nonparietal secretion. In Eq. 9, note that, for every millimole or milliosmole of \( \text{HCO}_3^- \) secreted, there is a loss of 2 molosm since both \( \text{HCO}_3^- \) and an equal amount of \( \text{H}^+ \) are lost from the osmotic balance. Substituting Eq. 7 into 9 and rearranging to solve for \( V_{\text{NP}} \):

\[
\text{OSM}_{\text{GJ}}\text{Osm}_{\text{NP}} \]

plasma; PEG, polyethylene glycol; PGE, 11,16,16-trimethyl prostaglandin \( \text{E}_2 \), \( V_{\text{GJ}} \), volume of gastric juice sample; \( V_{\text{NP}} \), volume of nonparietal secretion; \( V_{\text{P}} \), volume of parietal (acid) secretion.

1 Abbreviations used in this paper: AO, acid output; AS, acid secretion; [\( \text{BNP} \)], bicarbonate concentration of nonparietal secretion; BS, bicarbonate secretion; [\( \text{H}^+ \)], hydrogen ion concentration; \([\text{H}_2\text{CO}_3] \), hydrogen ion concentration of gastric juice sample; \([\text{H}_2\text{O}] \), hydrogen ion concentration of parietal secretion; OSM\(_{\text{GJ}} \), osmolality of gastric juice sample; OSM\(_P \), osmolality of pure parietal secretion; OSM\(_{\text{NP}} \), osmolality of nonparietal secretion; OSM\(_{\text{PL}} \), osmolality of free bicarbonate present in the gastric juice. Thus, when \([\text{H}_2\text{CO}_3] = 0 \) and AO is “zero” by Eq. 4, it is necessary to measure the concentration of \( \text{HCO}_3^- \) in gastric juice directly to correct for free bicarbonate (see below).
Since both Eqs. 8 and 10 are equal to $V_{NP}$, they equal each other:

$$V_{CL} \left( 160 - [H_3 CO_3] \right) - BS = V_{CL} \left( OSM_p - OSM_{GJ} \right) - 2BS \over 160$$

and we solve (11) for BS:

$$BS = V_{CL} \left( 160 \Delta OSM - K\Delta H \right)^3 \over 320 - K$$

To calculate BS from Eq. 12, it is necessary to measure $V_{CL}$, OSMGJ, and $[H_3 CO_3]$ and assign a value for $OSM_{NP}$ and OSMGJ. Several investigators have reported that OSMNP is equal to the osmolality of plasma (OSMPL), i.e., $OSM_{NP} = OSM_{PL}$ (9, 10, 13, 14). From references 10 and 15 and from data that will be presented below, it is reasonable to assume that OSMp = 1.06 OSMPL; i.e., OSMp is 6% greater than OSMPL. Thus, the terms $\Delta OSM$ and $K$ in Eq. 12 can be calculated by measuring OSMPL and OSMGJ. Once BS is calculated from Eq. 12 (or Eq. 13), $V_{NP}$ can be calculated from Eqs. 8 or 10. Then, $V_F$ can be calculated from Eq. 7. Finally, the bicarbonate concentration of the nonparietal secretion, $[BNP]$, can be calculated from the equation

$$[BNP] = BS/V_{NP}$$

Note that $[BNP]$ is a calculated value in this method. Previous methods have sometimes assumed $[BNP]$ to be the same as plasma (9, 10).

Statistics. Values are expressed as mean±1 SE. BS, $V_{NP}$, $V_F$, and $[BNP]$ were computed using a Hewlett-Packard 97 calculator (Hewlett-Packard, Palo Alto, CA) programmed with Eqs. 12, 8, 7, and 14, respectively. Statistical significance was tested by two-tailed paired t test or by two-tailed Wilcoxon’s signed rank test with $P < 0.05$ considered significant. Pearson’s correlation coefficient was used in the validation experiments.

RESULTS

In vitro validation. A pure “parietal” solution containing 160 mmol/liter HCl was prepared from a stock solution and the concentration of HCl confirmed by titration to pH 7.00 with 0.1 N NaOH. In addition to the “parietal” solution, 16 “nonparietal” HCO$_3^-$-containing solutions were prepared. These solutions contained from 6.0 to 88.1 mmol/liter of bicarbonate. Sufficient NaCl was added to the 16 solutions to make them approximately isotonic (osmolality 301±2 mosM/kg). Different volumes of one of the “nonparietal” solutions ($V_{NP}$) and the parietal solution ($V_F$) were mixed together in an open glass beaker at room temperature using gentle stirring. For simplicity, the final volume of the mixture was always 50 ml. $V_{NP}$, $V_F$, and the HCO$_3^-$ concentration of the “nonparietal” solution were selected by one of us and were unknown to the other who carried out the measurements and calculations. From the [H$^+$] and osmolality of the final 50-ml mixture, BS, $V_{NP}$, $V_F$, and $[BNP]$ were calculated.

28 separate in vitro experiments were performed using varying mixtures of the “parietal” solution (H$^+$] = 160 mmol/liter; OSMp = 307 mosM/kg) and one of the 16 “nonparietal” solutions. There were close correlations between the calculated and actual values for all four parameters: BS ($r = 0.98$); $V_{NP}$ ($r = 0.99$); $V_F$ ($r = 1.00$); and $[BNP]$ ($r = 0.97$). The lowest osmolality of a mixed sample, 238 mosM/kg, occurring when 30.0 ml “parietal” solution was added to 20.0 ml of a “nonparietal” solution containing 88.1 mmol/liter of bicarbonate.

In vivo validation. The purpose of these in vivo studies was to determine whether an intragastric infusion of an HCO$_3^-$-containing “nonparietal” solution, which simulates an increase in HCO$_3^-$ secretion by the stomach, could be detected quantitatively by our method. To do this, an intragastric HCO$_3^-$ infusion was superimposed on steady-state gastric secretion induced by a continuous intravenous infusion of 0.1–0.2 μg/ kg/h pentagastrin (Peptavlon, Ayerst Laboratories, New York) in eight subjects. These pentagastrin doses were submaximal in seven of the eight subjects (mean acid outputs were 60±7% of the maximal acid response to 6.0 μg/kg s.c. pentagastrin). In one subject, the dose of pentagastrin (0.2 μg/kg/h) proved to be maximal. Thus, for the eight subjects, acid secretion during pentagastrin infusion ranged from 27 to 100% of maximal.

After basal gastric juice and saliva were collected for two 15-min periods, the intravenous infusion of pentagastrin was begun (volumetric infusion pump model 922; IMED Corp., San Diego, CA). Pentagastrin was infused for twelve 15-min periods. During the seventh 15-min period of intravenous pentagastrin infusion, one of eight HCO$_3^-$-containing test solutions was infused into the stomach (IMED infusion pump) through a small polyethylene catheter attached to the nasogastric tube. The HCO$_3^-$-containing solutions were approximately isotonic (osmolality, 293±2 mosM/kg; plasma osmolality, 294±2 mosM/kg). The HCO$_3^-$ concentration of the solutions varied from 0 to 90.0 mmol/liter; the other electrolytes were Na$^+$ and Cl$^-$. The volume of the solution infused into the stomach varied from 12.0 to 56.0 ml. One of us selected the solution and volume to be infused; the other carried out measurements of $V_{CL}$, [H$^+$], and OSMGJ without knowledge of which solution was being infused.
of $V_{NP}$ or $[B_{NP}]$. Infusion of the test solution into the stomach was started 2 min after the beginning of the seventh 15-min period of pentagastrin infusion and was stopped 3 min before the end of the period (i.e., the infusion lasted 10 min). The test solution also contained 2 g/dl polyethylene glycol (PEG) as a nonabsorbable marker in order to estimate completeness of recovery of gastric juice (16).

An example of an experiment using this protocol is shown in Fig. 1. In response to intravenous pentagastrin infusion, $V_{GJ}$, $[H_{GJ}]$, and $OSM_{GJ}$ increased above basal levels and reached near steady values by the third 15-min period. In the seventh 15-min period, 25 ml of an $HCO_3^-$-containing solution was infused into the stomach. The solution contained 1.25 mmol HCO$_3^-$ (50.0 mmol/liter) and had an osmolality of 300 mosM/kg. This simulated increase in HCO$_3^-$ secretion in period 7 led to the expected increase in $V_{GJ}$ and decrease in $[H_{GJ}]$ and $OSM_{GJ}$ (Fig. 1). $V_{GJ}$, $[H_{GJ}]$, and $OSM_{GJ}$ returned to near control values during the eighth through twelfth periods of pentagastrin infusion. Using the values for $V_{GJ}$, $[H_{GJ}]$, and $OSM_{GJ}$ obtained in this experiment, it was possible to calculate BS, $V_{NP}$, $V_P$, and $[B_{NP}]$ for each 15-min period before, during, and after intragastric bicarbonate infusion. By comparing values in the seventh period with values before and after this period, changes in nonparietal alkaline secretion in period 7 were calculated and correlated with the amounts of fluid and HCO$_3^-$ actually infused into the stomach during period 7.

Results from experiments in which eight healthy subjects were studied according to this protocol are shown in Fig. 2. There was a good correlation between calculated and actual values for (a) the increase in calculated HCO$_3^-$ secretion during period 7; (b) the increase in $V_{NP}$ during period 7; and (c) $HCO_3^-$ concentration of the simulated secreted fluid during period 7 (corrected for percent polyethylene glycol recovery). Calculated $[B_{NP}]$ represented $ΔBS/ΔV_{NP}$ for period 7, whereas actual $[B_{NP}]$ represented the actual bicarbonate concentration of the fluid infused into the stomach in period 7.

**Figure 1.** In vivo validation experiment in one subject. Volume of gastric juice ($V_{GJ}$), H$^+$ concentration of gastric juice ($[H_{GJ}]$), and osmolality of gastric juice ($OSM_{GJ}$) were measured for two 15-min periods (Basal). Then, intravenous pentagastrin (0.1 μg/kg/h) was infused for twelve 15-min periods. In response to pentagastrin, $V_{GJ}$, $[H_{GJ}]$, and $OSM_{GJ}$ increased above basal values. Note that $OSM_{GJ}$ increased above the osmolality of plasma ($OSM_{pl}$). During the seventh 15-min period of pentagastrin infusion, when secretion was nearly steady, a HCO$_3^-$-containing solution was infused into the stomach (solid bar). This was accompanied by an increase in $V_{GJ}$ and a decrease in $[H_{GJ}]$ and $OSM_{GJ}$ during period 7. These values returned to control values during the eighth through twelfth 15-min periods. From the changes in $V_{GJ}$, $[H_{GJ}]$, and $OSM_{GJ}$ in period 7, the increase in simulated $HCO_3^-$ secretion during period 7 could be calculated (Fig. 2).
relation between basal $V_{NF}$ and basal $V_P$ ($r = 0.75, P < 0.005$). The HCO$_3^-$ concentration of basal nonparietal secretion averaged 99.0 ± 13.5 mmol/liter (median, 82.8 mmol/liter).

Effect of pentagastrin on gastric secretion. Mean calculated values for H$^+$ and HCO$_3^-$ secretion, $V_P$ and $V_{NF}$, and [B$_{NF}$] before and during pentagastrin infusion in eight subjects who participated in the in vivo validation experiments are shown in Fig. 3. HCO$_3^-$ secretion did not change significantly from basal rates during pentagastrin infusion, despite a large increase in H$^+$ secretion. Pentagastrin caused a small but significant increase in $V_{NF}$ ($P < 0.01$) and a much larger increase in $V_P$ ($P < 0.001$). [B$_{NF}$] decreased to an average concentration of 61.9 mmol/liter during pentagastrin infusion ($P < 0.005$). Thus, pentagastrin increased $V_{NF}$ and reduced [B$_{NF}$] by approximately the same extent.

Fig. 4 shows the relationship between [H$_3^+$] and OSM$_{GJ}$ (expressed as a fraction of plasma osmolality) during pentagastrin infusion. Each point represents a separate gastric juice sample. A sample from a patient with pentagastrin-fast achlorhydria is shown as a triangle. When [H$_3^+$] was zero after pentagastrin (achlorhydric patient), the osmolality of gastric juice was the same as that of plasma (i.e., OSM$_{GJ}$/OSM$_{PL} = 1.00$). Gastric juice was always hypotonic to plasma when [H$_3^+$] > 0, but < 120 mmol/liter. On the other hand, when [H$_3^+$] > 127 mmol/liter, gastric juice was always hypertonic to plasma. The osmolality of the 28 gastric juice samples with [H$_3^+$] > 127 mmol/liter averaged 1.05 OSM$_{PL}$ (range, 1.01–1.10 OSM$_{PL}$). The highest observed [H$^+$] in a sample of gastric juice was 154 mmol/liter. The osmolality of this sample was 312 mosM/kg (1.08 OSM$_{PL}$). The highest observed osmolality of a gastric juice sample was 320 mosM/kg (1.16 OSM$_{PL}$).

Effect of bethanechol on gastric secretion during pentagastrin infusion. One day, after basal gastric secretion was measured, an intravenous infusion of bethanechol (Urecholine; Merck Sharp and Dohme Co., West Point, PA) plus pentagastrin was begun and continued for eight 15-min periods. The dose of bethanechol, 50 µg/kg/h, is a maximally tolerated dose in humans (15). The dose of pentagastrin was 0.1 µg/kg/h. On a separate day, the same dose of pentagastrin was infused without bethanechol as a control. As shown in Table I, bethanechol significantly increased saliva and V$_{GJ}$. The increase in V$_{GJ}$ was due to significant stimulation of both parietal and nonparietal secretion. Bethanechol significantly stimulated both H$^+$ secretion (AS) and HCO$_3^-$ secretion (BS), so that net acid output in gastric juice increased slightly but not significantly with bethanechol. The HCO$_3^-$ concentration of nonparietal secretion [B$_{NP}$] was significantly higher during bethanechol plus pentagastrin infusion than during infusion of pentagastrin alone (Table I).

Effect of prostaglandin E$_2$ on gastric secretion during pentagastrin infusion. The effect of an orally administered prostaglandin E$_2$ analogue (11,16,16-trimethyl PGE$_2$, RO21-6937; Hoffman-LaRoche Inc.,
Nutley, NJ) on pentagastrin-stimulated gastric secretion was evaluated in 10 subjects. Fasting subjects were intubated and then capsules containing 0 (placebo), 0.25, 0.75, 1.5, or 3.0 mg PGE₂ analogue were swallowed. Studies were performed in random order on separate days with at least 1 wk between studies. All subjects received all dosages, except that only five received the 3.0-mg dose. After allowing 75 min for emptying the drug from the stomach and for absorption, gastric contents were aspirated and pentagastrin (0.1 μg/kg/h) was infused intravenously for eight 15-min periods. Gastric juice and saliva were collected as described previously. Salivary output was unaffected by the prostaglandin compound.

As shown in Fig. 5 (upper left), there was a dose-related increase in HCO₃⁻ secretion in response to the PGE₂ analogue, with the peak response following 0.75 mg. With this dose, HCO₃⁻ secretion increased from 4.3 to 6.1 mmol/2 h (P < 0.05), and [B₃₆₅] increased from 45.0 to 74.9 mmol/liter (P < 0.005, Fig. 5, lower right). PGE₂ did not stimulate nonparietal volume secretion; in fact, Vₚ increased significantly (Fig. 5, upper right). PGE₂ also decreased parietal volume secretion significantly. The 0.75-mg dose of PGE₂, for example, reduced pentagastrin-stimulated parietal secretion by 73.4 ml/2 h (P < 0.05, Fig. 5, lower left). Thus, this dose of prostaglandin reduced H⁺ secretion more than it increased HCO₃⁻ secretion (11.7 mmol/2 h vs. 1.8 mmol/2 h).

**DISCUSSION**

**Validity of basic assumptions.** One assumption of the two-component model of gastric secretion is that H⁺ is secreted at a concentration of 160 mmol/liter, even at submaximal rates of acid secretion (7, 10, 12, 13). Thus, this model assumes that increases or decreases in H⁺ secretion result from increases or decreases in parietal volume secretion. In our in vivo validation experiments, which were carried out mainly during submaximally stimulated conditions, we found a close correlation between actual and calculated values for changes in nonparietal secretion when we assumed that [H⁺] = 160 mmol/liter and OSMₚ = 1.06 OSMₚL. If H⁺ had been secreted at <160 mmol/liter under submaximal stimulatory conditions, it would have not have been possible to obtain the highly correlative data shown in Fig. 2. Thus, our in vivo validation studies indirectly support the assumptions that [H⁺] = 160 mmol/liter and OSMₚ = 1.06 OSMₚL when acid output ranges from 27 to 100% of maximal. Our own experimental data from highly acid specimens of gastric juice also support these assumptions (Fig. 4). That the nonparietal component of gastric secretion is approximately isotonic to plasma is supported by several previous studies in animals and humans (9, 10, 13, 14) and by results in our patient with pentagastrin-fast achlorhydria and isotonic gastric juice (Fig. 4).

Our in vitro validation studies support the assumption that decreases in [H₂₃₅] and OSMC₃ below [H₂₃₅] and OSM₃ are a direct result of neutralization and dilution by alkaline nonparietal secretion. Another mechanism (besides neutralization and dilution) by which [H₂₃₅] and OSM₃ could decrease in vivo is gastric ion absorption. However, the healthy stomach is highly impermeable to passive diffusion of ions from the lumen into the mucosa (17). It has even been suggested that the disappearance of H⁺ from the lumen by apparent diffusion...
fusion into the mucosa may actually represent surface neutralization by bicarbonate secretion (10). Nevertheless, the rate of apparent absorption of $H^+$ by the stomach is $<0.1\%$/min (18, 19), so that under the conditions of our experiments, in which secreted gastric juice was aspirated from the stomach continuously rather than remaining in contact with the gastric mucosa for a prolonged period, it is likely that absorption of $H^+$ and other ions by gastric mucosa was negligible.

Thus, our validation experiments indicate that it is possible to estimate gastric HCO$_3^-$ secretion (BS) from measurements of gastric juice volume, $H^+$ concentration, and osmolality. In Fig. 6, a nomogram has been provided for determining BS once $V_{GJ}$, [H$_2$C], and OSM$_{GJ}$ are known. This particular series of curves is applicable when plasma osmolality is 290 mosM/kg.

**Physiology and pharmacology of gastric nonparietal volume secretion and bicarbonate secretion.** The calculated basal nonparietal volume secretion rate averaged 25.8 ml/h (0.4 ml/min) in the 14 healthy subjects in this study. This rate agrees closely with nonparietal flow rates calculated by others (9, 10, 20). Under basal conditions, nonparietal volume secretion accounted for $\sim$45% of total gastric volume secretion and parietal secretion for the remainder. We found that nonparietal volume secretion was not constant, as had been assumed by Hollander (7) and by Makhlouf et al. (9, 10), because it could be stimulated significantly by pentagastrin and bethanechol. Furthermore, pentagastrin-stimulated nonparietal volume secretion could be decreased significantly by the prostaglandin $E_2$ analogue. Thus, our data support Hunt’s suggestion that both parietal and nonparietal volume secretion (and their ratios) can vary under different experimental conditions (8, 20).

Despite our agreement with previous studies regarding basal nonparietal volume secretion, our calculated values for basal HCO$_3^-$ secretion are greater than those that have been estimated previously (3, 10, 21). Thus, we estimated that the healthy human stomach secreted $\sim$2.6 mmol HCO$_3^-$/h. Previous two-component models, which automatically assumed that nonparietal secretion had a [B$_{NP}$] equal to plasma (9, 10), would result in lower calculated secretion rates. For example, if [B$_{NP}$] were assumed to equal 25 mmol/liter and basal $V_{NP}$ = 0.35 ml/min (10), calculated basal HCO$_3^-$ secretion would only be 0.5 mmol/h. Rees et al. recently attempted to calculate basal gastric HCO$_3^-$ secretion directly during intravenous cimetidine infusion using pH and $PCO_2$ measurements (3). They estimated that basal HCO$_3^-$ secretion was 0.3 to 0.4 mmol/h with a basal HCO$_3^-$ concentration of only 2 to 20 mmol/liter. However, because pH of gastric juice was $\sim$6 in those studies, it is almost certain that $H^+$ was still being secreted despite cimetidine. In that case, HCO$_3^-$ secretion could be underestimated (2). Our estimate that basal HCO$_3^-$ secretion is 50% of basal $H^+$ secretion and 8% of peak $H^+$ secretion is in good agreement with in vivo and in vitro studies by Garner and Flemstrom (2, 22).

Measured basal acid output averaged 2.4 mmol/h in our healthy subjects, whereas mean basal $H^+$ secretion was calculated to be 4.9 mmol/h. Thus, basal HCO$_3^-$ secretion reduced acid output in gastric juice to $\sim$50% of the amount of hydrogen ions actually secreted. Stated in another way, basal $H^+$ secretion was $\sim$15% of peak pentagastrin-stimulated $H^+$ secretion, whereas basal acid output was only 8% of peak acid output when assessed by conventional methods, which do not consider basal HCO$_3^-$ secretion. Basal [H$_2$C] averaged $\sim$40 mmol/liter, whereas [H$_2$] was assumed to be 160 mmol/liter. Therefore, HCO$_3^-$ secretion appears to play a major role in regulating basal gastric acidity.

There was a significant ($P < 0.001$) correlation between basal HCO$_3^-$ secretion and basal $H^+$ secretion in the 14 subjects studied. Thus, subjects who secreted high amounts of acid basally tended also to secrete high amounts of HCO$_3^-$. Furthermore, this suggests that subjects with low basal $H^+$ outputs that use standard methods actually have low $H^+$ secretion rather than excessive basal HCO$_3^-$ secretion. Because penta-

**Figure 6** Nomogram for determining HCO$_3^-$ secretion (BS) per 100 ml gastric juice from measurement of hydrogen ion concentration of gastric juice, [H$_2$C], and osmolality of gastric juice, OSM$_{GJ}$. Curves for OSM$_{GJ}$ from 160 to 300 mosM/kg at 10 mosM/kg intervals are provided, assuming plasma osmolality = 290 mosM/kg. As an example (dotted lines), for a 50 ml sample of gastric juice collected over a given time period with a [H$_2$C] = 40.0 mmol/liter and OSM$_{GJ}$ = 200 mosM/kg, BS = 5.0 mmol/100 ml gastric juice, or 2.5 mmol HCO$_3^-$ for this 50 ml sample of gastric juice. Note that if [H$_2$C] = 0, it is also necessary to multiply the free HCO$_3^-$ concentration of gastric juice, [B$_{GJ}$], by $V_{GJ}$ and to add this product to the value for BS derived from the nomogram.

The author will provide nomograms for plasma osmolality values other than 290 mosM/kg upon request. The author will also provide nomograms for determining nonparietal volume and parietal volume secretion upon request.
gastrin markedly increased H⁺ secretion but had no effect on HCO₃⁻ secretion (Fig. 3). [H⁺] increased during pentagastrin infusion and approached 160 mmol/liter in some subjects (Figs. 1 and 4).

In this study, the HCO₃⁻ concentration of basal gastric nonparietal secretion averaged 99.0 mmol/liter (median, 82.8 mmol/liter). This apparently high HCO₃⁻ concentration is in the range for pancreatic HCO₃⁻ secretion (75–130 mmol/liter) (23). A previous study in healthy humans studied at low rates of H⁺ secretion estimated a basal HCO₃⁻ concentration of nonparietal secretion of only 13 mmol/liter (21). However, as emphasized by Flemstrom (2), under those experimental conditions, there may have been residual, but masked, H⁺ secretion leading to falsely low estimates of [B₅]. However, another study of peptic ulcer patients calculated from pH and PCO₂ a mean HCO₃⁻ concentration of gastric juice of 57.3 mmol/liter (range, 38.0–67.7 mmol/liter) when H⁺ secretion had been blocked by intravenous secretin (24). Moreover, using a two-component model of gastric secretion, Fisher and Hunt calculated that the HCO₃⁻ concentration of nonparietal secretion could be as high as 107.8 mmol/liter (8).

In 1948, Hollander et al. measured the pH of gastric secretions from Heidenhain pouch dogs and found a median pH of 7.65 and some pH values as high as 9.22 (25). More recently, Turnberg and his associates (26–28) used microelectrodes and recorded the pH near the gastric mucosal surface to be as high as 8.65, 7.95, and 8.10 in rabbits, rats, and humans, respectively, when luminal pH was ~2.0. As an example, a pH of 8.10 corresponds to a HCO₃⁻ concentration of 83 mmol/liter when PCO₂ = 40 mmHg. Furthermore, in our experience with 13 patients with pentagastrin-fast achlorhydria, maximal gastric juice pH ranged from 7.86 to 8.48 (Cowley, Y., and M. Feldman. Unpublished data.) Thus, current evidence suggests that both the HCO₃⁻ concentration and the pH of nonparietal gastric secretion are much higher than plasma.

Because the gastric lumen is negatively charged (~40 mV) with respect to the mucosa (17, 19), HCO₃⁻ appears to be secreted by the mucosa into gastric juice against both an electrical and a chemical gradient. This suggests that HCO₃⁻ secretion in humans is, at least in part, an active process. A similar conclusion has been reached in previous animal studies that measured HCO₃⁻ secretion in vitro by titration with HCl (and which, therefore, did not assess HCO₃⁻ concentration of secreted fluid) (2, 29). Because stimulation of HCO₃⁻ secretion is not accompanied by a change in potential difference, it has been suggested that active HCO₃⁻ secretion is an electroneutral process, which is possibly mediated by luminal Cl⁻/HCO₃⁻ exchange (2). In support of this concept, fundic bicarbonate secretion can be blocked in vitro by removing chloride from luminal fluid (2).

Pentagastrin caused a significant decrease in [B₅] and a significant increase in V₅ compared with basal values. This suggests that factors that control HCO₃⁻ concentration of nonparietal secretion differ from those that control nonparietal fluid. Although [B₅] decreased during pentagastrin infusion, mean [B₅] remained significantly higher than plasma HCO₃⁻ concentration. Addition of bethanechol or 11,16,16,-trimethyl PGE₂ to pentagastrin infusion caused a significant increase in [B₅] (Table I, Fig. 5). This suggests that cholinergic stimulation and prostaglandins may be factors that regulate active gastric HCO₃⁻ secretion in humans as well as animals (2).

Bethanechol caused a simultaneous and significant increase in pentagastrin-stimulated H⁺ and HCO₃⁻ secretion (9.0 and 4.1 mmol/h, respectively). Although net acid output increased somewhat during bethanechol infusion, this was not a significant change (Table 1). Thus, the significant increase in H⁺ secretion during bethanechol infusion was masked somewhat by a concurrent stimulation of HCO₃⁻ secretion. The prostaglandin E₂ analogue also caused an increase in gastric HCO₃⁻ secretion while causing a much larger decrease in gastric H⁺ secretion. Therefore, the significant reduction in net acid output in gastric juice due to the prostaglandin E₂ analogue was more due to inhibition of H⁺ secretion than to stimulation of HCO₃⁻ secretion. It is possible that other prostaglandin compounds will affect the relationship between gastric HCO₃⁻ and H⁺ secretion differently (30).

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