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Eradication of *Helicobacter pylori* Infection in Patients with Non-Ulcer Dyspepsia

Effects on Basal and Bombesin-Stimulated Serum Gastrin and Gastric Acid Secretion

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Background: This study evaluates the effect of eradicating *Helicobacter pylori* on basal and bombesin-stimulated gastric acid secretion and serum gastrin in non-ulcer dyspepsia. **Methods:** Before and 1 month after an attempt to eradicate *H. pylori* basal and bombesin-stimulated gastric acid outputs were measured in 23 patients. *H. pylori* was eradicated in 15 patients (group A) but not in the other 8 (group B). Incremental gastric acid output was calculated by subtracting basal from bombesin-stimulated values. **Results:** Basal acid output increased significantly ($p = 0.01$) after therapy in group A ($\Delta 1.6 \pm 0.6$ mmol/h) but not in group B ($\Delta 0.2 \pm 0.5$ mmol/h). Incremental gastric acid output decreased distinctly ($\Delta -3.9 \pm 1.4$ mmol/h) after therapy in group A ($p = 0.02$) but not in group B ($\Delta -2.2 \pm 1.7$ mmol/h). Basal serum gastrin decreased significantly ($p < 0.005$) after therapy in group A ($\Delta -9 \pm 4$ pM) but not in group B ($\Delta -1 \pm 2$ pM). Integrated serum gastrin responses to bombesin decreased markedly ($p < 0.001$) after therapy in group A ($\Delta -5.0 \pm 1.6$ nM*60 min) but slightly in group B ($\Delta -0.9 \pm 1.3$ nM*60 min) ($p < 0.05$). **Conclusions:** In patients with non-ulcer dyspepsia basal serum gastrin concentrations decrease but basal gastric acid outputs increase after eradication of *H. pylori*. Bombesin-induced increments in gastric acid output, however, decrease in parallel with gastrin release.

Key words: Bombesin; gastric acid; gastrin; *Helicobacter pylori*; non-ulcer dyspepsia

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Infection with *Helicobacter pylori* is now recognized as the main factor in the pathogenesis of duodenal ulcer disease and is strongly associated with an increased risk of gastric carcinoma (1,2). *H. pylori* predominantly colonizes the antral mucosa, where it causes chronic, diffuse, superficial gastritis (3,4). After eradication of the organism, gastritis and duodenal ulcer recurrence disappear (3-5). Infection with *H. pylori* also increases serum gastrin concentrations (6,7). It has been shown that *H. pylori*-related hypergastrinemia is the result of a selective increase of gastrin-17 (8), a molecular form that is almost exclusively released from the antrum (9). This raises the possibility that hypergastrinemia due to *H. pylori* infection is responsible for the abnormalities of gastric acid secretion which have been described in patients with duodenal ulcers (10). However, despite a reduction of serum gastrin after eradication of *H. pylori*, no consistent changes in gastric acid secretion have been reported (10-14).

Absence of a parallel reduction of circulating gastrin levels and gastric secretion after eradication of *H. pylori* has been attributed to the hypothesis that *H. pylori* decreases parietal cell sensitivity to gastrin (15), but other studies do not support this hypothesis (16-18). Studies on the effect of eradicating

H. pylori on gastric acid secretion and gastrin release have mainly focused on duodenal ulcer patients (6-8,12,13,18,19) or have compared *H. pylori*-positive volunteers with *H. pylori*-negative subjects (11,14,20,21). To elucidate the effect of *H. pylori* on gastric acid secretion and gastrin release in non-ulcer dyspepsia, we have measured basal and stimulated gastric acid secretion and serum gastrin concentrations before and 1 month after eradication therapy for *H. pylori*. For this purpose we have stimulated gastric acid secretion by infusion of bombesin. This peptide selectively releases gastrin from the antrum (22), which is the main location affected by *H. pylori* infection (3,4). Bombesin-stimulated gastrin release is, unlike meal-stimulated gastrin release, not sensitive to luminal factors such as pH (7). Furthermore, intravenous stimulation avoids the technical difficulties encountered in the measurement of gastric acid secretion by meal stimulation. To try to exclude possible interference of anti-*H. pylori* drugs with gastrin release and gastric acid secretion, we have used two different treatment regimens to eradicate *H. pylori* and have studied patients before and 1 month after discontinuation of medical therapy.

PATIENTS AND METHODS

Twenty-five *H. pylori*-positive patients (8 women, 17 men; mean age, 42 ± 8 years) with upper abdominal complaints without a history of peptic ulcer disease or previous surgery were studied. Reflux esophagitis and gastric or duodenal ulcer disease were excluded by endoscopy. In all patients medication was stopped at least 10 days before the study. None of the patients had used proton pump inhibitors. *H. pylori* infection was confirmed in all patients by histologic examination of antral biopsy specimens, by rapid urease test (CLO test) on antral specimens, and by culture of antral specimens. All these showed *H. pylori* in the patients selected for this study.

To define a normal range for bombesin-stimulated gastric acid secretion, we have also included a group of nine *H. pylori*-negative healthy control subjects (six women, three men; mean age, 26 ± 5 years).

Secretory studies

After a 12-h fast all patients and healthy subjects reported to the gastrointestinal research laboratory at 0830 h. Two indwelling intravenous catheters were placed, one in each forearm. One of these catheters was used for collection of blood samples and was kept patent with a heparin-saline solution, whereas the other was used for infusion of bombesin. For this purpose, synthetic bombesin (UCB, Brussels, Belgium) was dissolved in saline containing 2% human albumin under aseptic conditions and stored at -20°C in aliquots of 3 nmol/ml. An orogastric drainage tube with multiple side holes and a metallic tip at the end was swallowed. The patient was then positioned on the left side in a bed. A small-bore perfusor tube (NPBI b.v. Emmer Compascuum, The Netherlands) was inserted into one of the side holes of the drainage tube. After the position of the drainage tube had been checked by means of the water recovery test (23), the perfusor tube was pulled back 10 cm to disconnect this tube from the drainage tube. After the stomach was emptied, 200 ml/15 min saline with phenol red (23) as a recovery marker was perfused through the perfusion tube during the entire study period. Intermittent suction was applied to the drainage tube, using an intermittent suction unit (Medela median, Hoek-Loos, The Netherlands) that applies suction for 60 sec in each 120-sec suction cycle. After an equilibration period of 30 min four 15-min collections were obtained under basal conditions followed by four 15-min collections during intravenous infusion of 90 pmol/kg·h of bombesin. After each 15-min collection period one blood sample was drawn for measurement of gastrin, and the serum was stored at -20°C .

The volume of the aspirates was recorded, and the concentration of H^+ was measured in the samples by titration to pH 7.0 with 0.1 N NaOH, using an autotitrator (ETS 822, Radiometer, Copenhagen). Aliquots for phenol red measurement in the perfusates and aspirates were taken and centrifuged. Phenol red concentrations were determined

spectrophotometrically. The data were used to calculate recoveries of gastric juice (23).

After correction for recoveries, basal gastric acid output (BAO) was calculated by summation of the four 15-min samples before infusion of bombesin and expressed in mmol/h. Stimulated gastric acid output was calculated by summation of all four 15-min samples during infusion of bombesin after correction for recovery. Incremental gastric acid output was calculated by subtracting BAO from bombesin-stimulated gastric acid output. These values are also expressed in mmol/h.

Gastrin was measured by radioimmunoassay (24). The antiserum used was raised in a rabbit to non-sulfated human gastrin-17 coupled with *n*-(3-dimethylaminopropyl)-*N'*-ethyl-carbodiimide hydrochloride to bovine serum albumin. The antibody binds to the COOH-terminal bioactive site of sulfated and non-sulfated gastrins and binds gastrin-17 and gastrin-34 with almost equal affinity. Cross-reaction with structurally related (cholecystokinin (CCK)) and unrelated peptides was negligible. The intra-assay variation was below 10% in the working range of the standard curve. All serum samples were measured in one run.

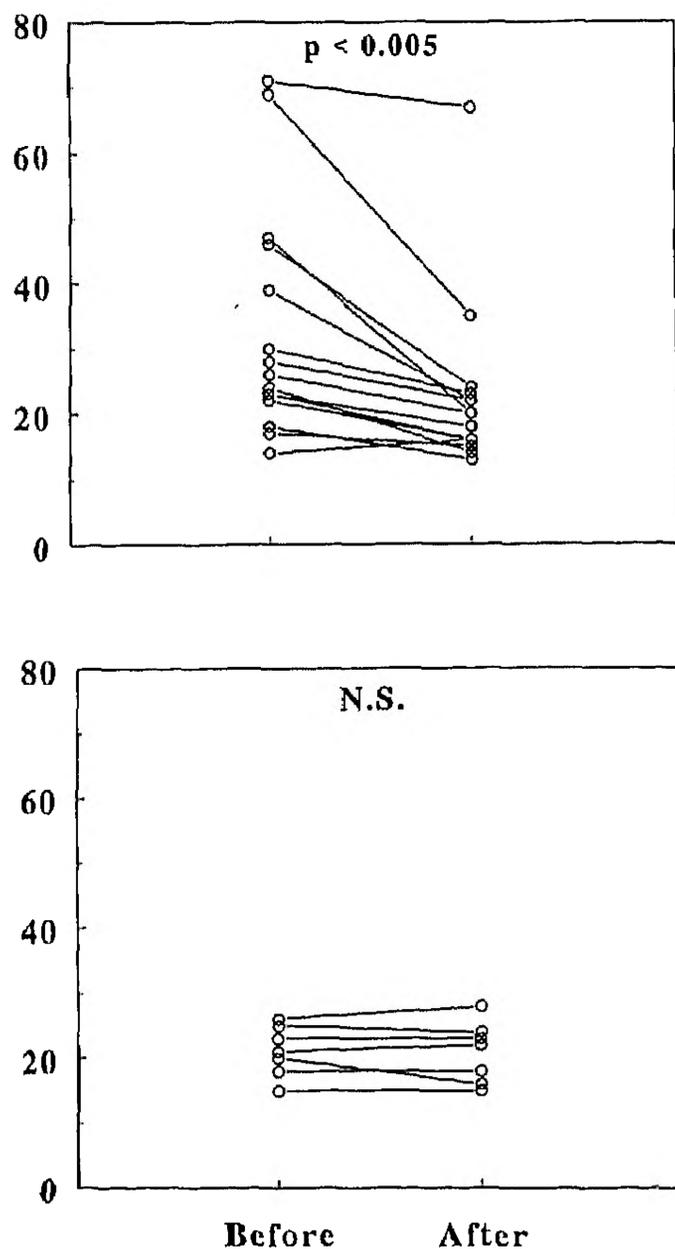


Fig. 1. Basal serum gastrin levels (pM) before and after therapy in patients in whom *Helicobacter pylori* eradication treatment was successful (upper panel) or in whom eradication of *H. pylori* had failed (lower panel).

The basal serum gastrin value for each patient was determined by taking the mean of the two serum gastrin concentrations obtained before the start of bombesin infusion. Integrated serum gastrin responses to bombesin were calculated by the trapezoidal rule after subtraction of basal values (25) and expressed as nM*60 min.

Eradication of H. pylori

After the gastric acid secretion studies, *H. pylori*-positive patients were treated either with 120 mg bismuth subcitrate four times daily ($n = 14$) or 1 g sucralfate four times daily ($n = 11$) for 4 weeks. During the last 10 days of the treatment course all patients also used 500 mg metronidazole three times daily and 500 mg amoxicillin three times daily. One month after completion of this treatment the endoscopy was repeated, and antral biopsy specimens were taken for histologic examination, for the CLO test, and for culture. The secretory studies were also repeated at this point, in accordance with the same protocol. The study protocol was approved by the local ethical committee of the University Hospital, Nijmegen, and all patients gave their informed consent.

Statistical analysis

Statistical analysis of paired data was done with the Wilcoxon test and of unpaired data with the Mann-Whitney U test. Differences with a two-tailed probability (p) value of less than 0.05 were considered significant.

RESULTS

Two patients refused to participate in the gastric acid secretion study 1 month after therapy and were excluded from the study.

Histologic examination of antral biopsy specimens, CLO tests, and cultures of antral tissue 1 month after completion of triple therapy showed that *H. pylori* had been eradicated in 15 of the remaining 23 non-ulcer dyspeptic patients (group A), whereas in the other 8 patients *H. pylori* infection persisted (group B). No significant differences in *H. pylori* eradication rates were observed between the two treatment regimens.

Basal serum gastrin concentrations before triple therapy were 33 ± 5 pM in group A and 22 ± 2 pM in group B. These values were not significantly different from each other ($0.05 < p < 0.10$). One month after triple therapy basal serum

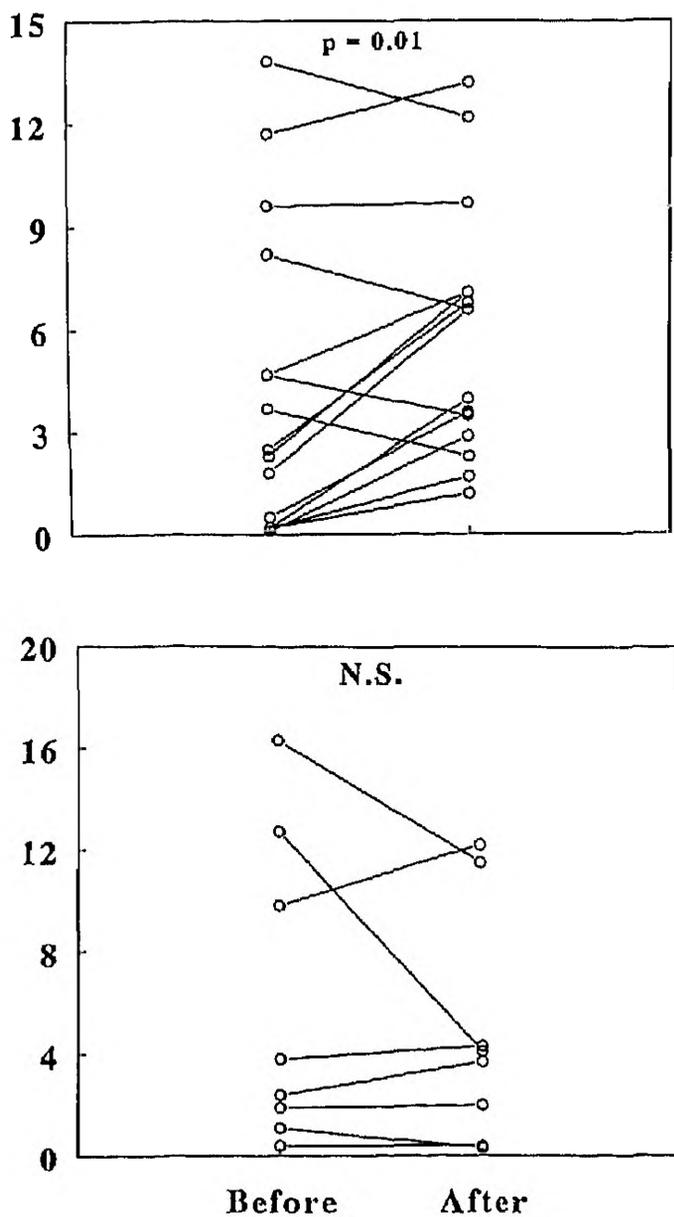


Fig. 2. Basal gastric acid secretion (mmol/h) before and after therapy in patients in whom *Helicobacter pylori* eradication treatment was successful (upper panel) or in whom eradication of *H. pylori* had failed (lower panel).

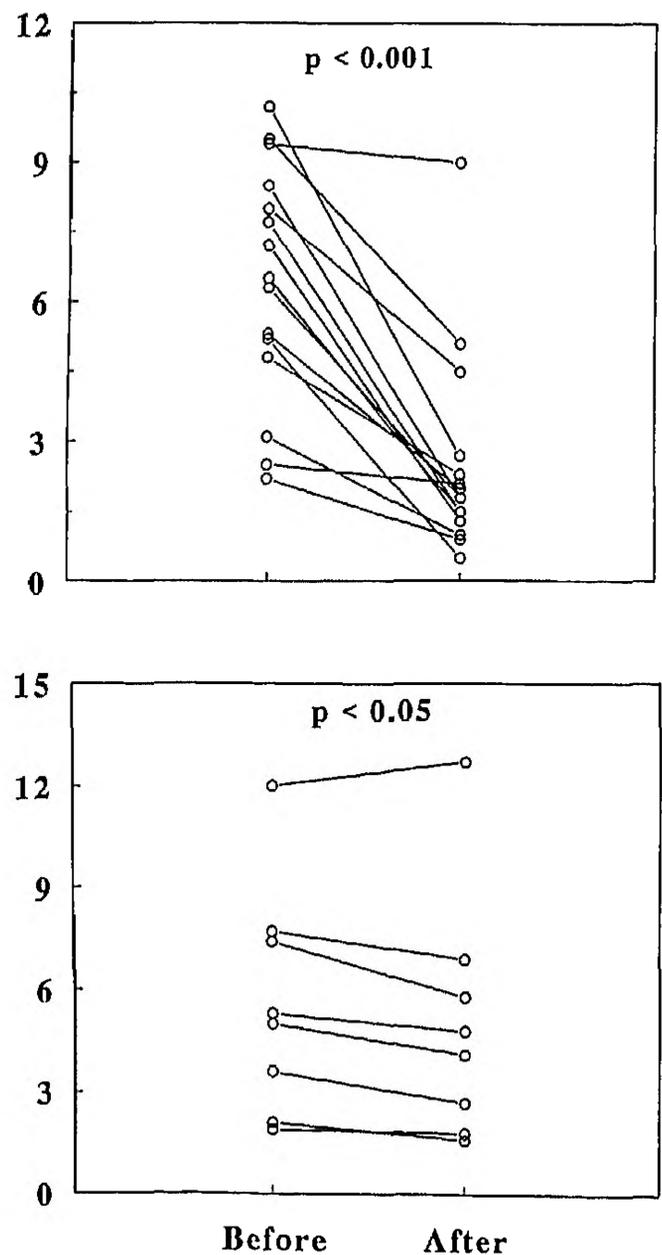


Fig. 3. Bombesin-stimulated serum gastrin concentration time curves (pM*60 min) before and after therapy in patients in whom *Helicobacter pylori* eradication treatment was successful (upper panel) or in whom eradication of *H. pylori* had failed (lower panel).

gastrin concentrations were markedly lower than before therapy (24 ± 4 pM) in the group-A patients ($p < 0.005$) but remained at the same level as before therapy (21 ± 2 pM) in the group-B patients (Fig. 1).

The BAO before therapy in group A was 4.3 ± 1.1 mmol/h and in group B 6.0 ± 2.2 mmol/h. These values were not significantly different from each other ($0.40 < p < 0.50$). One month after triple therapy BAO was markedly higher ($p = 0.01$) than before therapy in group A (5.9 ± 1.0 mmol/h) but remained at the same level as before therapy in group B (6.2 ± 1.8 mmol/h) (Fig. 2).

The gastrin responses to bombesin for the patients in groups A and B, before and 1 month after therapy, are depicted in Fig. 3. Integrated serum gastrin responses to bombesin in group A and group B before therapy were 8.3 ± 1.9 nM*60 min and 5.8 ± 1.4 nM*60 min, respectively. These values were not significantly different from each other. One month after triple therapy integrated serum gastrin responses to bombesin had decreased significantly to 3.2 ± 1.3 nM*60 min ($p < 0.001$) in group A and to 4.9 ± 1.3 nM*60 min in group B ($p < 0.05$). The decrease in integrated serum gastrin responses to bombesin in group A was significantly greater than in group B ($p < 0.01$).

Bombesin markedly stimulated gastric acid output ($p < 0.01$). Bombesin-stimulated gastric acid output before triple therapy was 12.5 ± 2.1 mmol/h in the group-A patients and 15.3 ± 2.5 mmol/h in the group-B patients. These values were not significantly different from each other. One month after triple therapy bombesin-stimulated gastric acid secretion was 10.1 ± 1.6 mmol/h in group A and 13.2 ± 1.4 mmol/h in group B. Neither in group A nor in group B was the bombesin-stimulated gastric acid response significantly different from pre-treatment values (Fig. 4). However, after subtraction of basal gastric acid responses from bombesin-stimulated gastric acid responses in group A, post-treatment values (4.3 ± 0.9 mmol/h) were significantly ($p < 0.01$) lower than pre-treatment values (8.3 ± 1.5 mmol/h), whereas in group B post-treatment values (7.0 ± 1.4 mmol/h) were not significantly different from pre-treatment values (9.3 ± 2.0 mmol/h) (Fig. 5). In the healthy *H. pylori*-negative volunteers delta gastric acid responses to bombesin (3.8 ± 2.0 mmol/h) were not significantly different from corresponding values after successful eradication of *H. pylori* in the patients of group A (4.3 ± 0.9 mmol/h).

Before therapy the ratio of incremental gastric acid and integrated gastrin response to bombesin in group A (1.6 ± 0.3)

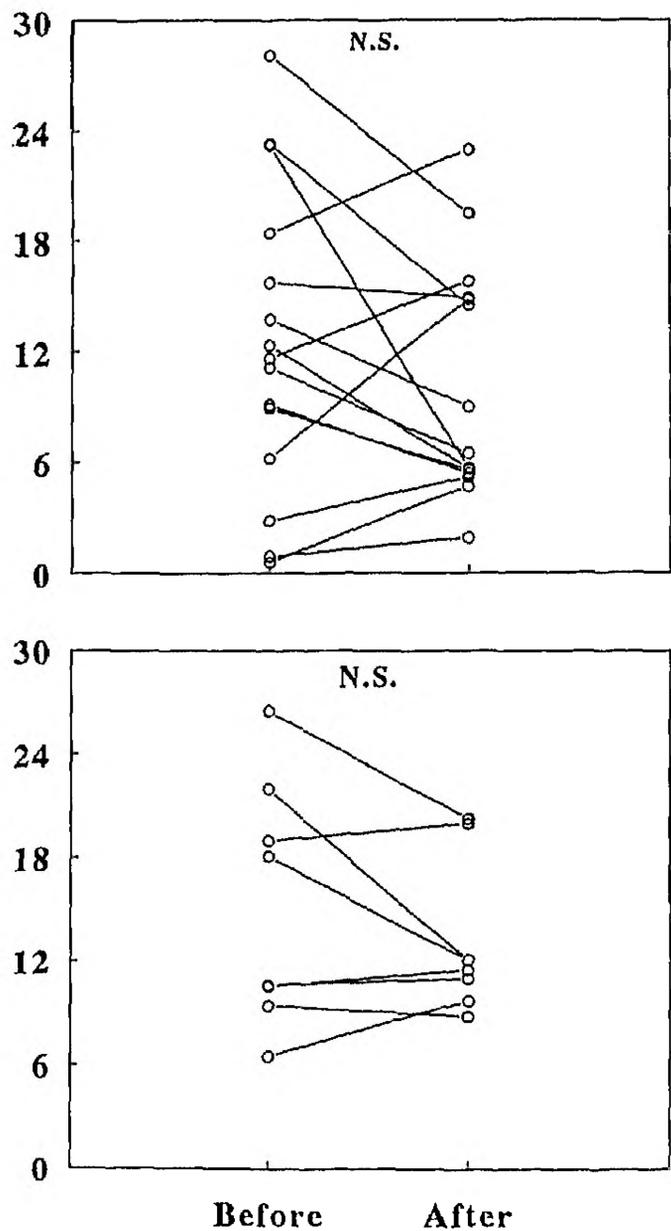


Fig. 4. Bombesin-stimulated gastric acid secretion (mmol/h) before and after therapy in patients in whom *Helicobacter pylori* eradication treatment was successful (upper panel) or in whom eradication of *H. pylori* had failed (lower panel).

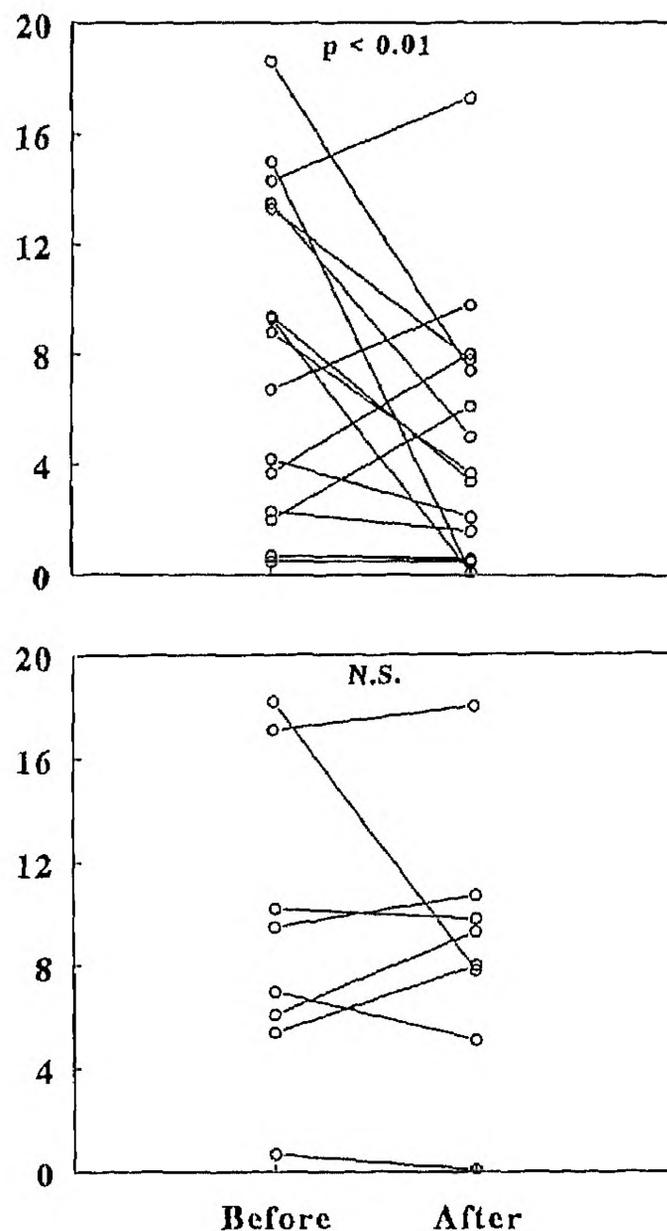


Fig. 5. Incremental bombesin-stimulated gastric acid secretion (mmol/h) before and after therapy in patients in whom *Helicobacter pylori* eradication treatment was successful (upper panel) or in whom eradication of *H. pylori* had failed (lower panel).

was not significantly different from the ratio in group B (1.8 ± 0.4). After therapy this ratio increased markedly by $190 \pm 80\%$ ($p < 0.05$) in the patients of group A but not in those of group B ($20\% \pm 30\%$).

DISCUSSION

This study shows that basal gastric acid output slightly increases after eradication of *H. pylori* in patients with non-ulcer dyspepsia, notwithstanding a distinct decrease of serum gastrin concentrations. These findings were not expected, since gastrin is a powerful stimulus of gastric acid secretion and since previous studies have shown that basal gastric acid secretion was either unaffected or decreased in parallel with basal serum gastrin levels after eradication of *H. pylori* in duodenal ulcer patients (10–14). However, our findings are in line with a recent uncontrolled study showing that basal gastric acid output in *H. pylori*-positive normal subjects is significantly lower than basal gastric acid output in *H. pylori*-negative controls and duodenal ulcer patients (26).

These are several studies indicating that infection with *H. pylori* may decrease gastric acid secretion. It has been shown in vivo that acute infection with *H. pylori* causes hypochlorhydria (27) and that chronic infection is inversely correlated with gastric acid secretion (20, 28), whereas in vitro *H. pylori* also inhibits gastric acid secretion, suggesting that *H. pylori* produces a gastric acid-inhibiting factor (29) or lowers gastric histamine levels (30). In addition, in previous studies no or a negative correlation was found between basal serum gastrin levels and basal gastric acid output (31–33), suggesting that a decrease of basal serum gastrin levels must not inevitably be accompanied by a decrease of basal gastric acid output.

Differences in the effect of eradication of *H. pylori* on basal gastric acid secretion between non-ulcer dyspepsia patients and duodenal ulcer patients may also be explained otherwise, since previous studies have found differences in sensitivity of parietal cells for gastrin between patients with and without duodenal ulcer (14–17) or differences in cholinergic activity (34). Furthermore, a fall in basal acid secretion in duodenal ulcer patients may not necessarily be due to the eradication of *H. pylori*, since Achord (35) has shown that basal acid output decreases after healing of an ulcer by drugs that do not eradicate *H. pylori*, implying that the ulcer itself is associated with increased basal acid secretion. Finally, extension of *H. pylori* infection into the gastric body in patients with non-ulcer dyspepsia, but not in duodenal ulcer disease, may be another possibility for explaining differences in basal gastric acid secretion between these patient groups.

Notwithstanding a higher basal gastric acid output in duodenal ulcer patients when compared to *H. pylori*-positive controls (26), basal gastric acid output varies considerably among *H. pylori*-positive duodenal ulcer patients (20). Previous studies on gastric acid secretion in such patients were mainly performed in individuals with high BAOs

(10, 12). These duodenal ulcer patients may respond differently after eradication of *H. pylori*. Nevertheless, in our series 4 of 15 non-ulcer dyspeptic patients had BAOs exceeding $5 \text{ mmol H}^+/\text{h}$, and 2 of these 4 patients secreted even more than $10 \text{ mmol H}^+/\text{h}$ under basal conditions, but no consistent decrease of BAO was found in these patients after eradication of *H. pylori*. Therefore, high BAOs by themselves are probably not responsible for the difference in responses to successful *H. pylori* eradication therapy by duodenal ulcer patients and *H. pylori*-positive patients with non-ulcer dyspepsia.

Stimulation with bombesin resulted in comparable gastric acid outputs before and 1 month after eradication of *H. pylori*, despite a marked decrease of the serum gastrin response 1 month after eradication of *H. pylori* when compared with before triple therapy. At first glance these data suggest that gastrin release and gastric acid secretion are also independent from each other under stimulated conditions. However, after subtraction of gastrin-independent basal gastric acid secretion, incremental gastric acid secretion in response to bombesin significantly decreased 1 month after successful eradication of *H. pylori* to values comparable to those found in healthy *H. pylori*-negative control subjects. The data therefore suggest that stimulated but not basal gastric acid secretion is regulated by gastrin and that the decrease of gastrin release after successful eradication of *H. pylori* is in fact responsible for the significantly lower stimulated incremental gastric acid output when compared with before triple therapy. In the patients in whom eradication of *H. pylori* was not successful a small but significant decrease of bombesin-stimulated gastrin was also observed. This may indicate that *H. pylori* was suppressed but not eradicated in these patients and that a reduced bacterial load resulted in the observed decrease of gastrin release. It is of interest that the ratio of incremental gastric acid and integrated gastrin response to bombesin increased significantly after eradication of *H. pylori*. This finding is compatible with the hypothesis that eradication of *H. pylori* increases parietal sensitivity to gastrin or increases the number of parietal cells, thereby augmenting the gastric acid response to endogenous gastrin.

In conclusion, the present data demonstrate that in patients with non-ulcer dyspepsia basal gastric acid secretion increases after eradication of *H. pylori* despite a decrease of basal serum gastrin concentrations. Stimulated gastric acid secretion, however, decreases in parallel with gastrin release, suggesting that the decrease of stimulated gastric acid secretion but not basal gastric acid secretion is mediated by gastrin.

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