

The Effect of Pyloromyotomy on Serum and Luminal Gastrin in Infants with Hypertrophic Pyloric Stenosis

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Previous studies of the pathogenesis of congenital hypertrophic pyloric stenosis (CHPS) have implicated immunoreactive gastrin, although no consistent relationship has been demonstrated. In this study we have examined the effect which pyloromyotomy has on serum and luminal gastrin concentration after a mechanical and protein stimulus. Seventeen infants were examined preoperatively, and 1 week after pyloromyotomy. On each occasion, samples of serum and gastric contents were collected from fasting infants. Sixty cubic centimeters of water was placed into the stomach and further samples collected 20 min later. The water was then aspirated and replaced by 60 cc of 10% peptone broth and a third set of samples collected after 20 min. All samples from each patient were analyzed for immunoreactive gastrin in the same assay. Pyloromyotomy did not alter fasting serum gastrin ($119.3 \text{ pg} \pm 11.9$ preop vs 164.7 ± 29.9 postop) nor did it alter the gastrin response to water. Pyloromyotomy decreased the incremental serum gastrin response to peptone broth (66.6 ± 16.9 preop vs 18.9 ± 11.7 postop). Luminal gastrin concentration was not significantly affected by pyloromyotomy. When the pre- and postoperative serum gastrin increments for water and peptone were plotted against the fasting gastrin levels, an inverse relationship was apparent which was statistically significant by regression analysis. Seen in this way, intragastric water and peptone have a dual effect on serum gastrin; a rise if the fasting serum gastrin concentration is low; a fall or lesser rise if the fasting serum gastrin concentration is high. The data suggest that the direction and magnitude of serum gastrin response to intragastric water or peptone is set by the fasting level, and is independent of pyloromyotomy.

Recent efforts to determine the etiology of congenital hypertrophic pyloric stenosis (CHPS) have focused on the possible role of gastrin, first suggested by Dodge in 1970 when he reported pyloric tumors in puppies following injection of adult female dogs with pentagastrin during pregnancy [2]. Since then, studies by several investigators have focused on the differences between serum gastrin in fasting infants with pyloric stenosis and normal fasting infants. These studies have resulted in conflicting data (Table 1). Some investigators have found significant differences between mean serum gastrin levels in fasting infants with CHPS and levels in fasting controls, and concluded that elevated serum gastrin is related to CHPS. Other investigators have reported no sig-

nificant differences, and concluded the opposite. Except for Moazam and her colleagues, no group of investigators has examined the gastrin response to feeding in infants with CHPS. The present study was designed to evaluate the effect of pyloromyotomy on the serum and intraluminal gastrin levels after giving water and a standard protein meal in order to determine how pyloromyotomy alters the gastrin response to feeding and whether this alteration might be a factor in the etiology of the disorder.

MATERIALS AND METHODS

During the 22 months between December 1977 and October 1979, 17 infants with CHPS were evaluated. There were 15 males and 2 females, ranging in age from 3 to

TABLE 1
FASTING SERUM GASTRIN LEVELS IN CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

	Preop	Postop	Normal controls	<i>P</i> -value ^b	
Rogers <i>et al.</i> [6]					
1975					
14 infants	163 ± 97	205 ± 71	193 ± 105	NS	
Spitz and Zail [7]					
1976				Preop	0.0015
18 infants	170 ± 76	204 ± 77	99 ± 23	Postop	0.0015
				Preop vs postop	NS
Moazam and Rodgers <i>et al.</i> [5]					
1978					
11 infants	128 ± ?	105 ± ?	125 ± ?	NS	
Bleicher <i>et al.</i> [1]					
1978					
20 infants	256 ± 111	—	103 ± 40	Preop	0.001
Wesley <i>et al.</i> ^c					
1980				Preop	0.05
17 infants	119 ± 49	165 ± 124	84.6 ± 31.6	Postop	0.02
				Preop vs postop	NS

^a Summary of data reported in five studies of infants with CHPS comparing preop with postop, and normal infants with preop and postop. All values are expressed as pg/ml with SD except Moazam and Rodgers *et al.* where confidence limits were not reported. Normal infants were in the same age range as those with CHPS.

^b Preop vs postop; normals vs pre- and postop.

^c Present reported series.

11 weeks at the time of diagnosis. Body weights ranged from 1.9 to 4.4 kg with an average of 3.6 kg. All infants were rehydrated as necessary prior to the study, and any electrolyte abnormalities were corrected. A nasogastric tube was placed for gastric decompression, and each infant was fasted for 2 to 4 hr prior to the preoperative study. Two milliliters of venous blood and an aliquot of gastric fluid were drawn in the fasting state, 20 min after placement of 60 cc of tap water in the stomach, and again 20 min after placement of 60 cc of a standard protein meal consisting of 10% peptone broth. The stomach was aspirated clear between each 60 cc of fluid instillation. Blood samples were immediately placed on ice, and the serum separated and frozen within 20 min to 1 hr for later gastrin determination. The gastric fluid was immediately boiled to deactivate pepsin and pepsinogen, and frozen for later gastrin measurement. In addition, the pH of each gastric sample

was measured by standard pH electrode. An identical evaluation was performed 1 to 2 weeks postoperatively after the infant was eating a normal diet and gaining weight. Each infant was fasted for 3 to 4 hr prior to the follow-up study.

Serum gastrin levels were also determined in 17 control patients between 3 and 11 weeks of age after a 6 hr fast (14 males and 3 females). These were healthy infants undergoing elective herniorrhaphy or circumcision.

This study protocol was approved by the University of Michigan Human Use Committee and informed consent was obtained from the parents of each infant.

Pre- and postoperative serum and gastric juice samples from each patient were analyzed at the same time for gastrin by radioimmunoassay according to methods previously described [4, 9]. The antiserum used recognizes the biologically active carboxyl terminus of all molecular forms of

TABLE 2
CHPS
MEAN SERUM IMMUNOREACTIVE GASTRIN^a

	Fasting	60 cc Water	Water – fasting	60 cc Peptone	Peptone – fasting
Preop	119.3 ± 11.9	133.0 ± 20.2	17.0 ± 14.3	182.6 ± 21.1	66.6 ± 16.9
Postop	164.7 ± 29.9	145.8 ± 20.8	–18.9 ± 14.1	183.6 ± 26.3	18.9 ± 11.7
<i>P</i> -value	NS*	NS	0.065** NS	NS	0.010**

^a Mean serum gastrin response 20 min after water and peptone instillation expressed as absolute values and as increments (positive or negative change) between water or peptone and fasting levels. Results are expressed as pg/ml ± SE; *n* = 17.

* paired *t* test, two sided.

** paired *t* test, one sided.

gastrin. Measurements were determined in duplicate and the average recorded as the value of gastrin for each specimen. The within assay coefficient of variation was 1.97–6.44% for concentrations of human serum gastrin between 25 and 1000 pg/ml.

Statistical analysis was primarily accomplished using two sample or paired *t* tests. In several analyses of data from the CHPS patients, a repeated measures design with covariate adjustment was utilized [8].

RESULTS

The mean serum gastrin level in fasting infants with CHPS was not changed significantly by pyloromyotomy (Table 2). When compared with 17 normal infants in the same age range, both preoperative and postoperative pyloric infants had significantly higher mean fasting gastrin levels (normal 84.6 ± 7.9 pg/ml; preop pyloric

119.3 ± 11.9, *P* < 0.05; postop pyloric 164.7 ± 29.9, *P* < 0.02). Mean serum gastrin levels measured 20 min after instillation of 60 cc of tap water (distention stimulus) into the stomach of infants with CHPS showed no significant difference from fasting levels, and no significant difference when preoperative and postoperative levels were compared. Mean serum gastrin levels measured 20 min after instillation of 60 cc of 10% peptone broth (distention plus protein meal stimulus) showed no significant difference between preoperative and postoperative levels (Table 2).

When the increments (positive or negative change) between fasting and distention stimulus (water – fasting) or fasting and distention plus protein stimulus (peptone – fasting) were compared, the preoperative water increment showed no significant difference from the postoperative increment. How-

TABLE 3
CHPS
MEAN LUMINAL IMMUNOREACTIVE GASTRIN^a

	Fasting	60 cc Water	Water – fasting	60 cc Peptone	Peptone – fasting
Preop	42.4 ± 15.8	1.8 ± 1.8	–40.5 ± 14.9	99.1 ± 15.6	56.7 ± 20.0
Postop	23.8 ± 8.3	3.5 ± 1.9	–20.4 ± 7.4	89.3 ± 10.2	65.5 ± 13.4
<i>P</i> -value	NS	NS	NS	NS	NS

^a Mean luminal gastrin response 20 min after water and peptone instillation expressed as absolute values and as increments (positive or negative change) between peptone and fasting levels. Results are expressed as pg/ml ± SE; *n* = 11.

TABLE 4
CHPS
pH AND VOLUME RECOVERED^a

	Fasting pH	Water pH	Peptone pH	Volume recovered
Preop	3.2 ± 0.29	3.3 ± 0.23	6.9 ± 0.12	58.6 ± 1.5
Postop	3.8 ± 0.58	3.8 ± 0.27	6.9 ± 0.10	31.6 ± 3.5
P-value	NS	NS	NS	<0.001

^a Mean gastric fluid recovery and pH 20 min after water and peptone instillation. Results are expressed as units ± SE; *n* = 11.

ever, the preoperative peptone increment was reduced postoperatively, and the difference was statistically significant (Table 2).

Pre- and postoperative fasting intraluminal gastrin levels showed no statistically significant difference, nor did the preoperative response to 60 cc of water or 10% peptone broth show any significant difference from the postoperative response, both with respect to actual values or increments (Table 3). Likewise, the preoperative pH of the intraluminal fluid in the fasting pyloric infant showed no statistically significant difference from the postoperative determination; this finding was also true after instillation of water or peptone broth (Table 4). The volume recovered after instillation of either water or peptone was nearly complete preoperatively and about two-thirds complete postoperatively (Table 4). There was no significant effect of this pre- and postoperative volume difference on either the serum or luminal gastrin as analyzed using repeated measures design with covariate adjustment.

When the increment of serum gastrin was plotted against fasting serum gastrin concentration, an inverse relationship was found for both water and peptone broth. Figs. 1 and 2 display these plots and the best fitting regression line for the 34 pre- and postoperative increments as a group. Both regression lines fit well with respective *r* values of 0.766 and 0.307. One point in Fig. 1 was 11 SD higher than the regression line and was judged to be an outlier and was not used in the regression analysis.

After adjusting for preoperative and postoperative effect and individual patients in a repeated measures analysis with a covariate, the regression effect between the increment and fasting level was even stronger in the same direction. This relationship was not statistically different for the preoperative, postoperative, or combined categories with respect to water or peptone.

DISCUSSION

In our patients, serum gastrin in the fasting state is unchanged by pyloromyotomy. This is in agreement with the findings of Rogers *et al.* [6], Spitz and Zail [7], and Moazam *et al.* [5]. When compared to healthy fasting infants, however, our patients had significantly higher fasting serum gastrin levels both pre- and postoperatively. This agrees with the findings of Spitz and Zail [7] and Bleicher *et al.* [1] but contrasts with the findings of Rogers *et al.* [6] and Moazam and co-workers [5] who reported no significant differences between serum gastrin levels in fasting infants with CHPS and age-matched controls. These conflicting results might be explained by technical factors, such as the length of the fasting state as suggested by Spitz and Zail [7] or by the small sample size of the studies coupled with the high variability of the serum gastrin levels. Small sample size and high variability make it difficult to achieve statistical significance, even if there is a true difference. Fasting serum gastrins in adults generally fall within a narrow range of 20–

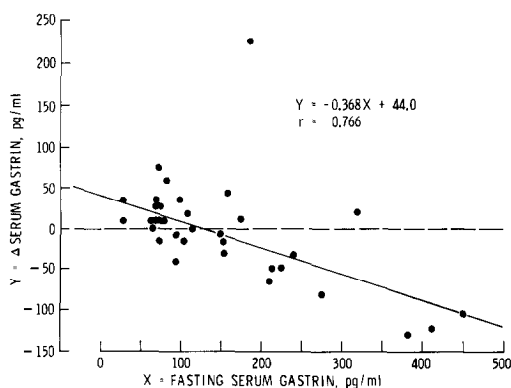


FIG. 1. Plot of the increment (positive or negative change) in serum gastrin after 60 cc water against the fasting serum gastrin level for the combined pre- and postoperative group. The best fitting regression line is displayed.

100 pg/ml, and rarely exceed 200 pg/ml, whereas those in infants vary widely between 20 and 500 pg/ml with 13% of one large group studied exceeding 200 pg/ml [3].

The present study included a control for patient variability by analyzing the *increment* between fasting and postprandial serum and luminal gastrin in each patient with CHPS, both pre- and postoperatively. This protocol differs from the study of Moazam *et al.* [5] in that we first instilled 60 cc of water to look at the effect of distention alone, and then 60 cc of peptone broth to measure the effect of distention plus a protein stimulus. Moazam and her colleagues fed 11 infants with CHPS a standard protein meal (Sustagen) preoperatively and repeated the study 2 to 10 weeks postoperatively. They reported no significant differences in the mean serum gastrin level between the preoperative and postoperative groups at 15, 30, and 45 min following the standard meal.

Upon examining the water-distention effect on serum gastrin (Table 2), there was an apparent increase in gastrin over fasting levels preoperatively and a decrease postoperatively. However, these incremental differences were not statistically significant when tested in a repeated measures

analysis. Therefore, distention alone with 60 cc of water appeared to have no effect on serum gastrin when compared in preoperative and postoperative groups.

Instillation of peptone broth resulted in a significantly positive gastrin increment preoperatively which was still positive but decreased after pyloromyotomy. The increased gastrin response to peptone instillation preoperatively can be explained by protein stimulation of gastrin release by the obstructed stomach. The reduced rise in serum gastrin after peptone postoperatively can be explained by the simple passage of gastric fluid through the postoperative open pylorus and the resultant diminished intensity and duration of contact of the stimulus with the gastric and duodenal mucosa. Alternatively, this finding is compatible with the activation of a duodenal inhibitory mechanism by resumption of gastric emptying.

When the serum gastrin response to water and peptone instillation was viewed as an increment with respect to fasting levels, a different pattern emerged. Eight out of nine patients with high fasting serum gastrin levels (greater than 200 pg/ml) had a lower gastrin response to intragastric water, and thirteen out of sixteen patients with a low fasting serum gastrin (less than 100 pg/ml) had a higher response. This pattern ap-

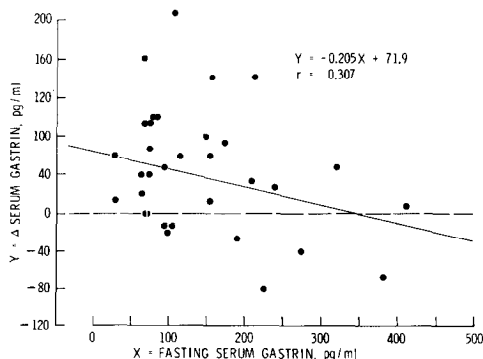


FIG. 2. Plot of the increment (positive or negative change) in serum gastrin after 60 cc peptone against the fasting serum gastrin level for the combined pre- and postoperative group. The best fitting regression line is displayed.

peared to be independent of the pyloromyotomy. When this observation was tested by a regression analysis, an inverse relationship was established between the fasting gastrin level and the water or peptone increment response according to the equation in Figs. 1 and 2; the r -value being 0.766 and 0.307, respectively. After adjustment for pre- and postoperative effect and patient variation, the regression correlation between the increment and fasting level was even stronger.

From our data, therefore, it appears that intragastric water has a dual effect on serum gastrin: a rise if the fasting serum gastrin concentration is low; and a fall if the fasting serum gastrin concentration is high. Intragastric peptone generally causes a rise in serum gastrin, but less of a rise when the serum gastrin is high. This effect is independent of the pyloromyotomy. The latter finding makes it less likely that activation of a duodenal inhibitory mechanism is involved, but leaves open the possibility of an inhibitory mechanism at the gastric level.

Previous work by Fiddian-Green *et al.* demonstrated that intraluminal gastrin may influence gastric acid production [4]. In the present study, intraluminal gastrin levels showed no statistically significant difference when fasting preoperative levels were compared to fasting postoperative levels, or when the preoperative response to 60 cc of water or peptone broth was compared to the postoperative response (Table 4). The large number of values at the lower sensitivity limits of the gastrin immunoassay make any conclusion from statistical analysis tentative.

Although pH can have an important effect on gastrin production, it does not appear to elicit a response in this particular set of experimental circumstances since no significant difference was found in pH pre- and postoperatively with respect to fasting, in-

stillation of water, or instillation of peptone broth (Table 4).

It appears, therefore, that the serum gastrin response to intragastric instillation of water or peptone is set by the fasting level and is independent of pyloromyotomy. The relative contribution of gastric and duodenal gastrin mechanisms and the role of pyloromyotomy remain unclear.

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