PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 153, 379-382 (1976)

The Effect of Truncal Vagotomy on Lower Esophageal Sphincter Pressure and Response to Cholinergic Stimulation[1] (39550)

RICHARD H. HIGGS AND DONALD O. CASTELL

Gastroenterology Division, Internal Medicine Service, and Clinical Investigation Service, Naval Regional Medical Center, Philadelphia, Pennsylvania 19145

In man, truncal vagotomy is commonly performed for treatment of peptic ulcer disease. Previous observations suggest that vagotomy in man does not alter resting lower esophageal sphincter (LES) pressure (1-3). The effect of truncal vagotomy upon the cholinergic response of the LES has not been determined. Cholinergic stimulation with bethanechol has been shown to increase sphincter pressure both in control subjects and reflux patients (4). Further, cholinergic stimulation with bethanechol has therapeutic benefit in the treatment of gastroesophageal reflux (5). Thus, any effect of vagotomy on the LES response to cholinergic stimulation with bethanechol would have both physiologic and therapeutic implications.

The present studies were performed to determine the effect of vagotomy on the cholinergic response of the LES in man and an animal model.

Methods. Human studies. Patients studied. The patient groups included 7 male patients (mean age 44 years) having had prior truncal vagotomy with pyloroplasty (V&P), 10 male patients (mean age 41 years) having had prior vagotomy and antrectomy (V&A), and 4 male patients (mean age 46 years) having had prior antrectomy (A). All antrectomy patients had Billroth II procedures. All three groups consisted of patients in whom surgery had been required for complicated peptic ulcer disease. Ten healthy male volunteers (mean age 34 years) with no prior surgery formed the control group. All vagotomies were intra-abdominal in approach with sectioning of the vagal trunks as high as possible through the hiatus. The presence or absence of a complete vagotomy in V&P and V&A patients was confirmed by the appropriate acid response to insulin-induced (0.2 unit/kg iv) hypoglycemia, as previously described (6).

Intraluminal pressure measurement. Three water-filled polyvinyl tubes, 1.4-mm i.d., transmitted intraluminal pressure to external transducers (Statham Series p 23), and pressure was recorded on a multichannel direct-writing recorder (Hewlett-Packard 7700 Series). Intraluminal pressures were recorded through three lateral openings 1.3 mm in diameter placed 5 cm apart. The tube was passed into the stomach and slowly withdrawn until it was positioned with the middle aperture recording maximal LES pressure just below the respiratory inversion point. This position was verified at least once every 10 min throughout the entire study period. The system was infused with distilled water at a constant rate of 0.42 ml/min.

Sphincter pressure was recorded in millimeters of mercury with mean resting intragastric pressure used as zero reference. Average pressure was determined from the recording for each minute of the test. The basal pressure represented the mean value for 15 such determinations. Sphincter response was determined from the mean pressure level of the five highest consecutive 1-min values after stimulation. Student's *t* test was utilized for evaluating statistical significance between mean pressure levels.

Bethanechol stimulation. The effect of graded doses of bethanechol (0.01, 0.02, 0.04, and 0.08 mg/kg sc) was studied in all subjects. Significant side effects prohibited use of larger doses. On separate days after a 15-min basal period, a single dose was given randomly in a blinded fashion as to dose, and LES pressure was monitored for an additional 45 min.

[1] Supported by the Bureau of Medicine and Surgery, Clinical Investigation Program No. 5-05-530R.

Send reprint requests and correspondence to Dr. Donald O. Castell, National Naval Medical Center, Bethesda, Maryland 20014.

Cat studies. Because significant side effects prevented us from using larger doses of bethanechol in humans, we also used an experimental animal to obtain a complete dose-reponse curve. Five adult male cats, averaging 4 kg in body weight, received the following doses of bethanechol iv before and 8 weeks after bilateral transabdominal truncal vagotomy: 3.0, 6.0, 12.0, 25.0, and 50.0 μg/kg. Thirty minutes after being anesthesized with ketamine hydrochloride (20 mg/kg im), LES pressure was measured by a series of slow "pull-throughs" of the recording orifice from stomach to esophagus at 1-min intervals. Basal pressure represented the mean of the highest two pressures. After iv administration of bethanechol, "pull-throughs" were done every minute for 20 min and the peak response represented the two highest consecutive values. All manometric tracings were coded and interpreted blindly following completion of all studies. Student's *t* test was again utilized for evaluating statistical significance between mean pressure levels.

Results. Human studies. Basal LES pressure. Basal LES pressure for controls and V&P patients is shown in Fig. 1A. Mean basal pressure for controls (13.0 ± 1.5 mm Hg, ± SE) was not significantly different from that of V&P patients (11.6 ± 1.6 mm Hg). In addition, no significant difference was noted between mean basal pressure of V&A patients (12.6 ± 1.6 mm Hg) and A patients (12.5 ± 2.3 mm Hg), as shown in Fig. 1B.

Bethanechol. LES pressure changes following sc bethanechol in both controls and V&P patients are shown in Fig. 2A. The mean increase in pressure for V&P patients was significantly greater than that of the controls at the 0.02, 0.04, and 0.08-mg/kg dose ($P < 0.01$, 0.05, and 0.01, respectively). The maximal mean LES pressure change was 42.0 ± 2.2 mm Hg for V&P patients and 27.3 ± 2.3 mm Hg for controls. Figure 2B illustrates the pressure changes in V&A and A patients following sc bethanechol. At all four doses the response of the V&A group was significantly ($P < 0.02$) greater than that of A patients. The maximal mean LES pressure change was 34.7 ± 2.3 mm Hg for V&A patients and 12.0 ± 2.0 mm Hg for A patients.

Cat studies. Basal pressure. As shown in Fig. 3, the mean LES basal pressure in the cats before vagotomy (32.5 ± 4.7 mm Hg) was not significantly different from that after vagotomy (37.2 ± 3.6 mm Hg).

Bethanechol. The LES response to graded iv doses of bethanechol for the five cats before and after vagotomy is shown in Fig. 4. The mean postvagotomy responses to 3.0 (13.4 ± 1.5 mm Hg) and 6.0 μg/kg (34.0 ± 5.0 mm Hg) were significantly greater ($P < 0.05$) than those found prior to vagotomy (7.5 ± 3.5 and 18.3 ± 3.8 mm Hg). However, the maximal mean LES responses before and after vagotomy were not statistically different, although occurring at a different dose. Prior to vagotomy, the mean maximal response (30.2 ± 2.9 mm Hg) occurred with the 25-μg/kg dose. After vagotomy, the mean maximal response of 34.0 ±

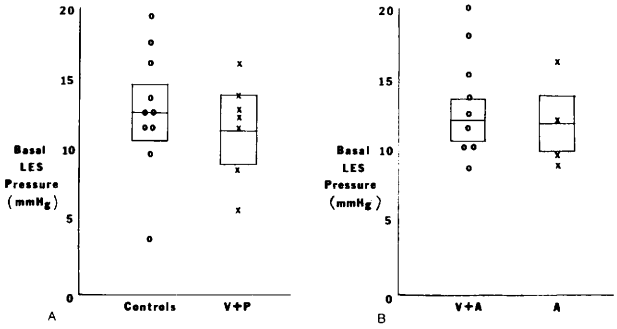

FIG. 1. Basal lower esophageal sphincter (LES) pressure for controls and patients having vagotomy and pyloroplasty (V&P) on the left (A) and for patients with vagotomy and antrectomy (V&A) and patients with antrectomy (A) on the right (B). Each point represents the mean of at least nine values for each individual. Vertical boxes are ± SE.

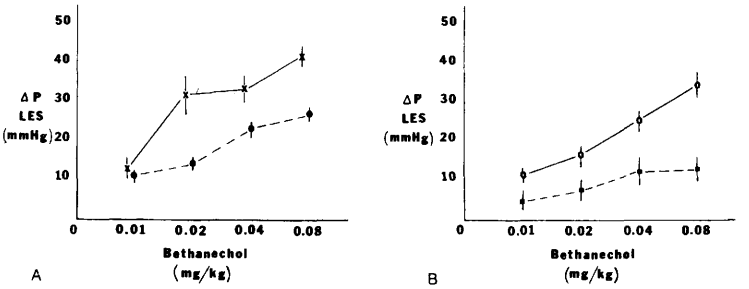

FIG. 2. Dose-response curves for change in lower esophageal sphincter (LES) pressure (ΔP) against log dose of sc bethanechol for controls (closed circles) and patients having vagotomy and pyloroplasty (x's) on the left (A) and for patients with vagotomy and antrectomy (open circles) and patients with antrectomy (squares) on the right (B). Points indicate mean values and vertical lines ± SE.

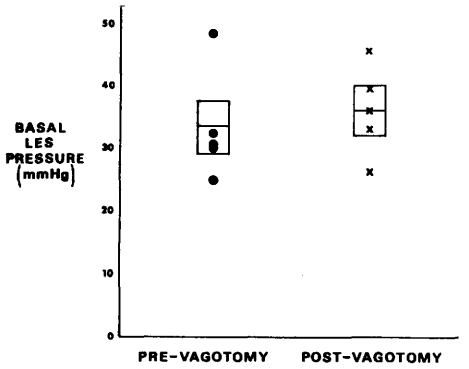

FIG. 3. Basal lower esophageal sphincter (LES) pressure for cats prevagotomy and postvagotomy. Each point represents the mean of at least five values for each cat before and after vagotomy. Vertical boxes are ± SE.

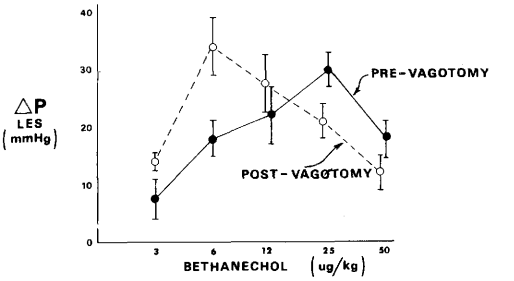

FIG. 4. Dose-response curves for change in lower esophageal sphincter (LES) pressure (ΔP) against log dose of iv bethanechol for cats prevagotomy and postvagotomy. Points indicate mean value and vertical lines ± SE.

5.0 mm Hg occurred with the 6.0-μg/kg dose.

Discussion. Our studies show that the LES pressure response to bethanechol in humans with truncal vagotomy (V&P and V&A) is significantly increased when compared to the response of those without vagotomy (controls and A). These results indicate that vagotomy produces an increased sensitivity of the LES to cholinergic stimulation. This increased sensitivity to cholinergic stimulation following truncal vagotomy was confirmed in the cat.

Although it is of interest to speculate concerning the cause of the increased sensitivity, the cause of this increased responsiveness of the sphincter to cholinergic stimulation is not readily apparent. Classically parasympathetic fibers were thought to be carried in the vagus (7). Thus, vagotomy might produce denervation of cholinergic pathways resulting in the increased sensitivity to cholinergic stimulation, as has been postulated to occur in achalasia (8-10). Studies with cervical vagotomy in the opossum, however, have failed to demonstrate that any stimulatory efferent cholinergic pathways were carried in the vagal nerves to the sphincter (11). Thus, interruption of parasympathetic pathways per se in the vagus is not a likely cause of this enhanced responsiveness of the LES to bethanechol after vagotomy.

Certain types of denervation supersensitivity have been postulated; however, to be nonspecific, that is, when innervation of an end organ is interrupted, the end organ may demonstrate increased responsiveness to any agent which ordinarily effects a response (12). Therefore, the increased response to bethanechol after vagotomy does not necessarily indicate that a cholinergic pathway per se has been interrupted. Thus, one might speculate that truncal vagotomy may interrupt noncholinergic neural path-

ways to the sphincter which have been shown to be carried in the vagus (13, 14), an interruption of which, because of nonspecificity of denervation supersensitivity, might produce the increased response to bethanechol.

The absence of a significant difference in basal LES pressure between patients with and without vagotomy supports previous studies in man showing that truncal vagotomy does not alter resting sphincter tone (1–3), as well as studies with cervical vagotomy in the opossum (15). This observation is of interest in light of the simultaneous supersensitive response of the LES to cholinergic stimulation. If cholinergic mechanisms or agents which act via cholinergic mechanisms do affect basal LES pressure such as has been postulated in achalasia, it seems reasonable to expect vagotomy to have increased resting sphincter tone. Therefore, on the basis of our studies in man and cats, it seems unlikely that cholinergic mechanisms have any major effect in maintaining basal LES pressure.

Summary. The effect of truncal vagotomy on the lower esophageal sphincter pressure and the response to cholinergic stimulation have been studied in humans as well as an animal model, the cat. Vagotomy was found to result in enhanced responsiveness to cholinergic stimulation. However, basal sphincter pressure was unchanged. These observations suggest that cholinergic mechanisms do not have a major effect in maintaining basal LES tone.

1. Crispin, J. S., McIver, D. K., and Lind, J. F., Canad. J. Surg. **10,** 299 (1967).
2. Blackman, A. H., Rakatansky, H., Nasrullah, M., and Thayer, W. R., Arch Surg. **102,** 6 (1971).
3. Mazur, J. M., Skinner, D. B., Jones, E. L., and Zuidema, G. D., Surgery **73,** 818 (1973).
4. Roling, G. T., Farrell, R. L., and Castell, D. O., Amer. J. Physiol. **222,** 967 (1972).
5. Farrell, R. L., Roling, G. T., and Castell, D. O., Ann. Int. Med. **80,** 573 (1974).
6. Castell, D. O., Gastroenterology **61,** 10 (1971).
7. Goodman, L. S., and Gilman, A., *in* "The Pharmacological Basis of Therapeutics," p. 464. MacMillian Company, New York (1965).
8. Cohen, B., and Guilrud, M., Gastroenterology **60,** 769 (1971).
9. Cohen, S. W., Lipshutz, W., and Hughes, W., J. Clin. Invest. **50,** 1241 (1971).
10. Cohen, S., Fisher, R., and Tuch, A., Gut **13,** 556 (1972).
11. Rattan, S., and Goyal, R., J. Clin. Invest. **54,** 899 (1974).
12. Fleming, W. W., Phillips, J. J., and Westfall, D. P., Reviews of Physiology **68,** 55 (1973).
13. Tuch, A., and Cohen, S., J. Clin. Invest. **52,** 14 (1973).
14. Mitchell, A. G., Brit. J. Surg. **26,** 333 (1938).
15. Christensen, J., Freeman, B. W., and Miller, J. K., Gastroenterology **64,** 1119 (1973).

Received February 17, 1976. P.S.E.B.M. 1976, Vol. 153.