

Vagus nerve integrity in patients who underwent laparoscopic esophagectomy for the treatment of megaesophagus

Integridade Vagal em Pacientes Submetidos à Esofagectomia Laparoscópica no Tratamento do Megaesôfago

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ABSTRACT

Introduction: During a subtotal esophagectomy and esophagogastroplasty for the treatment of grade IV megaesophagus, partial or total damage to the vagus nerve can occur. Vagal excitation observed in normal controls is altered. The measurement of plasma pancreatic polypeptide (PP), whose secretion is induced by hypoglycemia, is an indicator of vagal integrity. **Methods:** Twenty-two patients who underwent laparoscopic transhiatal subtotal esophagectomy were divided into groups: A) 11 patients with vagal preservation, and B) 11 patients without preservation of the vagus nerve. The following procedure was performed before and after surgery in group A and during the late postoperative period in group B: a blood sample was collected, regular human insulin was administered intravenously, and collection of a new blood sample after 45 and 90 minutes. The serum PP measured in the six specimens of each subject. **Results:** In group A, mean PP levels were higher during the postoperative period before stimulation when compared to the preoperative period. A small variation in preoperative PP levels was observed in this group 45 and 90 min after the stimulus, probably because of the high baseline value. After surgery, PP levels were markedly lower in vagotomized patients before stimulation when compared to the group with vagal preservation. Comparison of mean postoperative PP levels 45 min after stimulation showed higher concentrations in the group with vagal preservation compared to vagotomized patients, suggesting anatomical and functional preservation of the vagus nerve. **Discussion:** Regarding treatment of advanced idiopathic megaesophagus, preservation of vagus nerve integrity seems to be important for the maintenance of gastric emptying, since parasympathetic innervation of the stomach is preserved in these cases. **Conclusion:** Anatomical preservation maintains the function of the vagus nerve evaluated based on PP levels after laparoscopic subtotal esophagectomy for the treatment of advanced megaesophagus.

Key words: Esophagectomy. Pancreatic Polypeptide. Vagus Nerve.

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INTRODUCTION

In the chronic phase of Chagas disease, 6% to 7% of patients develop megaesophagus ou megacolon, represented by muscle hypertrophy and dilation of the esophagus and/or colon, due to the destruction of the myoenteric and submucosal plexuses.¹¹ Megaesophagus is manifested in advanced phases of the disease and is classified into types I to IV.

Classically the treatment of achalasia types I, II and III, is Heller's modified cardiomyotomy associated with an anterolateral partial antireflux valve. The treatment of type IV megaesophagus is esophagectomy with esophagogastroplasty.^{4,5,13} During surgery, we consider the possibility of partial or total severing of the vagus nerve, with consequent delay in gastric emptying, reduction of pancreatic secretions and gastric acid secretion. Truncal

vagotomy completely denervates the stomach and pylorus. Thus, the electrical activity of the distal stomach is disorganized for a period of days or weeks after total gastric vagotomy.^{9,12,17,20,9} The vagal excitation induced by the hypoglycemia induced with the administration of insulin observed in healthy controls is abolished after gastric vagotomy.^{9,20}

Measurement of pancreatic polypeptide (PP) affords a reliable way of monitoring the integrity of the vagus nerve, without the need for intragastric monitoring. The main regulatory mechanism of nerve activity is the cholinergic vagal stimulation of the gastric antrum.^{6,8}

Pancreatic polypeptide release is a marker of vagal efferent activity that plays a role in glucose homeostasis. Stimulation of the secretion of PP by hypoglycemia and its inhibition by hyperglycemia are mediated as well through an efferent vagal mechanism. In the basal state, this secretion is under oscillating cholinergic tone.

Pancreatic polypeptide release has been shown to be biphasic.^{1,7} In the first 30 minutes after a meal, its release appears to be mediated exclusively by the vagus nerves, as it is abolished by truncal vagotomy^{1,15} and is increased in response to insulin-induced hypoglycemia^{1,16} and sham meals. The second, longer-lasting phase persists for several hours after meals and is maintained after vagotomy.^{18,19}

The aim of this study was to evaluate the functional integrity of the vagus nerve through the measurement of pancreatic polypeptide, whose secretion is induced by hypoglycemia, in the periods before and after laparoscopic subtotal esophagectomy for the treatment of Chagasic or idiopathic megaesophagus.

METHODS

We evaluated 22 individuals with advanced megaesophagus who underwent laparoscopic transhiatal esophagectomy and esophagogastric reconstruction at the cervical level. Fifteen patients (68.2%) were male and seven (31.8%) were female. Mean age was 53 years. There were 14 patients with Chagasic megaesophagus (63.6%) and eight patients with idiopathic achalasia (36.4%). All the patients evaluated postoperatively were asymptomatic and in good physical condition. Patients with Chagasic megaesophagus had at least two serological tests for *T. cruzi* and an histopathologic diagnosis characteristic of the disease. (Figure 1 - Chagas megaesophagus).

Patients classified as idiopathic did not have a positive serologic reaction to *T. Cruzi*, but the histopathology diagnosis confirmed idiopathic megaesophagus. (Figure 2)

In all cases the barium radiograph of the esophagus showed an advanced form of megaesophagus. Upper endoscopy, performed in all patients as mechanical preparation of the esophagus, did not detect esophageal neoplasia in any of the patients included in this study. In all cases electromanometry detected synchronous contraction waves of the esophagus body with low amplitude (<20 mmHg). Scintigraphy of the stomach and duodenum of Chagas cases preoperatively detected, in all patients, decreased gastric emptying of solids.

Patients were divided into two groups according to the surgical technique used in esophagectomy: the first group consisted of 11 patients with vagus nerve preservation and the second

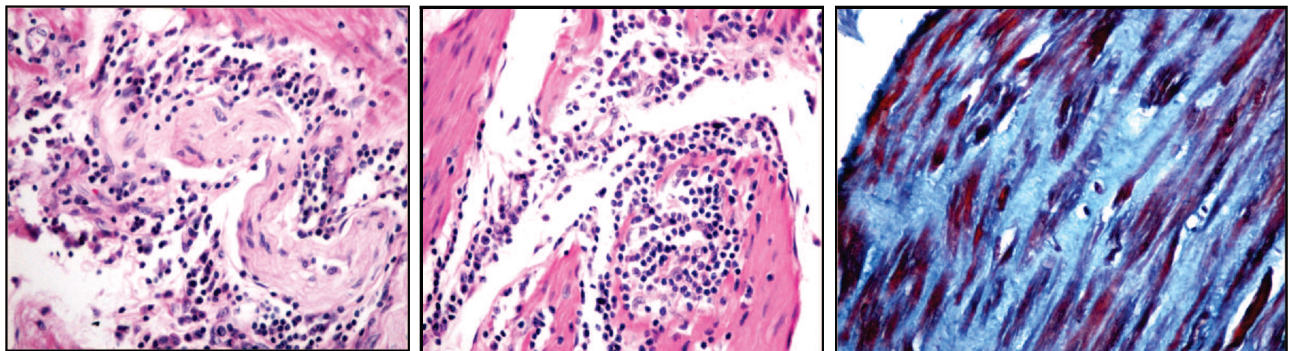


Figure 1 – The photomicrographs above show the hypertrophic muscular layer of the esophagus with gangliosis, myositis and hypoganglionose, which characterizes, in of the pathological terms, the Chagas megaesophagus.

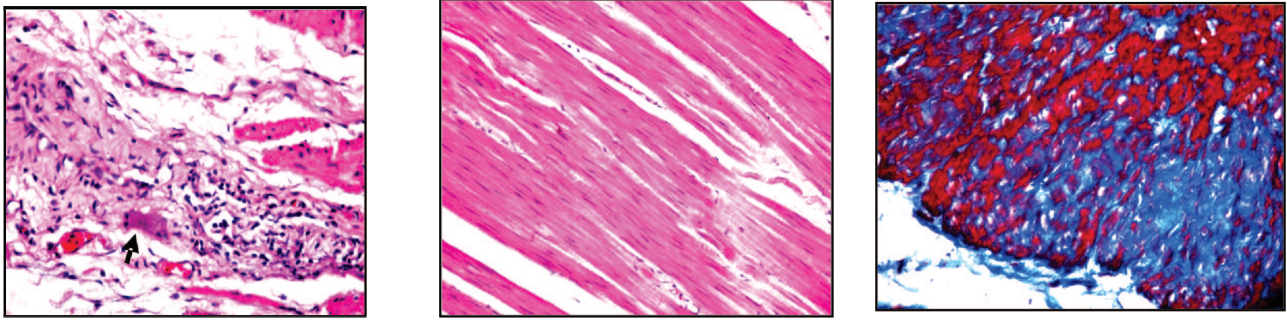


Figure 2 - Photomicrographs of cases of idiopathic achalasia, characterized by the absence of gangliosis, myositis and hypoganglionosis.

consisted of 11 patients without preservation of the vagus nerve.

In the vagal preservation group, the procedures to measure PP was performed in the preoperative period and again at least 3 months after surgery. Samples were collected from 10 ml of venous blood from the upper limb. Next, regular human insulin at a dose of 0.2 U/kg body weight, was administered intravenously in order to induce hypoglycemia. After 45 and 90 minutes, new blood samples were collected. Throughout the procedure, the patient remained in the supine position, with monitoring of heart rate, blood pressure and pulse oximetry. The material collected for each patient was centrifuged at 4°C, fractionated into plasma and cellular portions. The serum obtained was stored and maintained at an average temperature of -70° C for later assaying at one time. Thus six enzyme immunoassay (ELISA) tests to quantify PP were performed for each patient. The same process was carried out with the other group which consisting of the vagotomized patients, but the procedure took place only in the late post-operative period. The laboratory assays of pancreatic polypeptide were performed by UFTM's Department of Biochemistry.

Regarding statistical analysis, patients were grouped according to whether they underwent vagotomy or had preservation of the vagus nerve. The data exhibited a non-normal distribution and thus were analyzed using nonparametric methods. The Mann Whitney test was used for analyses between patients and control subjects. For analysis of variables comparing three or more groups, we applied the Kruskal Wallis test. Pairwise comparisons of differences indicated by the Kruskal Wallis test were analyzed using Dunn's post hoc test. The statistical significance of the Mann Whitney and Kruskal Wallis teste was determined using SigmaStat applications at a p-value of < 0.05 and the Dunn's test $Q > 2.5$.

RESULTS

During laparoscopic subtotal esophagectomy with esophagogastroplasty for the treatment of benign disorders, the dissection of the thoracic and abdominal esophagus is performed close to the muscle layer to prevent injuries to the pleural and adjacent organs or sectioning of the vagal trunks.

Esophagectomy with preservation of the vagal trunks has been employed in the treatment of Chagasic megaesophagus,^{4,5} although with this condition there is denervation of the entire parasympathetic autonomic nervous system (digestive tract myoenteric and submucosal plexuses). It is known that the chronically denervated stomach develops intrinsic mechanisms that maintain motility and emptying. In patients with idiopathic megaesophagus who undergo vagotomy, there is impairment of gastric emptying during the first months after surgery.

Within the group in which the vagal nerve was preserved, we compared the mean baseline pancreatic polypeptide (PP) values with values of specimens obtained 45 and 90 minutes after the preoperative stimulus. The mean baseline value was 263.95. An impressive increase in the mean PP 45 minutes after the stimulus (392.4) was noted. After 90 minutes, the mean value was 316.28 (Figure 3), probably due to the initially elevated baseline. A statistical analysis of these means determined that differences were not statistically significant.

The mean postoperative baseline value in the group with vagal preservation was 231.82; 45 minutes after the stimulus the mean value was 249.82. A statistical comparison of these values was not significant, which probably denotes the functional preservation of vagus nerve.

In the group with vagal preservation, the mean preoperative value before the stimulus (263.95)

was higher than the postoperative mean value in the same group also before the stimulus (231.82). The same was observed when analyzing the mean of the values obtained 45 minutes after the stimulus preoperatively (392.94) and postoperatively (249.82). The differences among these values were not statistically significant.

In the vagotomized group, the mean of the values obtained before the stimulus was 150.14 and 45 minutes after the stimulus (111.01); the difference did not attain statistical significance.

The mean of the values obtained postoperatively before the stimulus in the group with vagal nerve preservation (231.82) was notably higher than the mean in the group that had undergone vagotomy (150.14); this difference was statistically significant ($p = 0.008$).

It was noted that the mean of the values obtained postoperatively after 45 minutes of the stimulus in the group with vagal preservation (249.82) was significantly higher than the mean of the values after 45 minutes of the stimulus in the vagotomized group (111.01); this difference was significantly significant ($p = 0.006$). These data suggest the functional preservation of the vagus nerve.

DISCUSSION

There was no statistically significant difference between the mean of the values before and after the stimulus, both pre- and post-operatively, in the group with vagal preservation. Based on these data, it can be inferred that the anatomic presence of the vagus nerves was effective in the functional preservation of the same nerves.

Findings similar to the results we present were reported by BANKI *et al*, 2002; they showed baseline values for patients with vagal preservation higher than those found in the group without vagal preservation, before the stimulus.² These authors also reported increases in serum PP 30 minutes after a food stimulus, used in patients who had undergone vagal-sparing esophagectomy. This increase was considered similar to normal controls and was statistically higher than in vagotomized patients, suggesting functional preservation of the vagus nerve. There was no elevation of PP in patients who had undergone esophagectomy with vagotomy.

Koop H. *et al* (1979) noted that three months after truncal vagotomy there was slight increase in

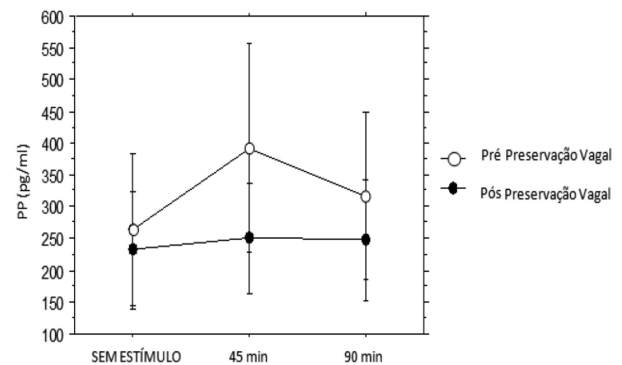


Figure 3 - PP serum levels in patients who underwent esophagectomy with vagal nerve preservation before and 45 and 90 minutes after the stimulation in the pre-and postoperative periods.

postprandial levels of PP after the stimulus, and that five years after truncal vagotomy the stimulation response had returned to normal values. The authors concluded that the measurement of serum PP levels is not a good marker for studying effectiveness of vagotomias in the long term.¹⁰ Insulin-induced hypoglycemia in humans can be blocked by truncal vagotomy, suggesting that vagal mechanisms are important in the release of PP.

Camilleri *et al* observed suppression of the increase of PP after the stimulus in patients after 12 weeks of intermittent vagal blockade employing VBLOC therapy.³

In earlier studies esophagectomies were performed without concern for the preservation of the vagus nerve and without any type of gastric drainage; nevertheless there was no reported impairment – in the medium term – in gastric emptying.^{4,5,14}

In the treatment of advanced idiopathic achalasia, it is possible that the preservation of the vagus nerve has – at least during the first few months after surgery – major importance in maintaining gastric emptying, because in these cases the parasympathetic innervation of the stomach is preserved, which can be inferred after analysis and comparison of the peak release of PP 45 minutes after the stimulus between groups of esophagectomized patients with and without preservation of the vagus nerve (Figure 4).

Despite the small series (in the present study) and the limited number of studies that address the functional evaluation of the vagus nerve using the release of pancreatic polypeptide, in patients who have undergone laparoscopic subtotal esophagectomy with

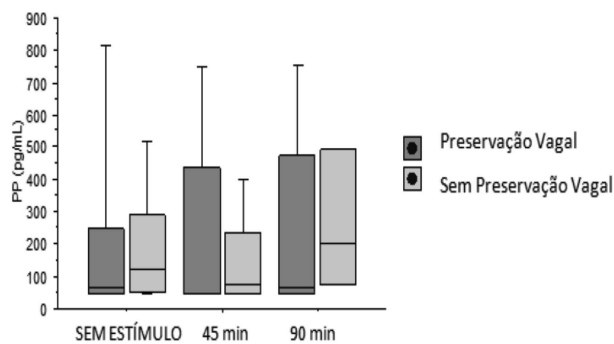


Figure 4 - PP serum levels of patients who underwent esophagectomy with and without vagal nerve preservation; samples before the stimulus and 45 and 90 minutes after the stimulus. Data are expressed in pg/ml. The horizontal line represents the median. The bar represents the range between the 25% and 75% percentiles. The vertical line represents the range between the 10% and 90% percentiles. There was no statistical difference between the groups (Mann-Whitney test).

esophagogastroplasty, the results suggest that there is functional preservation of the vagus nerves. Still, further studies should be conducted to evaluate and corroborate these findings.

CONCLUSION

Based on this material, we can infer that anatomical preservation of the vagus nerve maintains vagal nerve function, as assessed by pancreatic polypeptide levels, after esophagectomy for the treatment of advanced megaesophagus.

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RESUMO

Introdução: Durante a esofagectomia subtotal no tratamento do megaesôfago avançado considera-se possibilidade de lesão vagal, com alteração da secreção do Polipeptídeo Pancreático (PP). A dosagem plasmática do PP, cuja secreção é induzida por hipoglicemia, traduz a integridade nervosa. **Métodos:** Avaliaram-se 22 indivíduos submetidos à esofagectomia subtotal transhiatal laparoscópica: (A) 11 pacientes com preservação vagal e (B) 11 pacientes sem preservação. O procedimento foi realizado no pré e pós-operatório da cirurgia em (A) e no pós-operatório tardio em (B): coletou-se amostra de sangue, administrou-se Insulina Regular Humana e, após 45 e 90 minutos, novas amostras foram coletadas. O material foi submetido à dosagem do PP. **Resultados:** Em A, os valores antes do estímulo, no pós-operatório, foram superiores aos do pré-operatório. No pré-operatório, houve pequena variação dos valores após 45 minutos e 90 minutos do estímulo, provavelmente pelo elevado valor basal apresentado inicialmente. Notaram-se valores de PP antes do estímulo no pós-operatório dos pacientes vagotomizados expressivamente menores do que no grupo com preservação vagal antes do estímulo no pós-operatório. A comparação dos valores do PP após 45 minutos do estímulo no pós-operatório entre grupo vagotomizado (B) e com preservação vagal detectou concentrações maiores no grupo com preservação, sugerindo preservação anatômica e funcional dos nervos vagos. **Discussão:** No tratamento do megaesôfago avançado, a preservação vagal pode ter importância na manutenção do esvaziamento gástrico, pois, nesses casos, o estômago tem inervação parassimpática preservada. **Conclusão:** A preservação anatômica vagal mantém a função dos nervos vagos, avaliada pelos níveis de PP, após esofagectomia subtotal laparoscópica no tratamento do megaesôfago avançado.

Palavras chave: Polipeptídeo Pancreático. Esofagectomia. Nervo Vago.

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