Motility of the Canine Pyloric Ring Following a Pylorus-Preserving Pancreatoduodenectomy

Kazuhiro TOYOTA, Masazumi OKAJIMA, Yasutomo OJIMA, Toshimasa ASAHARA and Kiyohiko DOHI

Second Department of Surgery, Hiroshima University School of Medicine, Hiroshima 734-0037, Japan

Abstract

Recently, function-preserving operations have become popular, and pylorus-preserving pancreatoduodenectomy (PPPD) is frequently performed for diseases of the head of the pancreas. However, there are only a few basic studies on the pyloric function after PPPD. Using strain gauge force transducers (SGTs), we studied the pyloric motility of normal and PPPD dogs. We prepared three normal and three PPPD dogs in which the SGTs were implanted onto the antrum and pyloric ring, etc. In conscious dogs, the spontaneous gastrointestinal motility was recorded, and the plasma motilin concentration was measured during the interdigestive state. Following the administration of exogenous Leu13-motilin, the motility was again recorded. The relaxation and opening of the pyloric ring was observed synchronously with intense contractions of the antrum during the phase III of normal dogs. Phase III-like motility was recorded in the PPPD dogs, which was not a typical periodic motility. The plasma motilin concentration of one PPPD dog could be measured, and the motilin levels during the phase III-like motility were higher than during phase I. The phase III-like motility was induced by Leu13-motilin in both normal and PPPD dogs. The phase III-like motility recorded in the PPPD dogs was not a typical periodic one, and this aberrant motility was considered to be one of the causes of delayed gastric emptying. Phase III-like motility was induced by the administration of Leu13-motilin; therefore, it is possible that Leu13-motilin improved the motility of the pyloric ring after PPPD.

Key words: pylorus-preserving pancreatoduodenectomy (PPPD), gastrointestinal motility, pyloric motility, motilin

Introduction

Recently, function-preserving operations of the digestive tract have become popular due to progress in diagnostic techniques and curative surgery. One of these operations is the pylorus-preserving pancreatoduodenectomy (PPPD) (Traverso and Longmire, 1978), which has been used in some cases of chronic pancreatitis, and pancreatic and periampullary tumors (Grace et
The nutritional recovery of the patient following a PPPD operation is better than the traditional (Whipple's) pancreatoduodenectomy (PD) (Zerbi et al., 1995). However, only few basic studies have been performed on the preservation of pyloric function, and there are only a few reports on pyloric function following a PPPD operation. Strain gauge force transducers (SGTs) are superior devices that are frequently used when gastrointestinal motility is evaluated in animals such as dogs (Reinke et al., 1967; Bass and Wiley, 1972). We previously reported that the opening and closure of the canine pyloric ring could be recorded using SGTs, and that the pyloric ring opened when the antrum contracted strongly at phase III (Toyota et al., 1994). In this report, we study the pyloric ring motility of normal dogs and PPPD-model dogs using our previous methods.

It is not clear whether there is a change in the secretion of motilin, which is closely related with the appearance of interdigestive migrating contractions (Itoh et al., 1978; Lee et al., 1983; Hall et al., 1984), following the PPPD operation, and the relationship between motilin and gastrointestinal motility at the interdigestive state is also unknown. We measured the plasma motilin levels of normal dogs and PPPD-model dogs, and studied the relationship between postoperative gut motility and endogenous motilin levels. Furthermore, following the exogenous administration of motilin, the effects on the pyloric ring of normal and PPPD-model dogs were examined.

**Methods**

**Preparation of the animals**

The experiments were performed on healthy mongrel dogs of either sex, each weighing 10–16 kg. At first, the SGTs were implanted in normal dogs. The SGTs (F-12IS/F-12IS-P, Star Medical Inc., Tokyo, Japan) were sewn onto the antrum, the pylorus, and the first and second portions of the duodenum under aseptic conditions with general pentobarbital anesthesia (25 mg/kg of Nembutal, Abbott Laboratories, North Chicago, IL). The SGTs were sewn onto the seromuscular layer in the same direction as the circular muscle contraction. They were attached 5 cm orad from the pyloric ring in the antrum, right over this point in the pyloric ring, and 2 cm and 7 cm from the pyloric ring in the duodenum (Fig. 1A). Three normal dogs were prepared in this manner.

In the PPPD models, the duodenum 3 cm caudad from the pyloric ring and the head of the pancreas were resected, and continuity was restored with an end-to-side duodenojejunostomy. The common bile duct was ligated, and a cholecystojejunostomy was performed. The pancreatic duct was ligated and the cut end of the pancreas was oversewn. The SGTs were sewn in similarly to the normal dogs in the antrum and pylorus, and sewn 5 cm and 10 cm distal from the duodenojejunostomy junction in the jejunum (Fig. 1B, C). Three PPPD-model dogs were prepared.

The lead wires of the SGTs existed between both superior extremities of the scapula, from the abdomen through the subcutis. Using a multichannel pen recorder (WR3701, Graphtec Co., Ltd., Tokyo, Japan) through an amplifier (FA-01, Star Medical Inc.), the motility was then recorded.
Motility of the pyloric ring following a PPPD model

A. Normal dogs: The SGTs were sewn onto the antrum, the pylorus, and the first and second portions of the duodenum.
B. The resected areas of the PPPD animals: The resected areas are shaded.
C. PPPD dogs: A duodenojejunostomy and cholecystojejunostomy were performed.
The common bile duct and the pancreatic duct were ligated, and the SGTs were sutured onto the antrum, pylorus and two sites in the jejunum.

An intravenous cannula was kept in a branch of the femoral vein or external jugular vein in each dog in order to administer drugs and collect venous blood (Itoh et al., 1969). The intravenous cannula also existed between both superior extremities of the scapula through the subcutis.

The dogs were allowed to recover for 7 days after the surgery.

Experimental procedures
The interdigestive and digestive gastropyloroduodenal motility was recorded in the conscious, normal dogs without any restraints. Following the administration of Leu$^{13}$-motilin (KW-5139), the motility was also recorded. The gastropyloric motility of the three conscious PPPD dogs was recorded without restraint, and then Leu$^{13}$-motilin was also administrated. All dogs were fasted for more than 15 hours prior to the experiment, but were allowed free access to water. The experiments were performed for 3 months after the surgery.

The plasma motilin concentration was simultaneously measured in the two normal dogs, and the plasma motilin levels and blood sugar values were measured in all three PPPD dogs. The blood was collected at phase I or III. The blood collected was centrifuged at 3,000 rpm for 10 minutes, and was then frozen at $-20^\circ$C. The plasma motilin concentration was measured at the Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., Ltd. (Shizuoka, Japan) using a Motilin (Canine) RIA Kit (Peninsula Laboratories, Inc., Belmont, CA). The minimal value within the measurement limits was 40 pg/ml, therefore the motilin concentration of blood specimens obtained under this limit was regarded as 40 pg/ml when calculating the
mean value. The blood sugar value was measured using a Glucose Analyzer (YSI Model 23A, Yellow Springs Instrument Company, Inc., Yellow Springs, Ohio).

The PPPD dogs were sacrificed in order to confirm that there were no strictures at the anastomotic points when the experiments were finished.

The procedures used in this study were approved by the Animal Ethics Committee of Hiroshima University, Japan.

Paired Student’s *t* test was used for statistical comparisons; a *p* < 0.05 was considered to indicate significant difference. The data were expressed as means±SD.

**Drugs used in the study**

Leu$^{13}$-motilin (KW–5139) was a generous gift from Kyowa Hakko Kogyo Co., Ltd. (Tokyo, Japan). Leu$^{13}$-motilin was diluted to the appropriate concentration with physiological saline prior to use.

**Results**

Typical interdigestive migrating contractions (IMC) with about 100-minute cycles were recorded during the interdigestive state in conscious normal dogs. Clear relaxation of the pyloric ring was observed, and the contraction of the duodenum paused when the antrum showed intense phasic contractions at phase III (Fig. 2).

Phase III–like contractions were induced when 0.5 μg/kg of Leu$^{13}$-motilin was administrated intravenously for 15 minutes during the interdigestive quiescent period (Fig. 2). Relaxation of the pyloric ring simultaneous with strong contraction of the antrum was also observed.

The characteristic motility of the pyloric ring was recorded by the SGTs in the PPPD dogs. Thus, isolated pyloric contractions were recorded, as well as the phase III–like motility during the interdigestive state and the relaxation of the pyloric ring simultaneous with the strong

![Fig. 2. Record of the spontaneous phase III in normal dogs and following the administration of Leu$^{13}$-motilin.](image)

Relaxation and opening of the pyloric ring was observed when the antrum showed intense contractions during the spontaneous phase III seen on the left of this figure. Motility similar to the spontaneous phase III was induced when 0.5 μg/kg of Leu$^{13}$-motilin was administered intravenously over 15 minutes at 15 minutes after the end of the spontaneous phase III.
Motility of the pyloric ring following a PPPD contraction of the antrum (Fig. 3). However, the periodic gastric phase III which was typical of the normal dogs was not observed, and the IMC interval of the PPPD dogs was over 4 hours long (Fig. 4); the second IMC often did not appear until over 5 hours after the first IMC.

Phase III–like contractions, like those in the normal dogs were induced when 0.5 µg/kg of Leu¹³-motilin was given intravenously for 15 minutes during the interdigestive quiescent period (Fig. 5). Therefore, the pyloric ring was relaxed and opened when the antrum was strongly contracted.

The plasma motilin concentration in two normal dogs and the blood sugar values and motilin levels in the three PPPD dogs were measured (Table 1). We were able to measure the blood sugar values of all three PPPD dogs; the mean values were 83.2±10.8 (n=23), 55.3±15.3 (n=10), and 76.5±15.7 mg/dl (n=17). It was considered that no diabetic changes appeared in

![Fig. 3. Record of the spontaneous phase III–like motility in PPPD dogs. Phase III–like motility with relaxation (opening) of the pyloric ring was recorded.](image)

![Fig. 4. Continuous record of the PPPD dogs. This tracing was recorded on the forty–first day after the operation. The time from the end of the first phase III–like motility to the end of the next phase III–like motility (the IMC period) was about 4 hours.](image)
Fig. 5. Record of the Leu\textsuperscript{13}-motilin induced phase III-like motility in the PPPD dogs. Motility similar to the spontaneous phase III of normal dogs was induced when 0.5 \( \mu \text{g/kg} \) of Leu\textsuperscript{13}-motilin was administered intravenously over 15 minutes at 15 minutes after the end of the spontaneous phase III-like motility.

**Table 1. motilin level (pg/ml)**

|                  | Phase I     | Phase III   | \( p \) Value |
|------------------|-------------|-------------|---------------|
| Normal dog       |             |             |               |
| No. 1            | 155.7 ± 51.5 (\( n = 7 \)) | 259.0 ± 105.3 (\( n = 7 \)) | <0.05         |
| No. 2            | 159.0 ± 22.3 (\( n = 7 \)) | 332.4 ± 61.7 (\( n = 7 \)) | <0.05         |
| PPPD model       | 52.8 ± 10.0 (\( n = 12 \)) | 70.1 ± 8.9 (\( n = 11 \)) | <0.05         |

any of the dogs. The plasma motilin concentrations of two PPPD dogs were impossible to evaluate, because 90% of the specimens had values which were less than the measurement limit. The third PPPD dog had mean motilin levels of 52.8 ± 10.0 pg/dl (\( n = 12 \)) during phase I and 70.1 ± 8.9 pg/dl (\( n = 11 \)) during phase III. The plasma motilin concentration during phase III was significantly higher than during phase I (\( p < 0.05 \)). In the normal dogs, the plasma motilin levels during phase III were significantly higher than during phase I, which was similar to the results previously reported (Itoh \textit{et al.}, 1978; Sarna \textit{et al.}, 1983).

**Discussion**

PPPD has recently been performed for some pancreatic diseases, in which PD was thought to be the most suitable operation to perform, as a function-preserving procedure which considers the quality of life (Grace \textit{et al.}, 1990; Klinkenbijl \textit{et al.}, 1992). This technique aims to preserve the whole stomach and pylorus, which avoids side effects such as dumping and malnutrition following a gastric resection, and preserves postoperative gastrointestinal func-
Motility of the pyloric ring following a PPPD

It has been reported that delayed gastric emptying often occurred as a complication of this operation (Warshaw and Torchiana, 1985; Itani et al., 1986). Itani et al. (1986) hypothesized that the factors which contributed to the delayed gastric emptying were changes in the endocrinologic milieu, and an insufficiency or damage to the blood supply and nerves. However, the cause of the delayed gastric emptying is still unknown. Therefore, we prepared the PPPD-model dogs and studied changes in gastropyloric motility and the opening and closure of the pyloric ring by SGTs (Toyota et al., 1994). In these PPPD models, the pyloric branch of the vagus nerve and the tissues around the pyloric ring were preserved. Phase III-like contractions with the opening of the pyloric ring were recorded, but the typical periodic phase III of about 100 minutes duration, which was recorded in the normal dogs, was not recorded. This result is in agreement with the report in humans by Pastorino et al. (1995). They reported that gastrojejunal interdigestive motor activity shows a reduction in phase III, and a relative increase in phase II, in patients after the PPPD operation.

The head of the pancreas was resected in the PPPD dogs, and therefore it was possible that they might show diabetic changes. Diabetic mellitus is closely related with gastroparesis and delayed gastric emptying (Wooten and Meriwether, 1961; Marshak and Maklansky, 1964). Malagelada et al. (1980) reported that patients with diabetic gastroparesis do not have phase III in their stomachs. In humans, Barnett and Owyang (1988) reported that phase III was inhibited when the blood sugar value was over 140 mg/dl. However, the blood sugar values of our PPPD dogs were less than 110 mg/dl, and therefore it was unlikely that a high blood sugar value inhibited phase III. Other factors which may have attenuated or blocked the typical phase III contractions in our models may include the fact that the duodenum was almost resected, that the cholecystojejunostomy performed by ligating the common bile duct may have disrupted the coordination of the gallbladder and gastroduodenum, or that pancreatic exocrine activity was sacrificed because of the ligation of the pancreatic duct. It was impossible to determine the precise cause in this study, but it is certain that the typical gastric phase III did not appear in these PPPD dogs. It is believed that the delayed gastric emptying observed in patients after the PPPD operation is caused by this lack of a typical periodic phase III, and thus interdigestive gastric emptying, which has been termed “housekeeper” emptying (Szurszewski, 1969), does not occur normally.

Motilin is a 22 amino acid polypeptide known to be closely related with the occurrence of phase III (Itoh et al., 1976; Hall et al., 1984; Poitras, 1984). In our study, the gastropyloric motility, which was the same as spontaneous phase III was induced when Leu<sup>13</sup>-motilin was given to the PPPD dogs. Therefore, the possibility that this drug could improve delayed gastric emptying in patients after a PPPD operation is suggested.

Motilin is a 22 amino acid polypeptide known to be closely related with the occurrence of phase III (Itoh et al., 1978; Lee et al., 1983; Hall et al., 1984). However, controversy remains whether motilin is the trigger of the phase III or is released by the phase III contractions (Sarna et al., 1983). The major sources of motilin are cells that exist mainly in the duodenum and upper small intestine (Pearse et al., 1974; Polak et al., 1975). Chung et al. (1994) pointed out that the periodic rhythm of motilin secretion disappears after a total duodenectomy. The
plasma motilin levels in one of our PPPD dogs, which was markedly lower than the phase III
motilin levels in the normal dogs, showed a periodic increase and decrease. Moreover, the
motilin levels of this PPPD dog during phase III–like motility was lower than in the normal
dogs during phase I. These results suggest that the increase in the motilin concentration is not
the only factor to induce phase III–like motility but other mechanisms are involved into it, or
the increase in motilin levels is the effect of the phase III–like motility.

Based on the above-mentioned facts, this study suggested that: (a) the typical periodic
phase III contractions do not occur after the PPPD operation. However, Leu\textsuperscript{13}–motilin
induced phase III–like motility, and can be expected to be an effective pharmacologic treatment
for delayed gastric emptying; and (b) there is a periodicity to the plasma motilin levels after
the PPPD operation. However, the cause of the delayed gastric emptying after the PPPD
operation, and the cause and effect relationship between motilin levels and phase III contrac
tions are still indefinite in the present study. Therefore, further study is necessary.

References

Barnett, J.L. and Owyang, C. (1988). Serum glucose concentration as a modulator of interdigestive
gastric motility. *Gastroenterology* 94: 739-744.

Bass, P. and Wiley, J.N. (1972). Contractile force transducer for recording muscle activity in
unanesthetized animals. *J. Appl. Physiol.* 32: 567-570.

Chung, S.A., Rotstein, O., Greenberg, G.R. and Diamant, N.E. (1994). Mechanisms coordinating
gastric and small intestinal MMC: role of extrinsic innervation rather than motilin. *Am. J.
Physiol.* 267: G800-G809.

Grace, P.A., Pitt, H.A. and Longmire, W.P. (1990). Pylorus preserving pancreatoduodenectomy: an
overview. *Br. J. Surg.* 77: 968-974.

Hall, K.E., Greenberg, G.R., El-Sharkawy, T.Y. and Diamant, N.E. (1984). Relationship between
porcine motilin-induced migrating motor complex–like activity, vagal integrity, and end
dogenous motilin release in dogs. *Gastroenterology* 87: 76-85.

Itani, K.M.F., Coleman, R.E., Akwari, O.E. and Meyers, W.C. (1986). Pylorus-preserving pancreatoduodenectomy: a clinical and physiologic appraisal. *Ann. Surg.* 204: 655-664.

Itoh, Z., Carlton, N., Lucien, H.W. and Schally, A.V. (1976). Motilin–induced mechanical activity in the canine alimentary tract. *Scand. J. Gastroenterol.* 11 (Supple 39): 93-110.

Itoh, Z., Takeuchi, S., Aizawa, I., Mori, K., Taminato, T., Seino, Y., Imura, H. and Yanaihara, N.
(1978). Changes in plasma motilin concentration and gastrointestinal contractile activity in
conscious dogs. *Dig. Dis.* 23: 929-935.

Klinkenbijl, J.H.G., Schelling, G.P., Hop, W.C.J., Pel, R., Bruining, H.A. and Jeekel, J. (1992). The advantages of pylorus-preserving pancreatoduodenectomy in malignant disease of the pancreas and periampullary region. *Ann. Surg.* 216: 142-145.

Lee, K.Y., Chang, T-M. and Chey, W.Y. (1983). Effect of rabbit antimotilin serum on myoelectric activity and plasma motilin concentration in fasting dog. *Am. J. Physiol.* 245: G547-G553.

Malagelada, J-R., Rees, W.D.W., Mazzotta, L.J. and Go, V.L.W. (1980). Gastric motor abnormalities in diabetic and postvagotomy gastroparesis: effect of metoclopramide and bethanechol. *Gastroenterology* 78: 286-293.
Motility of the pyloric ring following a PPPD

Marshak, R.H. and Maklansky, D. (1964). Diabetic gastropathy. *Am. J. Dig. Dis.* 9: 366-370.

Newman, K.D., Braasch, J.W., Rossi, R.L. and O’Campo-Gonzales, S. (1983). Pyloric and gastric preservation with pancreatoduodenectomy. *Am. J. Surg.* 145: 152-156.

Pastorino, G., Ermili, F., Zappatore, F., Castagnola, M., Fazio, S. and Ciferri, E. (1995). Multiparametric evaluation of functional outcome after pylorus-preserving duodenopancreatectomy. *Hepatogastroenterology* 42: 62-67.

Pearse, A.G.E., Polak, J.M., Bloom, S.R., Adams, C., Dryburgh, J.R. and Brown, J.C. (1974). Enterochromaffin cells of the mammalian small intestine as the source of motilin. *Virchows Arch. B cell Path.* 16: 111-120.

Poitras, P. (1984). Motilin is a digestive hormone in the dog. *Gastroenterology* 87: 909-913.

Polak, J.M., Pearse, A.G.E. and Heath, C.M. (1975). Complete identification of endocrine cells in the gastrointestinal tract using semithin-thin sections to identify motilin cells in human and animal intestine. *Gut* 16: 225-229.

Reinke, D.A., Rosenbaum, A.H. and Bennett, D.R. (1967). Patterns of dog gastrointestinal contractile activity monitored in vivo with extraluminal force transducers. *Am. J. Dig. Dis.* 12: 113-141.

Sarna, S., Chey, W.Y., Condon, R.E., Dodds, W.J., Myers, T. and Chang, T-M. (1983). Cause-and-effect relationship between motilin and migrating myoelectric complexes. *Am. J. Physiol.* 245: G277-G284.

Szurszewski, J.H. (1969). A migrating electric complex of the canine small intestine. *Am. J. Physiol.* 217: 1757-1763.

Toyota, K., Okajima, M., Ojima, Y., Kawahori, K., Asahara, T., Dohi, K., Yamanaka, H. and Okamoto, E. (1994). Relation between canine pyloric motility and recordings made by means of strain gauge force transducers. *J. Smooth Muscle Res.* 30: 251-253.

Traverso, L.W. and Longmire, W.P. Jr. (1978). Preservation of the pylorus in pancreaticoduodenectomy. *Surg. Gynecol. Obstet.* 146: 959-962.

Traverso, L.W. and Longmire, W.P. Jr. (1980). Preservation of the pylorus in pancreaticoduodenectomy: a follow-up evaluation. *Ann. Surg.* 192: 306-310.

Warshaw, A.L. and Torchiana, D.L. (1985). Delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy. *Surg. Gynecol. Obstet.* 160: 1-4.

Wooten, R.L. and Meriwether, T.W. (1961). Diabetic gastric atony: a clinical study. *J.A.M.A.* 176: 1082-1087.

Zerbi, A., Balzano, G., Patuzzo, R., Calori, G., Braga, M. and Dicarlo, V. (1995). Comparison between pylorus-preserving and Whipple pancreaticoduodenectomy. *Br. J. Surg.* 82: 975-979.

(Received June 1st, 1998: Accepted August 17, 1998)