Government of South Australia
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ROYAL ADELAIDE HOSPITAL
North Terrace
Adelaide SA 5000
Australia

ABN 80 230 154 545

www.rah.sa.gov.au

Prof Lian-Sheng Ma,
President and Editor-in-Chief
World Journal of Gastroenterology

16 September 2013

Dear Prof Lian-Sheng Ma,

Re: Modulation of individual components of the gastric motor response to duodenal glucose. Manuscript Number: 1861

Thank you for your email dated 8 March 2013. On behalf of my co-investigators I thank the reviewers for their supportive comments. We have modified the manuscript according to the reviewer's suggestion and believe this has improved the quality of the manuscript.

All changes to the manuscript have been marked in red font. In particular, the following issues have now been addressed:

Reviewer 1

Could sequential different glucose loads affect APD motility intestinal responses as result of an adaption mechanism? Please, comment on this issue in the Discussion section.

This comment has been addressed in the Statistical Analysis section Page 10 Line 3:
On testing there was no order effect apparent.

And also addressed in the discussion section Page 15 line 21:
It should also be recognized that blood glucose concentrations were not clamped and hyperglycemia, even within the physiological range, affects APD motor responses and gastric emptying. However glucose concentrations were similar despite the differing loads, suggesting that this is unlikely to explain the adaptive response observed.

There are some spelling and/or grammar errors in the text: Abstract section Pag.3 Ln 19 - with in a dose-dependent fashion. Please omit the word with. A threshold for stimulation for was observed. Please, omit the (second) word for.

We apologise for these spelling/grammar oversights, the suggested errors have been amended.

Reviewer 2

Significance and mechanisms (i.e. the role of GLP-1, PYY and Ach) in the pathogenesis, such as obesity and diabetes, should be discussed. As author described, only occlusive pressure (but not non-occlusive pressure) waves are detected.

This comment has been addressed in the discussion section Page15 line 1:

While this study was undertaken in health, implications of these data for pathological conditions can be speculated upon. Gastric emptying is frequently slowed with healthy aging and in conditions such as diabetes and critical illness. This slowing has been attributed in part to 'hypersensitivity' to small intestinal nutrient, which appears to be, at least in part, hormonally-mediated via hormones such as cholecystokinin. These data in health suggest the hypothesis that the process of aging or the effects of critical illness exacerbates this hierarchical sensitivity. Further study in this area would be of interest.

Administrator

The following changes have been made in accordance with the administrator's comments:

- The title is now less than 12 words.
- The running title is now less than 6 words.
- The author contributions are now stated in accordance with the standard proposed by the International Committee of Medical Journal Editors.
- Correspondence address, phone and fax numbers are now provided for supportive foundations.
- Abstract format has been edited to comply with journal and a 100 word summary has been included.
- Pubmed citation numbers and DOI citation have been included for manuscripts in the reference list. For manuscripts that DOI citation could not be found (7 manuscripts), the first page of the article has been included as an appendix to this letter.
- More than 26 references are now cited in this manuscript.
- Figures are provided in adobe illustrator files (ai files) that are able to edited.

Once again we thank the reviewers for their constructive and insightful comments. We believe that the manuscript we are resubmitting is superior to the original manuscript.

Yours sincerely,

Dr Adam Deane MBBS, PhD, FCICM, FRACP
Intensive Care Consultant, Royal Adelaide Hospital
Senior Lecturer, Discipline of Acute Care Medicine, University of Adelaide
Email: adam.deane@adelaide.edu.au
Phone: + 61 8 8222 4000

Appendix - First page of articles without DOI

Reference 3

GASTROENTEROLOGY 1983;85:76–82

Regulation of the Gastric Emptying of Glucose

WILLIAM BRENER, THOMAS R. HENDRIX, and PAUL R. McHUGH
Departments of Psychiatry and of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland

The gastric emptying characteristics of physiological saline (0.9% NaCl) and glucose solutions of three different concentrations (0.05, 0.125, 0.25 g/ml) were examined in order to identify distinctions in the control of the stomach's activity. Saline emptied rapidly and exponentially. Glucose assumed, soon after filling the stomach, a slow and calorie-constant emptying pattern such that 2.13 kcal of glucose were delivered per minute to the duodenum for all three concentrations of glucose. When, by means of a catheter passed beyond the pylorus, glucose was infused into the duodenum in amounts varying from 26.5 to 120 kcal, an inhibition on the gastric emptying of physiological saline of 0.46 min/kcal of intraduodenal glucose was demonstrated. Since 2.13 kcal/min and 0.46 min/kcal are reciprocals, it appeared that in emptying saline, the gastroduodenal system acts as an "open-loop" system passing liquids from the stomach at a rate primarily determined by the volume of gastric contents. With glucose, however, a "closed-loop" system is established that assumes a steady-state balance between the delivery of glucose to the duodenum and the inhibition of this delivery evoked from the duodenum by the glucose that enters it.

The functional interrelations between the stomach and the duodenum have been extensively studied (1). In particular, mechanisms arising from the duodenum can, in response to such elements in the effluent from the stomach as hydrogen ions (2), osmoles (3,4), or calorie-bearing nutrients (5), alter gastric secretion, gastric peristaltic activity, and gastric emptying. These many investigations demonstrate that the activities of the stomach, including its emptying, are under the influence of the receiving duodenum, a relationship protecting the receptive compartment of the intestine from excessive or inappropriate gastric contents.

The characteristics of gastric emptying of liquids, however, have been recently restudied. The emptying of liquids through the pylorus had been thought to be an exponential function with the rate of emptying depending primarily upon gastric distention (1). The duodenal influences, including duodenal contractions (5), were thought to enhance or inhibit the rate of emptying, but were not believed to change the fundamental exponential feature.

In their work with rhesus monkeys, however, McHugh and Moran (6) demonstrated that although physiological saline emptied exponentially, glucose, casein hydrolysate, and medium-chain triglycerides followed a more linear than exponential course of emptying from the stomach. Also, the stomach slowed its emptying rate as its nutrient content increased in caloric concentration with the result that calories were delivered to the duodenum at a constant rate of 0.4 kcal/min in these animals regardless, within limits, of the concentration, osmolality, or volume of the intragastric meal.

These same investigators (7) also demonstrated that this constant emptying rate depended upon an inhibitory control arising from the duodenum, in which glucose in the duodenum would provoke an almost total cessation of gastric emptying lasting 2.5 min/kcal of duodenal glucose. The appreciation that the delivery rate, 0.4 kcal/min, and the inhibition duration, 2.5 min/kcal, were precise reciprocals led McHugh and his associates (7) to propose that within a few minutes after it is filled with a nutrient load the stomach settles into a steady state delivering nutrients to the duodenum at 0.4 kcal/min, because of the inhibition on gastric output of 2.5 min/kcal provoked from the intestine.

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Address requests for reprints to: Paul R. McHugh, M.D., Department of Psychiatry, The Johns Hopkins Hospital, Meyer Building 4-113, 600 N. Wolfe Street, Baltimore, Maryland 21205.
This work was supported by National Institutes of Health Grant #AM19302.
The authors thank Lee Riley III for his help in this study.

0016-5085/83/83.00

Reference 5

Antropyloroduodenal motor responses to intraduodenal lipid infusion in healthy volunteers

R. HEDDLE, J. DENT, N. W. READ, L. A. HOUGHTON, J. TOOULI, M. HOROWITZ, G. J. MADDERN, AND J. DOWNTON

Gastroenterology Units and Departments of Surgery, Royal Adelaide Hospital, Adelaide 5000, and Flinders Medical Centre, Bedford Park 5042, South Australia

HEDDLE, R., J. DENT, N. W. READ, L. A. HOUGHTON, J. TOOULI, M. HOROWITZ, G. J. MADDERN, AND J. DOWNTON. *Antropyloroduodenal motor responses to intraduodenal lipid infusion in healthy volunteers.* Am. J. Physiol. 254 (Gastrointest. Liver Physiol. 17): G671–G679, 1988.—The delivery of lipid to the duodenum has been shown to slow gastric emptying and to increase the resistance to gastric outflow. To investigate mechanisms responsible for these effects, we have recorded antropyloroduodenal motility in nine healthy volunteers during alternate intraduodenal infusions of normal saline and triglyceride emulsion (Intralipid 10%). During the lipid infusions there were reproducible, major changes in the patterns of motility. Pressure waves, apparently isolated to the pylorus, usually started within 10 min of initiation of the lipid infusion. After 20–25 min of lipid infusion these waves occurred at median rates of 2.4 and 2.8/min (1st and 2nd lipid infusions, respectively); these rates were significantly greater ($P < 0.05$) than the median rates (all ≤0.4/min) observed during the equivalent period of the succeeding saline infusions. During 10 of 22 lipid infusions, isolated pyloric pressure waves were associated with sustained pyloric tone. Infusion of lipid into the duodenum suppressed antral pressure waves in all subjects and initiated brief periods of regular duodenal contractions during 11 of 22 infusions. These studies have demonstrated alterations of antropyloroduodenal motor patterns in response to changes in the duodenal luminal content. The effects on antral and pyloric motility are probably of importance in the regulation of transpyloric flow by nutrients in the duodenal lumen.

pyloric motility; antral motility; fat

THE GASTRIC EMPTYING OF NUTRIENTS is known to be closely controlled, but the mechanisms underlying this regulation are incompletely understood. The emptying of triglycerides and fatty acids into the duodenum is associated with slowing of gastric emptying in animals and humans (16, 22), suppression of antral contractions (18, 23, 31), reduction of fundal tone in animals and men (3, 11), and stimulation of pyloric and duodenal resistances to liquid flow (22).

Some manometric studies in humans have demonstrated that phasic and tonic pyloric contractions are stimulated by intraluminal acid or lipid (12, 31), although this same phenomenon has not been recorded by other workers using similar methods (17, 21). These studies were performed with either pull-through methods that can only sample pyloric pressures for short time intervals (12, 17, 21) or with a stationed manometric side hole that may not have been correctly positioned for monitoring a narrow zone of pyloric contractions (31).

In this study an adapted sleeve sensor was used to obtain prolonged manometric recordings from the pylorus. The sleeve sensor, together with multiple side holes positioned in the antrum and duodenum, allowed us to examine the hypothesis that infusion of lipid into the duodenum would induce changes in the pattern of antropyloroduodenal motility likely to retard gastric emptying.

MATERIALS AND METHODS

Subjects

The studies were performed on nine healthy volunteers aged between 18 and 31 yr. None of the subjects complained of dyspepsia, had a past history of peptic ulcer or other gastrointestinal disease, or were taking any medication. Written informed consent was obtained from each subject. The study protocol was approved by the Research Review Committee of the Royal Adelaide Hospital and by the Committee on Clinical Investigation of Flinders Medical Centre in July 1984.

Experimental Protocol

On the morning after an overnight fast a manometric recording assembly was passed through the subject's nostril. This assembly was designed to monitor antropyloroduodenal motility and included a sleeve sensor (9) adapted specifically for measurement of pyloric pressure, together with perfused side holes for monitoring antral and duodenal pressures. After passage of the assembly into the stomach the subject lay on the right side to aid passage of the assembly into the duodenum.

The passage of the distal end of the manometric assembly was monitored by the recognition of manometric patterns. The correct position of the sleeve sensor across the pylorus was defined by measurement of transmucosal potential difference (TMPD), which was recorded at side holes situated at both ends of the 4.5-cm-long sleeve. Once the sleeve sensor was straddling the gastroduodenal TMPD gradient, test solutions were infused into the duodenum via an infusion port that was situated 8 cm distal to the end of the sleeve. In all nine subjects, after an initial 10-min period of recording of fasting activity,

Reference 10

GASTROENTEROLOGY 1988;94:1276–84

Motor Activity of the Gastric Antrum, Pylorus, and Duodenum Under Fasted Conditions and After a Liquid Meal

L. A. HOUGHTON, N. W. READ, R. HEDDLE, G. J. MADDERN, J. DOWNTON, J. TOOULI, and J. DENT

Departments of Medicine and Surgery, Flinders Medical Centre and Royal Adelaide Hospital, Adelaide, Australia; and Sub-Department of Human Gastrointestinal Physiology and Nutrition, Royal Hallamshire Hospital, Sheffield, United Kingdom

Because the mechanisms that control the movement of food and digestive juices across the human pylorus are not completely understood, the aim of this study was to document the normal patterns of pressure activity in the antrum, pylorus, and duodenum and the associated pH changes in 9 healthy volunteers. Studies were carried out under fasting conditions and after ingestion of 300 ml of chocolate milk, using a unique 11-channel intraluminal probe that incorporated a sleeve sensor positioned across the pylorus and pH electrodes situated in the terminal antrum and proximal duodenum. The most common motor pattern recorded under fasting conditions consisted of regular coordinated contractions, most of which (a) involved the antrum and duodenum, (b) showed evidence of propagation through two or more adjacent channels, and (c) were associated with transient reductions in duodenal pH and transient elevations in antral pH. Ingestion of milk changed the motor pattern to one that was composed of pressure waves, which were confined to the pylorus with few or no pressure waves in the terminal antrum or proximal duodenum. Isolated pyloric pressure waves were gradually replaced by propagated antroduodenal contractions, which eventually occurred at a regular frequency that was higher than that observed under fasting conditions. After ingestion of milk, only the coordinated contractions were associated with transient reductions in duodenal pH. Isolated pyloric pressure waves were also observed under fasting conditions just before or just after phase III of the migrating motor complex, and 17% of these were accompanied by episodes of duodenal acidification.

The mechanisms that control the movement of food and digestive juices across the pylorus are not completely understood. The contractile activity of the gastric fundus, antrum, pylorus, and duodenum must all participate in the transpyloric movement of luminal contents, but only two studies have attempted to study how these functions are integrated in humans. White and colleagues (1) used three perfused sideholes to simultaneously record from the antrum, pylorus, and duodenum during intragastric infusion of saline and nutrient solutions. Although this was the first study to suggest the existence of isolated pyloric contractions, the low number of recording sites used and the difficulty of maintaining a sidehole in such a short mobile structure as the pylorus (2–4) limits the interpretation of it. Dooley and colleagues (5) used a sleeve sensor to accommodate for the range of axial mobility of the pylorus (6) and to facilitate long-term pyloric recordings, but as the position of the sleeve sensor was not monitored continuously, it is uncertain whether the sensor was always correctly placed across the pylorus. This study, which was carried our under fasting conditions, also recorded pressure activity with sideholes at two sites in the antrum (2 cm apart) and two sites in the duodenum (5 cm apart). Neither the study of White nor Dooley attempted to correlate pressure patterns with measurements of transpyloric flow. Our study used a unique 11-channel manometric and pH catheter assembly that incorporated a transpyloric sleeve sensor positioned by continuous monitoring of the transmucosal potential difference (PD) at either end of the sleeve. With this set-up, it was possible to document the normal integrated motor activity of the gastric antrum, pylorus, and duodenum in normal healthy volunteers under

Abbreviations used in this paper: IPPW, isolated pyloric pressure wave; PD, potential difference.

0016-5085/88/$3.50

Reference 13

Adaptive Changes in the Pyloric Motor Response to Intraduodenal Dextrose in Normal Subjects

MICHELA EDELBROEK, MICHAEL HOROWITZ, ROBERT FRASER, JUDITH WISHART, HOWARD MORRIS, JOHN DENT, and LOUIS AKKERMANS

Department of Experimental Surgery, University Hospital Utrecht, The Netherlands; Department of Medicine and Gastroenterology Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia; and Division of Clinical Chemistry, Institute of Medical and Veterinary Science, Adelaide, South Australia, Australia

Gastric emptying of glucose is faster after dietary supplementation of glucose, suggesting specific adaptation to changes in nutrient intake. In the present study, the effects of a continuous long-term (0–120-minute) and two short-term (0–20- and 80–100-minute) intraduodenal infusions of dextrose (2.4 kcal/min) on antropyloroduodenal motility and blood glucose, plasma gastric inhibitory polypeptide, and insulin concentrations were evaluated in nine volunteers. In four volunteers, an intraduodenal infusion of triglyceride (2.4 kcal/min) was administered immediately after the long-term dextrose infusion. The long-term dextrose infusion initially increased isolated pyloric pressure waves (IPPWs) and basal pyloric pressure ($P < 0.05$ for both), but after about 30 minutes IPPWs and basal pyloric pressure decreased and returned to baseline within 80 minutes. Each short-term infusion increased IPPWs and basal pyloric pressure ($P < 0.05$ for both). Antral pressure waves remained suppressed during the long-term dextrose infusion. Intraduodenal triglyceride increased IPPWs and basal pyloric pressure ($P < 0.05$ for both). The long-term dextrose infusion was associated with a sustained increase, and both short-term dextrose infusions were associated with peaks in glucose, insulin, and gastric inhibitory polypeptide levels. There was no significant relationship between biochemical measurements and antropyloroduodenal motility. It is concluded that specific adaptive changes occur rapidly in the phasic and tonic pyloric motor response, but not the antral motor response, to intraduodenal dextrose.

Gastric emptying of nutrients and acid is regulated by luminal receptors in the small intestine.[1–14] It has been suggested that the rate of gastric emptying is calibrated precisely[5–8] and that the magnitude of the delay in gastric emptying produced by the presence of glucose,[1] triglyceride,[2] or acid[4] in small intestine is dependent solely on the num and site of the intestinal receptors exposed. This l pothesis has been challenged by recent observatic suggesting that the feedback of these receptors m be influenced by specific changes in nutrient take.[15,16] In healthy humans, gastric emptying of g cose is faster after dietary supplementation with gl cose for 3 days[15] and consumption of a high-fat d for 14 days is associated with more rapid emptying a fatty test meal.[16] Modulations in the sensitivity small intestinal feedback control may also be respo sible for the delayed gastric emptying seen in mar patients with anorexia nervosa[17–19] and the rap gastric emptying reported in some obese patients.[20] The modifications in motor mechanisms that unde lie these changes in gastric emptying have not bee examined.

Recent studies have provided insight into the mc tor mechanisms responsible for the slowing of gastri emptying by small intestinal nutrient infusion.[9–1 Short-term intraduodenal infusions of nutrients ar associated with suppression of antral contraction and stimulation of pyloric tone and pressure wave localized to the pylorus, known as isolated pyloric pressure waves (IPPWs).[9–12] Scintigraphic[9] and fluo roscopic studies,[14] performed concurrently with ma nometry during intraduodenal nutrient infusion, have shown that IPPWs and pyloric tone cause sustained localized pyloric luminal closure and are associated with cessation of transpyloric flow.

Both neural and hormonal pathways may be important mediators of changes of motility produced by the presence of nutrients in the small intestine.[22–26] Gastric inhibitory peptide (GIP), which is released by small intestinal exposure to nutrients, may be im-

0016-5085/92/$3.00

Reference 15

Am J Physiol Gastrointest Liver Physiol
280: G501–G509, 2001.

Nutrient-induced spatial patterning of human duodenal motor function

JANE M. ANDREWS,[1] SELENA M. DORAN,[2] GEOFFREY S. HEBBARD,[1]
CHARLES H. MALBERT,[3] MICHAEL HOROWITZ,[1] AND JOHN DENT[2]
Departments of [1]Medicine and [2]Gastrointestinal Medicine, Royal Adelaide Hospital, Adelaide, South Australia 5000, Australia; and [3]Institut des Reserches Porcines, Institut National de la Recherche Agronomique, St. Gilles 35590, France

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Andrews, Jane M., Selena M. Doran, Geoffrey S. Hebbard, Charles H. Malbert, Michael Horowitz, and John Dent. Nutrient-induced spatial patterning of human duodenal motor function. *Am J Physiol Gastrointest Liver Physiol* 280: G501–G509, 2001.—The spatiotemporal patterning of duodenal motor function has been evaluated comprehensively for the first time in humans, with a novel 21-lumen manometric assembly. In nine young, healthy volunteers (6 male, 3 female), duodenal motility was recorded during fasting and three 45-min intraduodenal (ID) nutrient infusion periods (Intralipid at 0.25, 0.5, and 1.5 kcal/min). Pressures were recorded along the length of the duodenum with an array of 18 sideholes at 1.5-cm intervals. Pressure patterns were compared for the final 20 min of each of the four periods. Compared with fasting, ID lipid was associated with regional variation in pressure wave (PW) sequences, with fewer proximally and more distally; this was not observed during fasting ($P < 0.001$). During fasting and all rates of lipid infusion, most (87–90%) PW sequences were short (1.5–4.5 cm), with a small number (2–4%) of 10.5 cm or longer. At all times, antegrade PW sequences occurred more frequently than retrograde sequences over all distances examined (3, 4.5, and >6 cm), and the proportion of antegrade sequences increased with greater PW sequence length ($P = 0.0001$). Increasing ID lipid rates appeared to produce dose-related suppression of PW sequences ($P < 0.001$). The frequency and spatial patterning of human duodenal motor function show substantial variability in response to different nutrient delivery rates. These complex patterns are likely to be involved in duodenal modulation of flow and gastric emptying rate.

pressure wave sequences; Intralipid; high-resolution manometry

THE HUMAN DUODENUM IS A SHORT but highly specialized region of the gastrointestinal tract. Its motor activity plays a role in retarding the rate of gastric emptying (31) and regulating the orderly delivery of chyme to the remainder of the small intestine (24). Rather than being merely a passive conduit, these mechanical functions appear to be highly modulated by luminal feedback control mechanisms (27, 31, 40). The duodenum also serves an important sensory function (23, 27, 29), containing both chemo- and mechanoreceptors (11), which when stimulated modulate the rate of gastric emptying directly by feedback onto gastric motor functions (1, 12, 17) and indirectly by varying duodenal resistance to gastric emptying (40). These effects are mediated by neural (1) and humoral means (14, 39). Absence or "malfunction" of the duodenum is associated with disordered gastric emptying and dyspeptic symptoms (21), due to the resulting mismatch between gastric emptying and subsequent digestion and absorption, attesting to the vital regulatory role of the duodenum.

Despite the recognized importance of the duodenum in humans, there is little detailed knowledge of its motor function in health. In part, this is a result of technical limitations. Most information on normal human upper gastrointestinal motility concentrates on the esophagus, stomach, and small intestine. The relatively few manometric studies (3, 4, 9, 31, 44, 45) that have focused on duodenal motility in humans are limited in their temporospatial resolution because of the relatively restricted number of recording sites placed in the duodenum. Scintigraphic studies are limited by the low spatiotemporal resolution of this technique (30), and fluoroscopic studies by the length of radiation exposure permissible in volunteers (31). In other regions of the gut, pressure patterns are known to vary over short distances (43); moreover, closely spaced pressure recordings have been found to be invaluable in defining some of the pressure-flow relationships in the esophagus (6). We have therefore sought to perform duodenal manometry with high spatiotemporal resolution.

Luminal manometry is the most direct method of assessing the forces applied to luminal contents by motor events, and closely spaced (1.5–2 cm) manometry gives better spatial resolution of these forces. High spatial resolution manometry has been facilitated by the recent development of fine-bore silicone rubber assemblies capable of recording intraluminal pressures concurrently from up to 21 channels. In this study, one such assembly, with an array of 18 sideholes

Address for reprint requests and other correspondence: J. M. Andrews, Dept. of Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia (E-mail: jane.andrews@adelaide.edu.au).

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Reference 16

GASTROENTEROLOGY 1989;97:83–90

Pyloric Motor Response to Intraduodenal Dextrose Involves Muscarinic Mechanisms

DAVID R. FONE, MICHAEL HOROWITZ, JOHN DENT, NICHOLAS W. READ, and RICHARD HEDDLE
Gastroenterology Unit and Department of Medicine, Royal Adelaide Hospital, Adelaide, Australia

The delivery of dextrose solutions to the duodenum is associated with the stimulation of phasic and tonic pyloric contraction. In this study, the effects of intravenous atropine on the antropyloroduodenal motor responses to intraduodenal infusions of 25% dextrose were assessed in 10 normal volunteers. Antropyloroduodenal pressures were recorded with a manometric assembly incorporating a sleeve sensor spanning the pylorus, and sideholes in the antrum and duodenum. In each experiment, three intraduodenal infusions of 25% dextrose were given at a rate of 4 ml/min, for a median duration of 19 min (range 17–20). During the second dextrose infusion, intravenous atropine was given as a bolus (15 μg/kg) followed by an infusion (4 μg/kg·min), which was continued until the end of each experiment. Before atropine was given, the pyloric motor response to the second dextrose infusion was not significantly different from the response to the first infusion, but after administration of atropine there was a rapid decrease in the rate of isolated pyloric pressure waves, from 0.8 to 0.1 per minute ($p < 0.05$). The isolated pyloric pressure wave response to the third dextrose infusion was completely blocked, and there was a much smaller maximum increase in basal pyloric pressure compared with the first infusion ($p < 0.01$). This study indicates that intraduodenal dextrose reproducibly stimulates isolated pyloric pressure waves and increases basal pyloric pressure by mechanisms that involve muscarinic receptors.

The emptying of nutrient-rich liquids from the stomach is closely regulated. Gastric emptying is slowest when liquid meals have a high calorie content (1,2), and this effect is mediated by the interaction of nutrients with mucosal receptors in the small intestine or duodenum (3).

Alterations in pyloric motility, which may be important in the control of gastric emptying, are induced by stimulation of duodenal receptors. Both ingestion of calorie-rich test meals (4,5) and intraduodenal infusion of lipid emulsions (6,7), acid (6), and dextrose (8) stimulate phasic pressure waves isolated to the pylorus and increase basal pyloric pressure (pyloric tone). Simultaneous fluoroscopic and manometric studies of the pylorus have shown that isolated pyloric pressure waves (IPPWs) and pyloric tone are associated with cessation of the transpyloric flow of barium (9).

Studies in the dog indicate that the canine pyloric motor responses to duodenal receptor stimulation by acid may be mediated by orally projecting cholinergic excitatory fibers within the duodenal wall (10,11). This may not be the case in the cat, where atropine was found to have no effect on the pyloric motor responses after intraduodenal acid or amino acid infusions (12,13), suggesting possible interspecies variations. The mediation of pyloric motor responses has been little studied in humans. Naloxone was found to have no effect on the response to intraduodenal lipid infusion (14). This stimulus has not been studied in animals, so it is not clear whether the human pylorus is pharmacologically similar to the dog or cat models in which most investigations have been performed.

The aim of this study was to investigate whether the pyloric motor responses to intraduodenal dextrose infusions in humans are mediated by atropine-sensitive pathways.

Abbreviations used in this paper: IPPW, isolated pyloric pressure wave; TMPD, transmucosal potential difference.

0016-5085/89/$3.50

Reference 24

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EDITORIAL

Mechanisms underlying feed intolerance in the critically ill: Implications for treatment

Adam Deane, Marianne J Chapman, Robert J Fraser, Laura K Bryant, Carly Burgstad, Nam Q Nguyen

Adam Deane, Marianne J Chapman, Intensive Care Unit, Royal Adelaide Hospital, Adelaide, South Australia
Robert J Fraser, Discipline of Medicine, University of Adelaide and Investigation and Procedures Unit, Repatriation General Hospital, Adelaide, South Australia
Laura K Bryant, Investigation and Procedures Unit, Repatriation General Hospital, Adelaide, South Australia
Carly Burgstad, Nam Q Nguyen, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, South Australia
Correspondence to: Dr. Adam Deane, Intensive Care Unit, Royal Adelaide Hospital, North Terrace, Adelaide 5000, Australia. adam.deane@adelaide.edu.au
Telephone: +61-4-31967560 **Fax:** +61-8-82225885
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http://www.wjgnet.com/1007-9327/13/3909.asp

Abstract

Malnutrition is associated with poor outcomes in critically ill patients. Although nutritional support is yet to be proven to improve mortality in non-malnourished critically ill patients, early enteral feeding is considered best practice. However, enteral feeding is often limited by delayed gastric emptying. The best method to clinically identify delayed gastric emptying and feed intolerance is unclear. Gastric residual volume (GRV) measured at the bedside is widely used as a surrogate marker for gastric emptying, but the value of GRV measurement has recently been disputed. While the mechanisms underlying delayed gastric emptying require further investigation, recent research has given a better appreciation of the pathophysiology. A number of pharmacological strategies are available to improve the success of feeding. Recent data suggest a combination of intravenous metoclopramide and erythromycin to be the most successful treatment, but novel drug therapies should be explored. Simpler methods to access the duodenum and more distal small bowel for feed delivery are also under investigation. This review summarises current understanding of the factors responsible for, and mechanisms underlying feed intolerance in critical illness, together with the evidence for current practices. Areas requiring further research are also highlighted.

Key words: Critical illness; Enteral nutrition; Gastric emptying; Gastric motility; Gastrointestinal hormones; Metoclopramide; Erythromycin; Prokinetic therapy

INTRODUCTION

Malnutrition in general ward patients is associated with a prolonged length of stay[1], and increased infective complications[2,3]. Evidence that nutritional support of critically ill patients results in improved outcome is, however, limited. Descriptive studies indicate that underfeeding in the critically ill may be associated with an inability to wean from mechanical ventilation[4] and an increase in complications, particularly infections[5]. It is not clear whether these effects are causal or relate to an inability to achieve nutritional goals in patients with increased illness severity. However, severe underfeeding (less than 25% of requirements), increases the risk of nosocomial blood stream infections independent of illness severity[6]. In addition, the implementation of an algorithm to improve nutritional delivery in intensive care showed that this approach not only improved the provision of nutrition, but was also associated with a decreased hospital length of stay and a trend to decreased hospital mortality[7]. Despite the lack of unequivocal benefit on mortality, nutritional support is an accepted standard of care.

All of the feeding approaches used in the critically ill are associated with potential complications. Enteral nutrition, usually *via* a nasogastric tube, may lead to gastro-oesophageal reflux, with both overt and micro pulmonary aspiration, which potentially increases the risk of nosocomial pneumonia[8,9]. Total parenteral nutrition (TPN) on the other hand is associated with complications due to the insertion and presence of a central line, sepsis, increased cost and possible bacterial translocation across an atrophic gut mucosa. While TPN readily provides full nutritional support, enteral nutrition is less successful and only 50% of patients' nutritional goals are met using the enteral route of nutrient delivery[6,10-12]. Inability to achieve an enteral feeding target is commonly due to cessation of feeds, with the decision to stop mostly due to delayed gastric emptying. In clinical practice this diagnosis is based on large gastric residual volumes (GRV)[11], despite a paucity of evidence to support this decision making process. The accuracy of GRV estimation and its use in