PYLORIC MOTOR FUNCTION IN THE CONTROL OF GASTRIC EMPTYING.

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by

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ABSTRACT

The role of the pylorus in the control of gastric emptying remains poorly defined. This thesis examines the relationship between pyloric motor function and gastric emptying of liquids and digestible solids in a pig model.

In unsedated pigs antral, pyloric and duodenal pressures were recorded with a sleeve sensor and multiple perfused side holes, positioned with dual point trans-mucosal potential difference measurements. Gastric emptying was measured by drainage of the proximal duodenum through a Thomas cannula.

In 6 pigs, motor activity of the pylorus and antrum was stimulated by ingestion of solid and liquid meals and modulated by infusion of differing contents into the duodenum. Duodenal infusion of saline was associated with antro-pyloric pressure waves (APW) and rapid emptying of an ingested radio-labelled liquid. Duodenal infusions of dextrose, fatty acid, amino acids and hyperosmolar solutions were associated with stimulation of isolated pyloric pressure waves (IPPW), suppression of APW and slowing of liquid gastric emptying. Distension of the duodenum produced similar effects.

Clearly defined episodes of pulsatile flow produced slightly more than half of the total liquid emptying that occurred. This pulsatile flow was intimately associated in time with APW.

In 6 pigs with pylorectomy, liquid emptying was unretarded by duodenal nutrient or hyperosmolar solutions. Pylorus excised animals emptied more of a radio-labelled digestible solid than control animals, but the proportion of particle sizes that emptied did not alter.

The role of ascending duodenal intramural nerves was investigated by duodenal transection. In 6 transection animals, both duodenal nutrient and hyperosmolar solutions and duodenal distension failed to stimulate IPPW. Liquid emptying was significantly more rapid in transection animals than control animals during duodenal nutrient and osmolar stimulation, but was unaltered during duodenal distension.

In a further series of experiments, the motor effects of the proximal stomach were minimised by a water barostat. With the gastroduodenal pressure gradient positive, duodenal dextrose infusion stimulated IPPW and retarded transpyloric flow. In pylorus excised animals, flow was unretarded.

The pylorus has a major role in the control of gastric emptying, both as a component of an antro-pyloric peristaltic pump and as a resistor to transpyloric flow. By contrast the pylorus is unimportant in determining the size of solid food particles emptied from the stomach. Ascending duodenal intramural nerves are one major pathway of feedback control of pyloric motility and gastric emptying.

DECLARATION

I declare that this thesis contains no material which has been accepted for the award of any other degree or diploma in any University and that to the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis. I further consent to the thesis being made available for photocopying and loan if applicable if accepted for the award of the degree.

PETER JOHN TREACY

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Most of all I wish to thank my wife Sue, who suffered in silence and was always highly supportive.

PREFACE

Part of the work described in this thesis has been published. These publications are listed below.

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SECTION 1

AIMS

1.1 TO DEVELOP AND APPLY ACCURATE METHODS OF MEASUREMENT OF PYLORIC MOTOR FUNCTION AND GASTRIC EMPTYING TO AN UNSEDATED LARGE ANIMAL PREPARATION

Although an array of investigations have been used in the study of pyloric motor activity, few investigators have combined intraluminal manometric techniques with precise measurements of gastric emptying. This thesis aims to answer several questions.

(i) Can existing techniques of intraluminal pyloric manometry be applied to the Kangaroo Island pig preparation?

(ii) Can pyloric motor activity be closely correlated with gastric emptying?

(iii) Is the Kangaroo Island pig a suitable model of pyloric motor function and gastric emptying?

1.2 TO USE THESE METHODS TO INVESTIGATE THE STIMULATION OF PYLORIC MOTILITY

Stimulation of pyloric motor activity may be through cephalic, gastric or intestinal mechanisms. Although stimulation of pyloric motility by dextrose and fat within the upper small bowel has been demonstrated, questions which have not been addressed directly include:

(i) What is the pyloric motor response to stimulation by infusion of various nutrient and hyperosmolar solutions into the duodenum, and to stimulation by duodenal distension?

(ii) Does the pylorus respond to cephalic stimuli such as the sight, smell or taste of food?

(iii) How does distension of the stomach influence pyloric motor activity?

1.3 TO APPLY THE PIG PREPARATION TO INVESTIGATE THE ROLE OF THE PYLORUS IN THE CONTROL OF GASTRIC EMPTYING OF LIQUIDS AND DIGESTIBLE SOLIDS

The role of the pylorus in the control of gastric emptying of both liquids and solids remains poorly defined. By closely correlating gastric emptying with manometry, this study aims to examine the following questions:

(i) Does the pylorus control liquid gastric emptying?

(ii) Does the pylorus influence sieving, grinding and emptying of digestible solids from the stomach?

(iii) How does loss or disablement of the pylorus influence gastric emptying?

1.4 TO INVESTIGATE THE PATHWAYS OF MEDIATION OF FEEDBACK CONTROL OF PYLORIC MOTOR FUNCTION AND GASTRIC EMPTYING

Pathways known to influence gastric motility and emptying include extrinsic nerves of the autonomic nervous system, intramural neurones of the enteric nervous system and endocrine mechanisms. Although endocrine mechanisms have not been investigated in this thesis, questions that have been addressed include:

(i) Do intramural neurones regulate pyloric motor function and gastric emptying?

(ii) How does interruption of vagal nervous pathways affect pyloric motility?

SECTION 2

INTRODUCTION

2.1 HISTORICAL PERSPECTIVE

The earliest reported description of pyloric motor function dates back to Rufus of Ephesus, in the fourth century b.c. (Shay and Gershon-Cohen 1934). Rufus is said to have described the pylorus as a doorkeeper. The word pylorus is derived from the Greek "pyle" meaning gate and "ouros" meaning warder.

Galen (130 to 210 a.d.) described the process of "facultas retentrix", or retention of food by the stomach as a whole, acting as a reservoir (Leichtenstern 1876). This notion was held until the nineteenth century when Fallopius (1822) changed the concept of facultas retentrix, by suggesting that the pylorus alone performed this function and that the muscles of the gastric wall could only help by being quiet.

The earliest reported studies of pyloric motor activity date from the seventeenth and eighteenth centuries (Wepfer 1679, Schwartz 1746, Haller 1764). These early investigators directly observed bowel motility through an abdominal incision, in conscious animals. More recently, bowel motility has been directly observed through a surgically constructed glass or celluloid abdominal window (Hukuhara et al 1936), or through skin and peritoneum, the muscle and fascia having been removed (Alvarez 1968).

By the nineteenth century traumatic gastric fistulas were utilised in the study of pyloric motor function (Helm 1801, Beaumont 1833, Quincke 1889, Hirsch 1893). The most famous account was by Beaumont. Beaumont accurately reported a grinding and sieving function of the pylorus: "the crude food excites the contractile power of the pylorus so as to prevent its passage into the duodenum, while the thinner chymified portion is pressed through the valve into the intestine" (Beaumont 1833).

The in vitro preparation to study isolated segments of the gastro-intestinal tract, maintained in a tank of oxygenated Locke solution, was first developed in 1854 (Haffter 1854). The terms "antral systole" and "peristole" were first coined in 1885, from observations of an in vitro canine stomach, to describe propagated rings of contractions (Hofmeister and Schutz 1885).

Since the start of the twentieth century, knowledge of pyloric motor function has progressed in pace with advances of technology to measure and record pyloric motor function. In 1898 Cannon applied radiology to follow the passage of bismuth through the stomach of a cat (Cannon 1898). Cannon later concluded that the stomach consists of two physiologically distinct parts, the fundus "an active reservoir pressing its contents little by little as the churning mechanisms of the pyloric end is ready to receive them" (Cannon 1911). The development and application of rapid serial radiography in 1909 enabled a semi-quantitation of retropulsion during the "terminal antral contraction" (Kastle et al 1909).

Intraluminal balloons were first applied to the measurement of gastric motility in 1882 (Morat 1883). In 1919 Luckhardt combined radiology with intraluminal balloon sensors, to demonstrate a pressure rise associated with the antral peristaltic contractions (Luckhardt et al 1919). The first recordings of the myoelectric activity of the gastro-intestinal tract were in 1907 (Marimon 1907). It was not until 1916 that technology was available to demonstrate the rapid electrical activities of the action potential (Bozler 1916). A causal relationship between action potentials and mechanical contraction was confirmed in 1917 (Ambache 1917).

There have been numerous changes of opinion as to the role of the pylorus in the control of gastric emptying. The ancient Greeks ascribed the pylorus as the gatekeeper of the stomach (Leichtenstern 1876). The work of Beaumont down played the role of the pylorus, by implying that the pylorus behaved merely as the terminal segment of the antrum (Beaumont 1833). Cannon reversed this view and once again suggested that the pylorus was the major regulator of transpyloric flow, the "gatekeeper" (Cannon 1911). From the early 1920's (Alvarez 1935) until the late 1970's (Kelly 1981), numerous studies, principally with intraluminal balloon sensors in combination with radiological imaging of flow of barium, implied a minor role for the pylorus, especially in the control of liquid gastric emptying (Kelly 1980). Throughout this era, the pylorus was once again believed to function only as the terminal segment of the antrum (Thomas 1957, Kelly 1981, Meyer 1987). This concept was upheld partly due to the inabilities of accurate pyloric measurement (Heddle et al 1988b) and partly due to a lack of understanding that adequate stimulation is necessary to demonstrate independent pyloric motor activity (White et al 1983, Heddle et al 1988c).

Opinion about the role of the pylorus is changing again, partly as a result of studies upon isolated strips of muscle from the pylorus, that demonstrated unique motor responses of the pylorus (Golenhofen et al 1980, Schulze-Delrieu and Shirazi 1983). These studies suggest that the pylorus may behave as an independent motor structure. With the recent application of appropriate manometric techniques (Heddle et al 1988b), it has been demonstrated that some motor patterns of the pylorus are distinctly different from those of the antrum. It is now well established that the pylorus can behave both as the terminal segment of the antrum (Kelly 1980) and also as an independently contracting structure (White et al 1983, Houghton et al 1988a, Heddle et al 1988a, 1988b, 1988c). However the relationship between each pattern of pyloric motility and gastric emptying has not been precisely defined (Meyer 1987). This thesis aims to define the role of each pattern of pyloric motility in the control of gastric emptying.

2.2 MEASUREMENT OF PYLORIC MOTOR FUNCTION

A variety of techniques have been used to measure pyloric motor function, with varying success. The characteristics of each recording technique dictate the type of information obtained. The swings of opinion as to the role of the pylorus in the control of gastric emptying (Section 2.1) have resulted in part from the inability of each technique to accurately measure pyloric motor function. This section reviews the characteristics and limitations of several useful techniques available to measure and record pyloric motor function.

Intraluminal Pressure Sensors

The intraluminal placement of a sensor may alter gut function, either by exerting a direct action on the mucosa and bowel locally, or by inducing pain and distress during passage of the tube. Several studies have compared gastric emptying with and without intraluminal tubes. Most studies have reported no significant alterations to emptying due to the presence of a tube into the stomach (Chaudhuri et al 1975, Delin et al 1978, Harding et al 1979, Blake and McKelvey 1981) or into the duodenum (Longstreth et al 1975, Muller-Lissner et al 1982a). One study has demonstrated alteration to solid gastric emptying due to the presence of a tube pass to the terminal ileum (Read et al 1983).

Intraluminal pressure sensors that have been used to study pyloric motility include balloons and closed tubes, perfused and non-perfused open ended tubes, sleeve sensors, strain gauges and impedance electrodes.

Balloons. A variety of sizes of balloons have been used to study pyloric motility, including large air filled balloons (Quigley and Meschan 1937, Meschan and Quigley 1938), small air filled balloons in an overlapping chain (Atkinson et al 1957, Carlson et al 1966), small water filled balloons (Anderson and Grossman 1965, Brink et al 1965) and closed air filled tubes (Thomas et al 1934). The properties of each balloon sensor influences its ability to record pyloric contractions accurately. For example, a large balloon may distend the stomach, or may be sensed as a bolus, to be either retropulsed or ejected. Such movement makes continuous placement at the pylorus difficult. A long flaccid balloon or tube may theoretically avoid both displacement from the pylorus and distension of the stomach. However contraction of the narrow pylorus around a long balloon may merely expand the adjacent part of the balloon, so producing minimal or no change in balloon pressure. When large balloons are used, pressures developed are dependent to an unpredictable extent on the volume, size and shape of the balloon (Brody et al 1940, Shepherd and Diamant 1972). Finally, balloons and closed air filled tubes are limited in their ability to record accurately sustained alterations in base line pressures.

Open ended tubes. Open ended non-perfused manometric tubes, first described in 1940, were considered superior to balloons, as they focus measurement of pressure over the narrow region at the site of opening of the tube (Brody et al 1940). Both air-filled and water-filled tubes have been applied to pyloric manometry (Brody et al 1940, Atkinson et al 1957, Brink et al 1965). The recording abilities of open ended tubes have been compared with small intraluminal balloons in two papers, during pull through studies across an in vitro sphincter model (Code and Schlegel 1974, Pope 1967). In both studies, the open tipped catheters seriously under-measured pressures at the sphincter, whereas the small balloons were quite accurate.

The modification to perfuse open ended tubes was conceived in 1959 (Pert et al 1959), but was only usefully developed for accurate quantitative measurements of pressure by the late 1960's (Pope 1967, Winans and Harris 1967, Harris et al 1966). Infusion eliminated dampening of the pressure trace, due to blockage of the side hole by mucosa or bowel contents (Harris et al 1966). The system was improved in 1977 by the use of a low compliance infusion system, which provided improved fidelity recordings with substantially reduced flow rates (Arndorfer et al 1977). Continuously perfused side hole catheter assemblies have become the most widely applied method of intraluminal manometry.

As with intraluminal balloons, the characteristics of open ended tubes have limited their ability to record pyloric pressures accurately. Side holes record the contractile activity of the gut over a narrow focused region. Numerous studies using radiology (Torgersen 1942, Keet 1957, Williams 1962), stationary side hole sensors (Biancani et al 1980, White et al 1983, Reynolds et al 1984, 1985, Pandolfo et al 1979, Heddle 1988b) and pull through side hole sensors (Brink et al

1965, Isenberg and Czendes 1972, Valenzuela et al 1976, Fisher and Cohen 1973, Phaosawasdi and Fisher 1982) have documented that the pylorus can contract over a very narrow zone (Section 2.4). A focal side hole recording from the narrow mobile pylorus may be readily displaced, resulting in significant and variable under-measurement of pyloric contractions (Heddle et al 1988b).

For accurate pyloric manometry, is necessary not only to position the side hole precisely at the narrow and highly mobile region of maximal pyloric pressure, but also to maintain position of that side hole and to confirm its position throughout a study. Techniques used to position a side hole include recognition of the gross anatomy of the distal pyloric loop, by fluoroscopic imaging (Pandolfo et al 1979), feeling for the thickened muscle during laparotomy (Seide & Ritman 1984, Kumar et al 1987) and endoscopy (Aste et al 1979). Endoscopy is unsuitable, as lumen occlusion associated with an antral and pyloric peristaltic wave obscures the view of any sensor at the pylorus at the very moment when displacement is most likely to occur. Other studies have located the gastroduodenal junction by recognition of a zone of high pressure (Bertiger et al 1987, White et al 1981, 1983) or by recognition of antral and duodenal motility patterns (Mearin et al 1986). As either the antrum or duodenum may be manometrically inactive for long periods of time (Houghton et al 1988b, Heddle et al 1988b, 1988c), localisations of the pylorus using recognition of motility patterns is not sufficiently reliable. Others have located the gastroduodenal junction by measurement of trans-mucosal potential difference across the gastro-duodenal junction (White et al 1981, 1983), there being a sharp gradient of trans-mucosal potential difference across the gastroduodenal junction (Anderson and Grossman 1965, Blackwood 1969). Measurement of trans-mucosal potential difference, at either side of the sensor, provides a continuous record of the relation of the sensor to the gastro-duodenal junction (White et al 1981, 1983). By this method, any episodes of displacement of the sensor from the junction can be immediately recognised and the recording assembly repositioned. Segments of the recording in which the assembly is not correctly positioned can be excluded with confidence.

Once a side hole has been correctly positioned, location at the pylorus must be maintained. Movement of the pylorus relative to the point of fixation of the manometric assembly (be it nose, mouth or intestinal cannula) may occur, as during gastric accommodation and gastric emptying (Dodds et al 1974, Heddle et al 1988b), when the dimensions of the stomach alter. To overcome such movement, side holes have been maintained at the pylorus by suction of the assembly to the mucosal surface (Aste et al 1979, Pandolfo et al 1979) and by pinning the manometric assembly to gut wall, in whole organ preparations (Bertiger et al 1987) or anaesthetised animals during laparotomy (Behar et al 1979, Biancani et al 1981, Reynolds et al 1984, 1985).

The problems of side hole misplacement or displacement from the narrow pylorus have been overcome by the use of a several closely spaced focal sensors, so that pressures are recorded over a length that can not be readily displaced from the pylorus. Both multiple closely spaced side holes (Heddle 1988b, Biancani et al 1981, Bertiger et al 1987) and a chain of overlapping balloons (Atkinson et al 1957, Carlson et al 1966,) have been positioned across the pylorus. The distance between sensors must not be greater than the manometric width of the pylorus, otherwise the manometrically active region of the pylorus may lie between the sensors. When combined with measurement of the trans-mucosal potential difference at either end of the chain of sensors, accurate measurement of pyloric motility, with continuous verification of the sensor position, becomes possible.

With the recognition that displacement occurs readily, the technique of <u>side hole pull through</u> was applied to pyloric manometry. Pull through techniques readily detect a narrow zone of sustained high pressure. This technique is very limited in value when applied to the pylorus if the pylorus is undergoing intermittent contractions, as during passage of the assembly the side hole may lie at the pylorus only during the interval between phasic contractions. Pull through studies may also fail to record pyloric contractions if there is a latency between the application of a stimulus and the pyloric response, or if the pyloric response to the stimulus is short lived. For example, the side hole may lie at the pylorus either before onset of the pyloric response, or after the pyloric response has ended. Pull through studies have been further criticised in that during withdrawal of the manometric assembly, the sharp angulation of the descending duodenum and pyloric canal may distort the assembly to produce spurious elevations of pressure (Kaye et al 1976). Such distortions may be accentuated if the pylorus is contracting asymmetrically. Repeated pull through studies can be uncomfortable and very time consuming if each pull through provides only short intervals of accurate recording. Finally, pull through studies may not produce even motion of the sensor through the pylorus, thus providing variable information.

Perfused Sleeve Sensor. The perfused sleeve sensor was developed and validated in 1976 for measurement of lower oesophageal sphincter pressures (Dent 1976) and has been applied successfully to pyloric manometry (Houghton et al 1988a, 1988b, Heddle et al 1988a, 1988b, 1988c, Maddern et al 1984, Tougas et al 1987). Since the sleeve indicates the highest pressure generated at any point along its length, accurate continuous recordings of pyloric motility have been possible despite minor movement of the sleeve at the pylorus. As the sleeve sensor extends into the antrum and duodenum, if it is used alone it is unable to discriminate among contractions of the duodenum, antrum and pylorus. When combined with side holes at either end of the sleeve, this problem is overcome (Houghton et al 1988a, 1988b, Heddle et al 1988a, 1988b, 1988c).

Impedance electrodes. With the recognition that sensors that record over a short length may fail to record motility of the narrow and highly mobile pylorus, Eyre-Brook et al (1983) developed a system of impedance electrodes, that monitor closure of the gut lumen over a 6 millimetre length. Pyloric closure was registered only when mucosa was in contact with the two pairs of wire electrodes. No estimate of the force of closure could be obtained. Radiographic studies have documented that the force of closure of the pylorus varies widely (Keet 1957, Williams 1962). The force of pyloric closure may relate to the degree of resistance offered by the pylorus to transpyloric flow (Meyer 1987). In their study, position of the electrodes was confirmed by endoscopic visualization. Impedance electrodes are expensive and fragile, and only provide a quantitative record of pyloric closure. Probably for these reasons impedance electrodes have not been used by other investigators.

Intraluminal pressure transducers incorporated into an assembly provide an alternative to the perfused side hole systems. Although intraluminal transducers provide frequency and dynamic responses superior to those of perfused side holes, this technical superiority is irrelevant to measurement of the relatively slow changes of pyloric pressure. Intraluminal transducers are particularly useful for ambulatory monitoring, or when posture is varied, since their baseline is unaffected by posture change. Limitations include high cost and fragility. Strain gauges are also difficult to mount close together.

Intraluminal recordings of myoelectric activity of the gut wall have been applied to the study of pyloric motility, with minimal success. Electrodes can be positioned at endoscopy (Akasaka et al 1975). It is probably not possible to position a fine electrode precisely at the inner ring of the distal pyloric loop during endoscopy and assume no subsequent movement. Electrode position has been maintained with suction (Couturier et al 1973, Waterfall et al 1973, Weisbrodt et al 1974, Monges & Salducci 1970).

Endoscopy has been utilized by a few investigators to study pyloric contraction (Aste et al 1979, Eyre-Brook et al 1983, Munk et al 1978). Narrowing of the pyloric canal and orifice is visualised directly, but only when the antral lumen is patent. As with all intubation techniques, the presence of a large diameter tube passed orally, with or without air insufflation and sedation, may profoundly alter pyloric motor function. Even with videotape recordings, the technique is at best semi-quantitative. Only short periods of observation are possible. Endoscopy can only be reliably performed during fasting, which eliminates any measure of the fed motor patterns. Little, apart from observation of duodeno-gastric bile reflux, has been gained with the use of the endoscope for the evaluation of pyloric motility.

Extraluminal Recording Techniques (serosally mounted sensors)

Serosally mounted sensors have only been used for human studies during operations, with removal of the sensors either before completion of the operation or at the time of removal of any wound drains (Duthie et al 1971, Schang et al 1974, Stoddard et al 1978). Both myoelectric and mechanical activity can be recorded. Sensors used include serosal strain gauges, displacement transducers and myoelectrodes. Serosally mounted sensors avoid the stimulation of mucosal receptors and interference with luminal flow. Disadvantages include the need for operative placement, the danger of erosion through the gut wall and complications due to intra-abdominal wires, such as entanglement of loops of bowel or infection tracking along the wires.

Serosally implanted strain gauges were first developed in 1963 (Jacoby et al 1963) and have since been made substantially smaller and more reliable (Bass and Wiley 1972, Cowles et al 1978). The gauges record changes in the distance between two fixation points in the bowel wall at the site of the sensor and thus isotonic muscle contraction. By resistance to movement, they also measure tension of the bowel wall. The sensors are attached to the gut, oriented either longitudinally to record longitudinal muscle contractions, or transversely to record contractions of the inner circular muscle layer.

Strain gauges record contractions over the width of the device, which may be wider than the width of the narrow pylorus. Thus they may not be able to discriminate between contractions of the narrow distal pyloric loop, and those of the adjacent proximal loop. A further limitation is the significant risk of baseline or amplitude drift, which cannot be corrected on in vivo preparations (You and Chey 1984). Thus precise recordings of baseline pressure or tone are difficult. In a comparison of strain gauges and intraluminal perfused side holes, You and Chey (1984) found that over 50% of contractions recorded by the strain gauges were not recorded by the side holes. This probably reflects the fact that side holes only record pressure rises, particularly those due to lumen-occluding contractions, whereas strain gauges record all narrowings of the bowel, whether or not they produce a pressure rise.

Serosally applied induction coils monitor the distance between two sensors, and thus act as displacement transducers.

Pyloric closure can be recognised by calibration. As with strain gauges, problems include difficulty of exact placement of the detectors and difficulties of calibration. Variable alterations of the gut wall thickness, such as during puckering of the mucosa at the pylorus to form a plug (Keet 1957, Williams 1962), or with pyloric shortening during pyloric closure (Keet 1957), are not registered. Closure of the pyloric lumen in these situations may be recorded as non-closure. Ehrlein (1988) claims that alterations in the thickness of the pylorus are minimal and that it is safe to assume the external diameter is a reliable indicator of internal diameter.

Serosal myoelectrodes. The electrical activity of the intestinal smooth muscle can be measured by implanted electrodes. Advantages include the collection of information about non-contracting as well as contracting muscle and the ability to study many sites simultaneously. Disadvantages include the difficulty of precise electrode placement at the pylorus, the potentials of electrode movement with contractions, loss of electrode contact and the hazards of erosion into the gut lumen if used for long periods of time.

2.3 ANATOMICAL MECHANISMS OF THE PYLORUS

Gross Anatomy

The ANTRUM is defined as that portion of the stomach lying between the incisura angularis and the duodenum. The antrum is divided into the PYLORIC ANTRUM or VESTIBULE, which narrows into the PYLORIC CANAL or SEGMENT, more distally (Figure 2.1). The distal end of the distal pyloric loop is termed the PYLORIC ORIFICE.

The pylorus is well defined in most species by its conspicuous, thick circular muscle layer forming two thirds of the thickness of the wall of the pylorus (Rudinger 1879, Torgersen 1942). This muscle thickening is formed mainly by the circular muscle layer and probably also by helical fibres, which are longitudinal in the stomach and more circularly arranged around the pyloric orifice (Didio and Andersson 1968). Although often simply viewed as a single ring of muscle, the sphincter component of the pylorus is organized into two distinct loops (Torgersen 1942), (Figure 2.2). The two loops are most readily defined on the greater curvature aspect, where they form a distinct angle. On the lesser curvature aspect the two loops are fused into one muscle knot, the PYLORIC TORUS. In the pig, in contrast to man, the torus is flat and consists predominantly of connective tissue, mucosa and submucosal fat (Torgersen 1942).

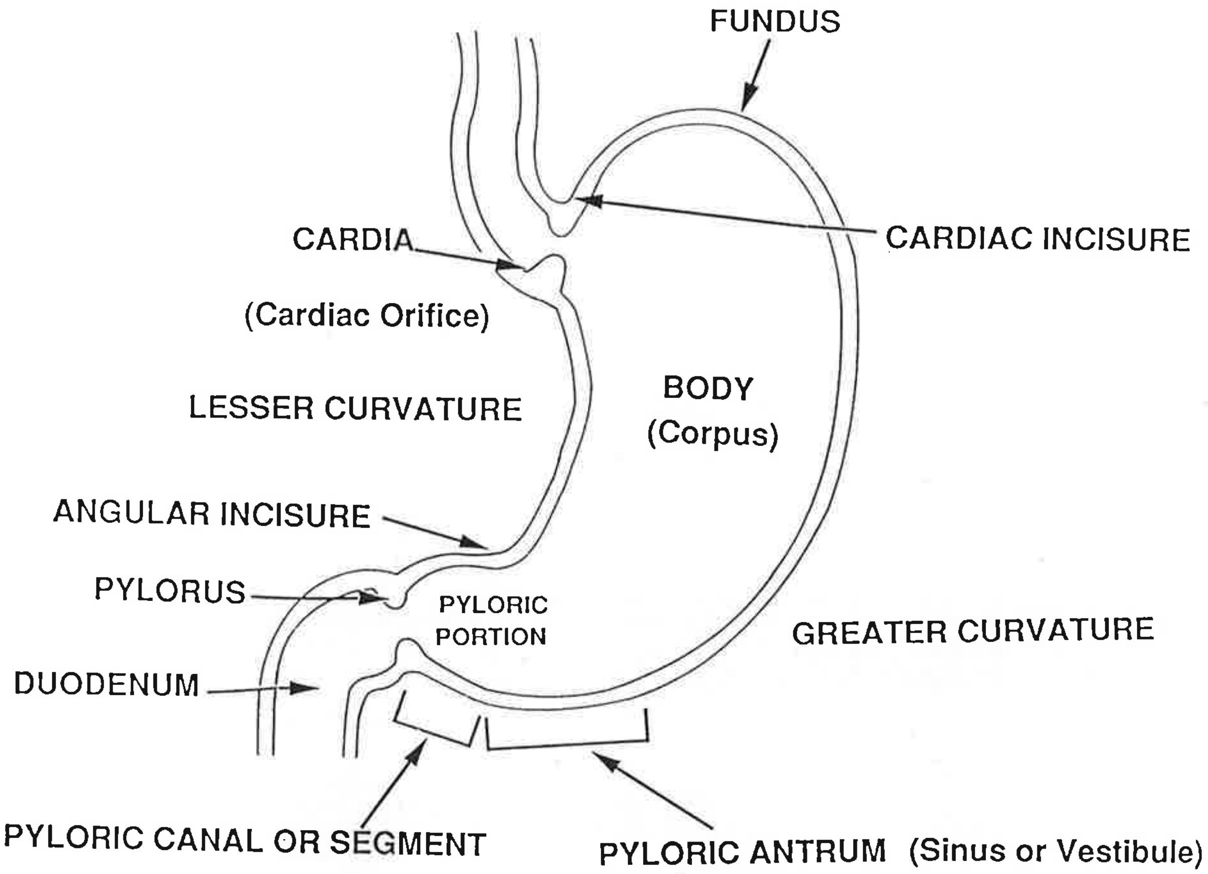


Figure 2.1: Gross anatomy of the pyloric region.

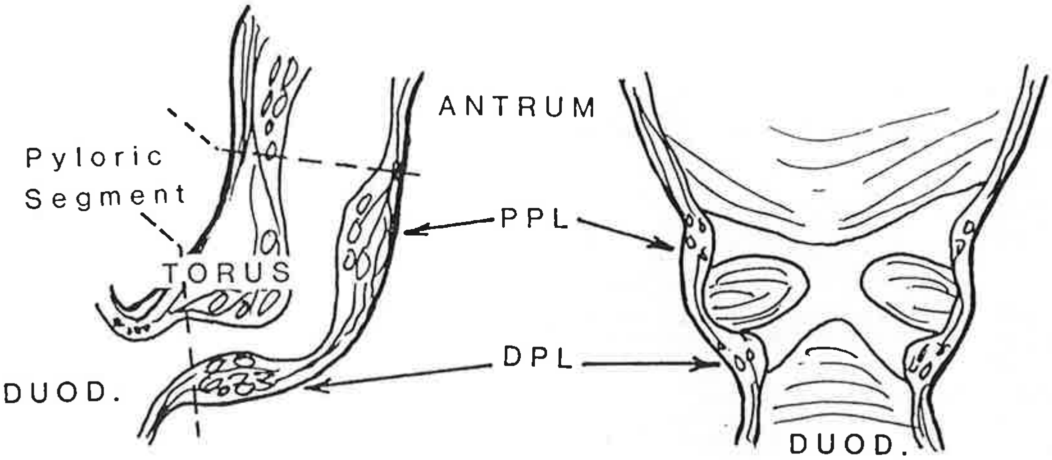


Figure 2.2: Muscular anatomy of the pylorus.

Muscular Components

The proximal loop is a broad muscle band that in many species is not much thicker than the circular muscle of the antrum. The distal pyloric muscle loop is a very thick muscle band that protrudes into the lumen of the gastroduodenal junction (Figure 2.2). The lumen of the segment between the two muscle loops is commonly referred to as the PYLORIC CANAL. Variation between species in the arrangement of the muscle fibres at the pylorus does exist, but the presence of proximal and distal muscle loops seems constant in all mammals with a simple stomach. Torgersen (1942) demonstrated that in most animals, the distal pyloric loop is the more prominent bundle.

The outer longitudinal muscle fibres form one third of the wall. These fibres are intertwined with the circular muscle fibres of the antrum, especially over the greater curvature side and lateral walls where they dip into the connective tissue of the pyloric canal (Horton 1928, Muller 1963, Torgersen 1942). Only a few superficial fibres on the lesser curvature side are described as connecting with the longitudinal fibres of the duodenum (Torgersen 1942). A thin fibrous septum of connective tissue separates and has been said to insulate the musculature of the pylorus from the duodenum (Bass et al 1961, Code 1970, Cunningham 1908, Horton 1928, Cai and Gabella 1984). Belding and Kernohan (1953) concluded that the longitudinal muscle fibres which are external to and penetrate into the circular muscle layer form a dilator component of the pylorus.

Mucosa

The gastro-duodenal mucosal junction is usually at the pyloric orifice, but may protrude into the duodenum. The mucosa is tightly adherent to the underlying muscle at the pyloric orifice, but is loosely attached more proximally (Code 1970, Edwards and Rowland 1968, Williams 1962). With narrowing and shortening of the pyloric canal during muscle contraction, the mucosa of the canal is thrown up into folds (Keet 1957) which fill the pyloric canal probably as a plug (Biancani et al 1980, Schulze-Delrieu et al 1984). Williams (1962) has suggested that the muscularis mucosae acts to condense the mucosa into a plug. During closure of the pylorus, the torus fits snugly into the groove between the two pyloric loops on the greater curvature aspect, to form a secure water tight seal between the stomach and the duodenum (Biancani et al 1980, Keet 1957, Williams 1962). Pyloric closure has been visualised radiographically as a "kinking" of the gastroduodenal junction around the torus (Schulze-Delrieu et al 1984).

Nerve Supply

Nerve supply to the gastroduodenal region includes the extrinsic innervation of the sympathetic and parasympathetic nervous system, afferent fibres travelling with these nerves and intrinsic neurones of the enteric nervous system. Sympathetic fibres pass alongside and within the wall of blood vessels to the pyloric region. In addition, some adrenergic fibres from the stellate ganglia pass within the abdominal vagus nerve (Ahlman et al 1979).

Parasympathetic input reaches the pylorus either by way of continuation of the nerves of Laterjet along the lesser curvature, via a branch descending to the pylorus from the hepatic division of the anterior vagal trunk or as an isolated pyloric nerve of McCrea (McCrea 1924, Skandalakis et al 1986). Afferent fibres pass along the same vagal pathways to spinal root ganglia (Roman and Gonella 1987). Afferent fibres greatly outnumber efferent fibres in the vagus nerves (Roman and Gonella 1987).

The stomach and in particular the pylorus is richly innervated by intrinsic nerves, that contains various chemical messengers such as hormones, paracrines and autacoids (Wood 1984). The intrinsic nerve plexuses of the gut, forming the Enteric Nervous System, acts as a semi-autonomous control system (Andrews et al 1980b, Roman and Gonella 1987). Wood (1984) has likened the relationship between the Enteric Nervous System and the Central Nervous System to that between an intelligent computer and a mainframe computer. Nerve cell bodies and fibres are found in the various plexuses (Gabella 1972, Schofield 1968). Extensive interconnections exist between the two main plexuses of the gut, the myenteric and submucosal plexuses, to extrinsic nerves and to the muscle cell. Evidence exists for a specialised function of the pylorus, as both the submucosal and myenteric plexuses are in greater abundance at the distal pyloric loop than elsewhere in the gastroduodenal region (Edin 1980, Irwin 1931, Wattchow et al 1987). This network of neural elements passes uninterrupted across the gastroduodenal junction from antrum to duodenum (Irwin 1931).

2.4 PATTERNS OF PYLORIC MOTILITY

Motor activity of the pylorus is usually described in terms of co-ordination of pyloric contractions with the antrum and/or the duodenum. The literature contains descriptions of two fundamental patterns of pyloric motility: contraction of the pylorus with the antrum and/or duodenum and contractions of the pylorus in the absence of both antral and duodenal contractions (isolated or localised pyloric contractions). This section will review the evidence for and against each pattern of pyloric motility.

(i) ISOLATED PYLORIC CONTRACTIONS

Isolated pyloric contractions, or contractions of the pylorus in the absence of both antral and duodenal contractions, have been reported as both sustained elevations of baseline pressure, or tonic contractions and phasic contractions. The evidence for isolated pyloric contractions is significant.

Heddle et al (1988b) placed an array of closely spaced stationary side holes across the gastro-duodenal junction in humans, positioned by measurement of the trans-mucosal potential difference at either end of the array. By this technique, both pressure waves localised to the pylorus alone, or isolated pyloric pressure waves and pyloric tone were demonstrated, following nutrient stimulation of upper small bowel receptors. These isolated pyloric pressure waves were localised to a very narrow region, of less than 9 millimetre length. Several other human studies have similarly demonstrated isolated pyloric pressure waves with stationary side hole manometry (White et al 1981, 1983, Pandolfo et al 1979, Heddle et al 1988b). It was fortunate during the studies by White et al (1981, 1983) and Pandolfo et al (1979) that the single side hole used to record pyloric contractions lay at least some of the time at the narrow pyloric contractile zone. Isolated pyloric pressure waves have also been recorded in animals, with an array of stationary side holes (Biancani et al 1981, Reynolds et al 1984, 1985). In each of these study the contractile zone of the pylorus was located by side hole pull through, then correct manometric assembly maintained by pinning the array in position. The methodologies of each of the above studies appear reliable. It is of note that isolated pyloric pressure waves were demonstrated only in response to intestinal stimulation by nutrient or hyperosmolar solutions.

Several studies utilising the <u>sleeve sensor</u> (Dent 1976) positioned at the pylorus have confirmed the findings of these stationary side hole studies, that the pylorus, when stimulated, undergoes isolated pressure waves and tone (Houghton et al 1988a, 1988b, Heddle et al 1988a, 1988b, 1988c, Allescher et al 1988, Dooley and Valenzuela 1988).

A number of <u>side hole pull through studies</u> in animals (Brink et al 1965, Isenberg and Czendes 1972) and man (Valenzuela et al 1976, Fisher and Cohen 1973, Phaosawasdi and Fisher 1982) have reported a zone of localised tonic high pressure at the pylorus, which was increased following stimulation by either duodenal intraluminal acid (Fisher and Cohen 1973, Brink et al 1965, Valenzuela et al 1976), nutrients (Fisher and Cohen 1973) or following intravenous injection of hormones (Isenberg and Csendes 1972, Phaosawasdi and Fisher 1982). In none of these studies were pyloric pressure waves specifically quantified, probably because pull through studies readily miss such events (Section 2.2). It cannot be excluded that distortion of the manometric assembly during pull through around the sharply angled gastro-duodenal junction falsely simulated a high pressure zone. However isolated pyloric pressure waves were recorded, even though not quantified, as shown on the manometric traces in some of these studies (Isenberg and Csendes 1972, Brink et al 1965, Phaosawasdi and Fisher 1982).

Bertiger et al (1987) demonstrated pyloric pressure waves and tone, with an in vitro whole organ preparation from cats. The manometric technique used appears reliable. A narrow zone of high pressure at the pylorus was located by side hole pull through studies. Manometric studies were then repeated with 3 side holes, located at 2 millimetre intervals, secured at the pylorus. Unfortunately pyloric pressures were not referenced to antral or duodenal pressures, but to pyloric pressures at times when contractions were not stimulated. Thus it is not possible to determine from the data presented whether the pyloric response was isolated to the pylorus alone, or included the antrum and duodenum.

Schulze-Delrieu and Shirazi (1983) reported greater pyloric tone in response to electrical stimulation, from muscle strips from the distal pyloric loop, when compared to the proximal pyloric loop, the antrum or the duodenum. However this study gave little indication of the contribution made by muscular activity. The thickness of the muscle wall rather than generation of tone by individual muscle cells may have accounted for the higher distal pyloric loop muscle tension. The most interesting finding from this study was that the distal pyloric loop responded to electrical stimulation by a definite relaxation, whereas muscle strips from the rest of the gastroduodenal region did not. Golenhofen et al (1980) similarly demonstrated different responses of the distal pyloric loop to a variety of electrical and chemical stimuli, when compared to the fundus, antrum or duodenum. Anuras et al (1974) demonstrated relaxation of pyloric muscle strips in response to electrical stimulation. This relaxation was blocked in opossums by tetrodotoxin, which blocks action potentials of nerves but not of smooth muscle. Anuras et al concluded a non-adrenergic inhibitory innervation of the pylorus, in contrast to the other areas of the stomach. However Anuras et al demonstrated significant variations of response of pyloric muscle between species (Anuras et al 1974). The unique response of the distal pyloric loop demonstrated in each of these studies, to the variety of stimuli, suggested a unique motor function of the distal pyloric loop.

Two recent studies have provided data that suggests that different regions of the distal pyloric loop may fulfil different functions: the outer margin of the circular muscle layer may function primarily for the generation of phasic contractions whereas the inner layer of the circular muscle may function primarily for the generation of pyloric tone (Ludtke et al 1989, Sanders and Vogalis 1989). Thus it is essential in studies of muscle strips to define precisely the site of origin of the tissue. Ludtke et al (1989) reported a strong stimulation of phasic activity of muscle taken from the outer layer of the distal pyloric loop, with a transition to tonic activity in the inner layer of the pyloric loop, in response to stimulation by the hormone motilin. Sanders and Vogalis (1989) investigated the myoelectric activity of the canine gastroduodenal junction using cross-sectional muscle preparations and intracellular recording techniques. They demonstrated that gastric slow waves pace all the longitudinal muscle layer of the pylorus, but only the myenteric portions of the circular muscular layer and not the majority of cells within the circular muscle layer of the pylorus. Within the pylorus slow waves decayed in amplitude with distance from the myenteric border of the circular muscle layer; the majority of pyloric circular cells were normally electrically quiescent. It is known that phasic contractions are intimately associated with gastric slow waves, by way of action potentials superimposed upon gastric slow waves, whereas tonic contractions are not closely connected with gastric slow waves (Meyer 1987).

Pyloric tone has been reported in several studies of conscious animals with serosal strain gauges and induction coils (Furukawa 1987, Ehrlein 1988, Keinke and Ehrlein 1983, Mir et al 1979, Telford et al 1979). The methodologies used in these studies are probably unreliable. Both strain gauges and induction coils do not detect pressures, but rather narrowing of the serosal diameter at the pyloric canal. Narrowing of the pyloric canal, which the authors have interpreted as tone, may not be active muscle contractions, but evacuation of luminal contents, reduced puckering of a mucosal plug, or a number of other possibilities. Further, sensors must be placed closer than the 5 centimetre spacing used in the studies by Ehrlein et al (1988) and Keinke et al (1983), to demonstrate contractions localised to the pylorus alone. Probably the most interesting result from all these studies was that the pyloric region responded uniquely to nerve stimulation (Mir et al 1979, Telford et al 1979), atropine (Mir et al 1979, Telford et al 1979), intraluminal nutrients (Keinke and Ehrlein 1983, Ehrlein 1988) and hormones (Telford et al 1979). These findings imply a uniquely functioning pylorus.

The evidence against isolated pyloric contractions is less substantial. A number of stationary side hole studies have reported no localised pyloric activity, either tonic or phasic (Aste et al 1979, White et al 1981, Mearin et al 1987b). Similarly several pull through side hole studies have also not demonstrated pyloric tone (Aste et al 1979, McShane et al 1980, Kaye et al 1976, Atkinson et al 1957). These studies were all performed during fasting, without pyloric stimulation. Possibly with adequate stimulation of pyloric activity isolated pyloric pressure waves would have been recorded. One side hole pull through through study of humans did provide intestinal stimulation, by way of hydrochloric acid and fat at the duodenum (Kaye et al 1976). There are a number of reasons why no pyloric tone was recorded in this study: inadequate stimulation of intestinal receptors, insufficient time between time of stimulation and measurement of response or even technical inability to measure the very small pyloric tonic pressures that might have been generated (Section 2.2). Clearly failure to demonstrate isolated pyloric pressure waves does not exclude their occurrence.

Taken as a whole, the conclusion must be that the stimulated pylorus can undergo isolated phasic and tonic contractions, but that the unstimulated pylorus does not. The functional significance of this pyloric motor activity, in terms of control of transpyloric flow, has not been fully determined.

(ii) CONTRACTION OF THE PYLORUS WITH THE ANTRUM AND/OR DUODENUM

Co-ordination of Antral with Pyloric Contractions

The timing of onset of antral contractions with the onset of pyloric contractions has been controversial in the past. In 1898 Cannon studied pyloric motility in cats with radiology (Cannon 1898). He reported that the pylorus remained closed most of the time and opened only with the approach of an antral peristaltic contraction. In 1922 Wheelon and Thomas positioned balloons at the antrum, pylorus and duodenum in humans and again reported that the pylorus remained relaxed with the approach of an antral peristaltic wave, followed by "(pyloric) sphincter contractions (that) reach their highest point at the time when the antrum is rapidly relaxing or completely relaxed" (Wheelon & Thomas 1922b). Other investigators also described relaxation of the pylorus with the approach of a gastric wave (Klein 1926). Numerous studies since, with radiology (Carlson et al 1966, Torgersen 1942, Keet 1957), endoscopy (Eyre-Brook et al 1983, Aste et al 1979), intraluminal balloons (Carlson et al 1966), side hole sensors (Fisher and Cohen 1973, White et al 1981, 1983), ultrasound (King et al 1985) and serosal strain gauges (Prove & Ehrlein 1982, Keinke & Ehrlein 1983, Keinke et al 1984) each and all have described contraction of the pylorus closely timed with antral contraction.

The simultaneous contraction of the antrum with the pylorus, the "terminal antral contraction", was first described by Kastle et al (1909) and later popularised by Carlson et al (1966). Keet (1957) proposed that the terminal antral contraction is due to the simultaneous contraction of the proximal and distal pyloric loops. However myoelectric studies have shown that contraction always commences earlier at the antrum than at the proximal pyloric loop than at the distal pyloric loop (Ehrlein et al 1980, Prove & Ehrlein 1982). As the internal diameter of the resting pylorus is smaller than of the resting antrum, lumen occlusion may occur sooner after commencement of contraction at the pylorus than at the antrum. This may produce what appears to be a simultaneous or retrograde contraction.

Co-ordination of Antro-Pyloric Contractions with Duodenal Contractions

The gastric pacemaker controls gastric contractions at an intrinsic frequency of 3 per minute in man (Kelly 1981, Meyer 1987), 5 per minute in the dog (Kelly et al 1969), 3 to 4 per minute in the cat (Biancani et al 1981) and 3.3 per minute in the pig (Ruckebusch and Bueno 1976). The intrinsic frequency of contractions of the duodenum is three to four times more rapid, approaching 11 per minute in man and 18 per minute in the dog (Meyer 1987). According to Wheelon and Thomas (1922a), Joseph and Meltzer in 1910 were the first to suggest co-ordination of contractions of the antro-pyloric segment with the duodenum. They recognised both the inherent duodenal frequency as well as the antral frequency in the duodenal contractile pattern. It was not until 1963 that new information could be gathered with the development of strain gauge transducers (Jacoby et al 1963) and their simultaneous use with electrodes implanted in dogs. It has been only recently that, with the aid of computer technology, a large amount of data could be analysed in an objective manner (Ehrlein and Heisenger 1982, Lederer et al 1983, Schuurkes et al 1984). The pattern of coordination of the distal stomach with the duodenum has been defined in many ways. Weisbrodt et al (1969) defined it as the motor gradient between antral and duodenal contractile activities. Albibi & McCallum (1983) used the term to describe the inhibition of duodenal contractile patterns during propagation of the gastric wave over the antrum. Schuurkes & Van Nueten (1984) described antro-pyloro-duodenal co-ordination descriptively, as contractions of the antro-pyloric segment linked in time to groups of 1 to 3 sequential duodenal contractions, separated by periods of relative quiescence, with the time interval between the groups of duodenal contractions reflecting the frequency of antral contractions. Most authors refer to antro-pyloro-duodenal co-ordination as the characteristic pattern emerging after the intake of food (Adam et al 1982, Allen et al 1964, Bedi and Code 1972, Ehrlein and Heisenger

1982, Johnson 1981, Reinke et al 1967, Thomas & Crider 1935).

Johnson (1990) concluded that in order to define antro-duodenal co-ordination most precisely, the word co-ordination should be qualified by several additional terms, such as normal or abnormal, integrated or disintegrated, fasting or post-prandial, and so on. Johnson defined the normal post-prandial motility pattern of the antrum and duodenum as "propagated antegrade antral contractions co-ordinated with those of the duodenal cap propelling small amounts of gastric contents into the duodenal cap" (Johnson 1990). This definition is the most useful, as it incorporates a functional component and avoids any description of the mechanisms that may produce antro-pyloro-duodenal co-ordination.

Antro-duodenal co-ordination has been recorded during fasting, but rarely and mostly during phase 2 of the migrating motor complex (Ehrlein & Heisenger 1982, Lederer et al 1983, Lewis et al 1979, Rees et al 1979a). Antro-duodenal co-ordination has been described in conscious man (Adam et al 1982, Lederer et al 1983) monkeys (Bortoff & Davis 1968), dogs (Allen et al 1964, Bedi and Code 1972, Carlson et al 1966, Ehrlein & Heisinger 1982, Reinke et al 1967, Thomas & Crider 1935, Wheelon & Thomas 1922a), cats (Bortoff & Davis 1968), rat (Pascaud et al 1978) and cattle (Ooms and Oyaert 1978). Antro-duodenal co-ordination has not been observed after induction of general anaesthesia, except following electrical stimulation of contractions (Schuurkes and Charbon 1978). In vitro, antro-duodenal co-ordination has been recorded following stimulation of contractions, in preparations from cats (Bortoff

& Davis 1968, Bortoff & Weg 1965), dogs, rhesus monkeys, baboons (Bortoff & Davis 1968) and guinea pigs (Schuurkes & Van Nueten 1984).

Co-ordination of Pyloric Contractions with Duodenal Contractions in the absence of Antral contractions

Contraction of the pylorus in time with contraction of the duodenum, in the absence of antral contraction, has been reported (Eyre-Brook et al 1984, Johnson 1981, Johnson et al 1983). The function significance of such motor activity is not known, but may relate to the prevention of duodeno-gastric reflux: duodenal contractions occurring prior to or in the absence of pyloric contractions have been reported during duodeno-gastric reflux (Ehrlein 1981, Code et al 1984).

2.5 THE PYLORUS AND LIQUID GASTRIC EMPTYING

Patterns of Liquid Gastric Emptying

Since the early 1950's, gastric emptying of liquids was most frequently described as following a simple exponential pattern, most rapidly initially, decreasing over time (Hunt and Spurrell 1951, Kelly 1981, Thomas 1957). This description implies that the rate of liquid emptying is only determined by the volume of the liquid remaining in the stomach and is not influenced by factors such as the motor activity of the pylorus. Numerous studies since have documented that liquid meals high in calories, osmolarity or acidity empty more slowly than inert meals such as normal saline (Hunt and Spurrell 1951, McHugh and Moran 1979, Thomas 1957). With a high calorie or osmolarity concentration, emptying follows a more linear pattern (McHugh and Moran 1979). For example, dextrose has been shown to empty at a calorie dependent rate of 2.1 kilocalories per minute in man (Brener et al 1983) and 0.4 kilocalories per minute in Macaca mulatta (McHugh and Moran 1979). Williams et al (1986) have suggested that most of the differences in slowing of liquid emptying occur in the first five minutes. Meyer (1987) has proposed that liquid gastric emptying follows a pattern of more rapid linear emptying initially, followed by a slower rate of emptying after the first five to ten minutes following ingestion.

Evidence for a Minor Role of the Pylorus

Until recently, the distal stomach and in particular the pylorus were believed to play a minor role in the control of liquid gastric emptying (Kelly 1980, 1981, Thomas 1957). This belief was based on several observations. First, liquid gastric emptying has repeatedly been observed in the absence of detectable antral contractions (Rees et al 1979b). Unfortunately the methodology used in these experiments were not able to adequately record isolated pyloric contractions (Section 2.2). Second, although distal gastrectomy, which removes both the pylorus and antrum, was shown to be associated with greatly increased gastric emptying rates of solids, no changes to gastric emptying rates of normal saline were demonstrated (Hinder & San Garde 1983). This study did not adequately assess emptying rates of nutrient rich liquids over the first five to ten minutes following ingestion. Such measurements may have demonstrated significant differences to liquid gastric emptying following distal gastrectomy. Liquid emptying has been reported as consisting of a rapid initial phase, lasting minutes only, followed by a constant slower linear phase (Brener et al 1983, Meyer 1987). Third, repeated studies demonstrated that clamping open the pyloric canal, by an intraluminal stent, did not alter rates of liquid gastric emptying (Crider & Thomas 1937, Stemper & Cooke 1976). It has recently been appreciated that multiple mechanisms act to control liquid gastric emptying (Meyer 1987). Presumably in these studies the pattern of liquid emptying was not altered as removal of the pylorus mechanism was compensated for by activity of the remaining mechanisms.

Evidence for a Major Role of the Pylorus

The evidence for a major role for the pylorus in the control of liquid gastric emptying is considerable. Numerous studies have demonstrated that loss of the pyloric mechanism produces to a reduction in the resistance to transpyloric flow (Edin 1980, Mearin et al 1987a, 1987b, Miller et al 1981) as well as more rapid liquid gastric emptying (Binswanger et al 1978, Faxen et al 1973, Groisman and Kharchenko 1989, Hinder and Bremner 1978, Malbert and Ruckebusch 1989b, Muller-Lissner et al 1982b, Ormsbee and Bass 1976, Symbas et al 1963, Williams et al 1986, Yamagishi and Debas 1978). Still other studies have demonstrated that a more normal pattern of gastric emptying results when the pylorus is left intact during gastro-duodenal resections, such as with supra-pyloric antrectomy (Isono and Kelly 1979, Killen and Symbas 1962, Maki et al 1967) or pylorus preserving pancreatico-duodenectomy (Patti et al 1987). Studies have shown that narrowing of the pyloric lumen occurs during slowing of liquid gastric emptying (Keinke and Ehrlein 1983, King et al 1987, Tougas et al 1987). Other studies have demonstrated an increase in the pressure recorded at the pylorus, both phasic and tonic, during that stimulation of receptors within the duodenum (Fisher and Cohen 1973, Heddle et al 1988b, Houghton et al 1988a, 1988b, White et al 1983) and during slowing of liquid gastric emptying (Dooley and Valenzuela 1988, Heddle et al 1988a, 1988c, Houghton et al 1988a, 1988b, Schulze-Delrieu and Wall 1983, Tougas et al 1987). Phasic contractions of the pylorus have been demonstrated during cessation of pulsatile transpyloric flow (King et al 1987, Schulze-Delrieu and Wall 1983). These findings all support the concept that the pylorus does plays a major role in the control of liquid emptying. It is possible that the pylorus plays a primary role in the control of liquid emptying during the initial rapid phase of emptying. Removal of the pyloric mechanism produces the greatest disorders to liquid emptying during this period (Hinder and Bremner 1978, Hinder and San Garde 1983, Williams et al 1986). The control of the later slower phase of liquid emptying may be due to other factors such as proximal gastric tone (Azpiroz and Malagelada 1985b, 1986) or duodenal contractility (Keinke and Ehrlein 1983, Keinke et al 1984, Williams et al 1986).

Recent studies have demonstrated that contractions of the antrum with the pylorus may play a role in the antral pumping mechanism (Bell 1978, Bell and Webber 1981, Carlson et al 1966, Jacobs et al 1982, King et al 1984, Malbert and Ruckebusch 1989a). Inhibition of antral contractions may decrease gastric emptying by removal of the propulsive antral pump. This concept fits with the reports that absence of antral contractions is associated a slowing of gastric emptying (Dooley and Valenzuela 1988, Rees et al 1979a, White et al 1981).

2.6 THE PYLORUS AND SOLID GASTRIC EMPTYING

(i) DIGESTIBLE SOLIDS

Patterns of Emptying of Digestible Solids

Digestible solids tend to empty from the stomach in a constant linear rate (Akkermans et al 1984, Collins et al 1983, Mayer et al 1982, Meyer et al 1981), after an initial lag period (Akkermans et al 1984, Collins et al 1983, Hinder and Kelly 1977, Lavigne et al 1978, Mayer et al 1982, Meyer et al 1976, Moore et al 1981). The lag period before food enters the duodenum reflects both redistribution of food from the fundus to the antrum (Collins et al 1988, Moore et al 1986) as well as the time taken to reduce large pieces of food to small particles (Camilleri et al 1986, Code 1970, Prove and Ehrlein 1982). Linear emptying of the solid meal suggests "zero order kinetics", that is, emptying rate is independent of the meal volume (Meyer et al 1976). It is probable that factors that influence the pressure and volume of the proximal stomach, such as the degree of proximal gastric wall tone (Azpiroz and Malagelada 1984, 1985a, 1985b, 1986), ability of the proximal stomach to relax to accommodate the ingested meal (Cannon 1898), the meal volume (Moore et al 1984), the extent of contraction of any mid-gastric band (Moore et al 1987, Collins et al 1988) each play a significant role in the control of solid gastric emptying, however few studies have addressed this directly (Meyer 1987).

Mechanism of Action of the Distal Stomach

The literature to date has favoured that the control of gastric emptying of solids is primarily due to motor activity of the distal stomach (Kelly 1980, 1981). Distal gastric peristaltic contractions act to propel solid food towards the pylorus and duodenum. Because of their large size and the rapid closure of the pylorus during such contractions, solid particles are not permitted to pass into the duodenum, being retropulsed back to the antrum (Carlson et al 1966, Code 1970, Kelly 1981, Prove and Ehrlein 1982). During this process particles are trapped and ground within the distal stomach region. Only small particles, less than about 1 millimetres, are able to pass the pylorus, before pyloric closure. Thus the stomach sieves what it delivers to the duodenum (Mayer et al 1982, Meyer 1980, Meyer et al 1979, 1981). During the grinding process, viscous and solid luminal contents collect in the pyloric groove between the proximal and distal pyloric loops. The pyloric torus presses into the groove (Kelly 1981, Prove and Ehrlein 1982, Torgersen 1942). It has been suggested that activity patterns of the pyloric canal contribute to the regulation of gastric emptying (Ehrlein 1976, Frik 1974). A sequential contraction of the proximal pyloric loop followed by the distal pyloric loops may accelerate gastric evacuation, while simultaneous contraction of both loops may increase grinding and retropulsion. However no alterations in the timing of contractions of the terminal antrum and distal pyloric loops have yet been demonstrated (Keinke and Ehrlein 1983), apart from the occurrence of localised pyloric contractions with absent antral contractions (Heddle et al 1988b). Keinke and co-workers (Keinke and Ehrlein 1983, Keinke et al 1984) have described changes in the diameter of the pyloric canal due to the physical properties of ingested food: the density and size of the food particles may control pyloric motility and handling of food (Bueno et al 1981, Mazzotta and Malagelada 1981, Rees et al 1979b). Prove and Ehrlein (1982) described an increase in the depth of antro-pyloric contraction waves with an increase in the viscosity of a meal.

Surgical Interventions

Vagal denervation of the antrum and pylorus, which has been shown to reduce antral motor activity, decreased the rate of emptying of solid spheres from the stomach (Mroz and Kelly 1977). Studies of humans with proven antral dysrhythmias secondary to diabetes have also demonstrated delayed gastric emptying of solids (Loo et al 1984, Malagelada et al 1980). These findings support the hypothesis that coordination of antro-pyloric contractions are necessary for gastric emptying of solids.

Resections of the distal stomach components have provided considerable understanding of the function of the pylorus. In dogs, ablation of the pylorus, by either pyloric myotomy or pylorectomy, did not alter the size of meat particles that emptied, but produced more rapid rates of solid emptying (Hinder and San Garde 1983, Meyer et al 1979). Resection of both the pylorus plus the terminal antrum resulted in a significant increase in both rates of solid emptying and the proportion of particles greater than 1 millimetre size that emptied, from 5% in control animals, to 30% following antro-pylorectomy (Mayer et al 1984). Meyer concluded that the sieving function depends on the narrowest terminal portion of the antro-pyloric segment, and that the size of the terminal orifice may be important. Isono and Kelly (1979) excised the antrum but left an intact pylorus. The emptying of solids was slowed. Unfortunately the size of particles emptied were not measured. Similarly Patti et al (1987) demonstrated a more normal pattern of solid gastric emptying following pancreatico-duodenectomy, when the pylorus was preserved than when the pylorus was excised. These findings are in keeping with the hypothesis that sieving and grinding is due to the antrum and or the pylorus, but that control of gastric emptying is due primarily to the pylorus.

Emptying of the Solid Meal once Liquified

The mechanisms that control gastric emptying of solids, once ground or liquified, have not been extensively investigated. Heading and King (1990) concluded that emptying of the 'liquified' solid is presumably effected by the mechanisms responsible for liquid emptying. One study has compared gastric emptying of solid meals and equivalent meals that have been homogenised (Malagelada et al 1979). The homogenised meals emptied immediately, with no lag period. However the linear emptying rates were comparable. Homogenised meals have been shown to empty at rates comparable to liquid meals with equivalent energy density (Gulsrad et al 1980). The slower rate of emptying of solid meals compared to liquid meals generally may simply be due to the greater calorie density, or greater osmolarity of solid foods generally. The rate of emptying of both solid and liquid may be controlled primarily by entero-gastric feedback from nutrient or osmolar receptors within the duodenum (Meyer 1987). The only difference between the patterns of solid and liquid gastric emptying may occur the initial few minutes, when liquids tend to empty rapidly whereas the emptying of solids lags behind.

(ii) GASTRIC EMPTYING DURING THE INTERDIGESTIVE PERIOD

Every 90 to 120 minutes during interdigestive periods a regularly occurring migrating motor complex (MMC) sweeps mucous, cellular debris and indigestible particles out the stomach and distally down the entire small bowel (Code and Marlett 1975). A full cycle consists of four phases, which pass through a period of relative quiescence (Phase 1), where slow waves are not associated with mechanical activity, through a phase of increasing mechanical activity (Phase 2), to a brief crescendo of activity (Phase 3), lasting approximately 5 minutes in the dog (Code and Carlson 1968). During this phase of maximal activity, each and every slow wave is accompanied by an action potential and contraction (Code and Carlson 1968). This phase is followed by a period of diminishing contractility (Phase 4), leading back to a phase of relative quiescence.

The motor activity of the pylorus and antrum during fasting has been extensively documented in radiological studies, to range from periods with no contractions, through times when the antrum undergoes weak contractions that die out before reaching the pylorus, to times when the lumen of the whole distal stomach is completely obliterated (Code and Carlson 1968). The motor activity of the pylorus during the interdigestive period has been described as significantly different to that during the digestive period. To permit the contractions of the MMC to clear the stomach of large sized particles (Meyer et al 1979), the pylorus has been described as NOT closing with the approach of the interdigestive peristaltic wave, as it does with contractions during the digestive period, but remaining wide open (Ehrlein et al 1980, Kelly 1981, Mroz and Kelly 1977). Only particles with a diameter that exceeds the diameter of the open pyloric orifice are retained in the stomach. This description is based upon radiological observations, and has yet to be confirmed by other methods of investigation. Mroz and Kelly (1977) have suggested that the contractions that occur during Phase 3 of the MMC are so powerful that they overcome the normal sieving function of the distal stomach, forcing all particles across the gastroduodenal junction.

2.7 MEDIATION OF CONTROL OF PYLORIC MOTILITY

Three mechanisms have been proposed to mediate the control of pyloric motility. They are intrinsic neural mechanisms of the Enteric Nervous System, extrinsic neural mechanisms and endocrine mechanisms.

(i) INTRINSIC NEURAL CONTROL OF THE PYLORUS

The intrinsic neural plexuses of the Enteric Nervous System appear to be the originator of a great deal of programmed motor activity, through complex neuronal circuitry, which regulate contractile patterns such as the peristaltic reflex proposed by Bayliss and Starling (Bayliss and Starling 1899). It has been shown that reflexes such as the peristaltic reflex remain intact despite removal of some or all extrinsic inputs that may modulate the reflex, such as by manipulation of extrinsic nerves (Hirst and McKirdy 1974), pharmacological interventions (Kosterlitz and Lees 1964) and even by the dissection of intestinal wall to flat segments (Grider et al 1987).

Control of Isolated Pyloric Contractions

Several studies have demonstrated a role for intrinsic neurones in the control of isolated pyloric contractions and pyloric tone. Reynolds and co-workers demonstrated a stimulation of isolated pyloric contractions, in anaesthetised cats, by either duodenal electrical field stimulation (Reynolds et al 1985) or duodenal luminal acid (Reynolds et al 1984).

This effect was blocked by tetrodotoxin, which blocks all motor neuronal discharge, but not by vagotomy. Bertiger et al (1987) similarly demonstrated in whole organ preparations of cat stomachs the stimulation of localised pyloric contractions by duodenal luminal acid, and that the motor pattern was blocked by antral electrical field stimulation. Bertiger et al demonstrated that this inhibition of isolated pyloric contractions by antral electrical field stimulation was mediated by intrinsic nerves, as tetrodotoxin abolished the effect. Allescher et al (1988) demonstrated in anaesthetised dogs that duodenal electrical field stimulation produced localised pyloric contractions and pyloric tone. These effects were blocked by intravenous atropine, hexamethonium and intra-arterial tetrodotoxin, confirming a neural component to the stimulation of isolated pyloric contractions, as well as by duodenal transection orad to the stimulating electrodes, to disrupt intrinsic duodenal intramural nerves. Allescher et al also demonstrated that antral field stimulation completely abolished localised phasic activity of the pylorus, as well as reduced the tonic activity. This inhibitory effect was blocked by tetrodotoxin and antral transection. Behar et al (1979) demonstrated in anaesthetised cats a relaxation of pyloric contractions by antral field stimulation. This effect was abolished by tetrodotoxin, implicating a neural control of the pylorus. It appears from these studies that appropriate stimulation of enteric nerves distal to the pylorus stimulates isolated pyloric contractions and tone, whereas appropriate stimulation of enteric nerves proximal to the pylorus induces a reduction of pyloric tone and abolition of isolated pyloric contractions.

Control of Antro-Pyloro-Duodenal Contractions

The role of intrinsic neurones in the control of co-ordinated antro-pyloro-duodenal contractions has not been fully resolved. Studies have demonstrated a loss of co-ordination following transection of the gastroduodenal junction (Atanassova 1976, Bortoff and Weg 1965, Bedi & Code 1972, Bortolotti et al 1981). Bedi and Code accounted the loss of coordination to a loss of neural or muscular transmission across the gastroduodenal junction, but could not distinguish which. Atanassova recorded from single duodenal muscle cells in a gastroduodenal muscle strip while stimulating transmurally at the antral end of the preparation. She recorded both myogenic activity, demonstrated by duodenal slow waves, and functional myenteric neurones, demonstrated by junctional potentials. She concluded that even though antral slow waves spread across the gastroduodenal junction, co-ordination was achieved through in intrinsic nervous system (Atanassova 1976). Although the experiments do provide evidence for functional myenteric neurones, they do not conclusively differentiate between myogenic and neurogenic co-ordinating mechanisms. Sanders and Vogalis (1989) also investigated the myoelectric activity of the gastroduodenal junction, in dogs, using intracellular recording techniques. They reported that gastric slow waves do not traverse the gastroduodenal junction. They concluded that other excitatory mechanisms, such as intrinsic nerve pathways, activate and co-ordinate duodenal with gastric motility.

(ii) EXTRINSIC NEURAL CONTROL OF THE PYLORUS

The extrinsic innervation of the pyloric region can be divided into parasympathetic vagal fibres and sympathetic (splanchnic) fibres, both afferent and efferent.

Parasympathetic Fibres

Some knowledge of the role of vagal parasympathetic fibres has been gained from vagal section studies. Following chronic vagotomy, studies using intraluminal balloon sensors have reported the pylorus of the unstimulated stomach as petioles and unchanged from prevagotomy (McSwine 1931, Quigley & Loukes 1951). Unfortunately the recording techniques used in these studies are unreliable (Section 2.2). In contrast, Slavchencho et al (1982) reported that acute vagotomy produced constant unremitting localised pyloric contractions. Maier et al (1968) studied anaesthetised dogs following chronic vagotomy. They reported "pylorospasm" during distension of the antrum. The true motor activity of the pylorus following vagotomy appears unresolved.

The stimulation of vagal fibres has provided more conclusive knowledge. It is now readily accepted from numerous studies that both excitation and inhibition of pyloric motility can be produced by vagal nerve stimulation (McSwine 1931, Thomas and Baldwin 1968, Roman and Gonella 1987). Behar et al (1979) demonstrated a relaxation of pyloric tone during electrical stimulation of the peripheral ends of the cut vagus nerves. In contrast the stimulation of afferent fibres of the central ends of the cut vagal nerves produced a stimulation of pyloric contractions (Behar et al 1979). Edin (1980) studied pyloric contractility indirectly by measurement of the transpyloric resistance to fluid flow. Electrical stimulation of the vagus produced an increase in transpyloric flow, which was interpreted an pyloric relaxation. Relaxation of the pylorus by electrical stimulation of efferent vagal fibres has been abolished by neuro-muscular blockade by atropine (Mir et al 1979) and tetrodotoxin (Telford et al 1979). Phaosawasdi and co-workers induced vagal stimulation by hypoglycaemia (Phaosawasdi et al 1978, Fisher & Phaosawasdi 1980). This stimulation was associated an increase in pyloric tone. Allescher et al (1988) demonstrated that stimulation of the cut peripheral ends of the vagus produced localised pyloric contractions at low levels of stimulation, and an abolition of localised pyloric contractions at higher levels of stimulation.

Vagal innervation has been proposed to mediate the gastric response to duodenal distension (Behar et al 1979, Deloof et al 1988, Mir et al 1979, Wilbur and Kelly 1973). A phenomenon called "mechanically induced entero-gastric inhibitory reflex" with both afferent and efferent pathways in the vagus has been reported (Miolan and Roman 1984, Youmans 1949), as has inhibition of gastric motility by painful stimuli, mediated via sympathetic outflow (Jansson and Martinson 1966, Sato et al 1975). Chemical sympathectomy and bilateral vagotomy, but not pyloric section, abolish the inhibition of gastric motility by duodenal distension (Daniel and Wiebe 1966).

The "antral reflex", or stimulation of antral motility by gastric distension (Andrews et al 1980a) is mediated through vagal pathways, as it is abolished by vagotomy (Andrews et al 1980a, Stadaas and Aune 1970).

Sympathetic Fibres

Considerably less is known about sympathetic fibres than vagal fibres in the control of pyloric motility. It is generally agreed that splanchnic nerve section produces less disturbing effects on gastric motor function than vagotomy (Miolan 1985, Roman and Gonella 1987).

Several studies have demonstrated an increase in the force of antro-pyloric peristaltic contractions following splanchniectomy (Alvarez 1948, Kosterlitz 1968, McSwine 1931, Deloof 1988). Both inhibition (Paton & Vane 1963, Ohta et al 1985) and facilitation (Kosterlitz 1968, Deloof 1988, Thomas and Baldwin 1968) of gastric motor function have been recorded in response to splanchnic nerve stimulation. Adrenergic fibres are believed important in inhibition, as both guanethidine (Beani et al 1971, Martinson 1965) and bretylium (Campbell 1966) block the response. These adrenergic fibres are believed to act at two different sites, the myenteric neurones (Furness and Costa 1974, Jansson 1969, Jansson and Lisander 1969, Jansson and Martinson 1966) and the muscle cells directly (Beani et al 1971, El Sharkawy and Szurszewski 1978, Furness and Costa 1974), through beta adrenergic receptors. The stimulatory effects of sympathetic fibres upon gastric motor activity are believed to be mediated through either muscarinic or alpha adrenergic receptors (Guimaraes 1969, Haffner and Stadaas 1972, Nakazato et al 1970, Ohkawa 1976). An intact adrenergic innervation has been shown important in the mediation of gastric inhibition by duodenal distension and duodenal inhibition by gastric distension (Daniel and Wiebe 1966). Kreulen et al (1983) demonstrated that splanchnic innervation (gastro-duodenal nerve) is involved in this gastro-duodenal inhibitory reflex.

Little information exists on the role of sympathetic fibres in the control of the pylorus. Deloof (1988) reported that stimulation of the cut peripheral and central ends of the thoracic sympathetic trunks in decorticate rabbits induced inhibition of myoelectric activity of the antrum and pylorus. Thomas et al (1934) described no change to pyloric motor activity following splanchnic nerve section in dogs, but the methodology used in this study is unreliable. Edin (1980) reported that splanchnic nerve stimulation and noradrenaline infusion produced a decrease in transpyloric flow, indicating pyloric contraction. Mir et al (1979) demonstrated that the stimulation of splanchnic nerves could not overcome the effects of stimulation of the vagus on pyloric motor activity. Allescher et al demonstrated that adrenergic beta-receptors mediate an excitatory response in the pylorus, probably by direct action at the pylorus (Allescher et al 1989c), and that adrenergic alpha-receptors mediate an inhibitory response at the pylorus (Allescher et al 1989c), possibly by direct action or possibly by acting upon cholinergic neurones (Daniel 1966, Allescher et al 1989c).

(iii) ENDOCRINE CONTROL OF THE PYLORUS

Gut endocrine mechanisms are intimately linked to neural mechanisms, as many hormones are peptides that are synthesized and secreted by neurones, of both the Enteric Nervous System and the Central Nervous System (Debas and Mulvihill 1991). Neuropeptides may mediate regulation of gut function by 3 delivery systems: transportation via the blood stream to a target organ (neuro-endocrine activity), diffusion via interstitial fluids to the site of action (neuro-paracrine activity) or released to cross a synaptic gap to a receptor on a target cell (neurotransmitter activity).

Hormones and neuroendocrine substances that are known to influence both gastro-duodenal motility and gastric emptying include cholecystokinin, gastrin, secretin, enkephalins, vasoactive intestinal peptide, dopamine, motilin, bombesin, gastric inhibitory polypeptide, glucagon, substance P, somatostatin, neurotensin, galanin, pancreatic polypeptide and peptide YY (Allescher et al 1990, Debas and Mulvihill 1991).

The action of cholecystokinin (CCK) on pyloric motor function has been the most extensively investigated. Numerous studies have demonstrated CCK to increase both pyloric tone and localised pyloric contractions, in vitro (Golenhofen et al 1980, Scheurer et al 1983a, Anuras & Cooke 1978, Cameron et al 1970, Morgan et al 1978, Margolis et al 1989), in anaesthetised animals (Allescher et al 1989a, Reynolds et al 1984, 1985, Behar et al 1979, Isenberg & Czendes 1972, Scheurer et al 1983b, Telford et al 1979) and in conscious humans (Phaosawasdi and

Fisher 1982, Tougas et al 1988, Fisher et al 1973, Munk et al 1978). In contrast, Behar et al (1979) demonstrated in anaesthetised cats that CCK primarily decreased pyloric tone, although CCK did increase tone on a few occasions and so inferred a dual action of CCK. Allescher et al concluded that CCK acts upon both peripheral nerves and pyloric muscle directly, in vivo, in the stimulation of isolated pyloric contractions (Allescher et al 1989a). CCK has been shown to inhibit gastric emptying of liquids (Debas et al 1975) through a vagally dependent mechanism acting on the pylorus and stomach, as pyloroplasty and antrectomy, as well as vagotomy prevented the inhibitory action of physiological doses of CCK on liquid gastric emptying (Yamagishi and Debas 1978).

The role of gastrin in the control of pyloric motility has been primarily assigned to the blocking of stimulation of the pylorus. Lipshulz & Cohen (1972) demonstrated that gastrin produced no direct effect on pyloric circular muscle, but could antagonise the stimulation of pyloric circular muscle by CCK. Fisher and Boden (1976) demonstrated the stimulation of pyloric tone by duodenal luminal acid, amino acids, and fats was decreased by the exogenous administration of gastrin.

Secretin has been shown to stimulate contraction of pyloric muscle (Lipshulz & Cohen 1972, Fisher et al 1973). This effect has also been blocked by gastrin (Lipshulz & Cohen 1972, Fisher et al 1973). Overall the role of secretin in the control of the pylorus remains uncertain.

Reynolds et al (1984) reported that encephalins produce potent pyloric spasm in the cat. Edin et al (1980) similarly demonstrated a stimulation of localised pyloric contractions in response to intra-arterial injection of encephalins. However naloxone did not prevent pyloric excitation due to duodenal field stimulation (Allescher et al 1988a) or to intraduodenal acid infusion (Allescher et al 1988b). Edin demonstrated the presence of significant immuno-reactivity to both encephalins and vasoactive intestinal polypeptide (VIP) at the pylorus (Edin 1980, Edin et al 1980). VIP has been shown to relax and open the pyloric orifice in sheep (Ruckebusch and Merritt 1985) and inhibit both spontaneous and acetyl-choline induced pyloric contractions in anaesthetised dogs (Allescher et al 1989b). VIP has been proposed as a non-cholinergic non-adrenergic neurotransmitter of pyloric motility (Edin 1980). The dopamine-antagonist domperidone was shown to increase pyloric diameter and gastric emptying rate (Baeyens et al 1979). Ludtke et al (1989) reported both phasic and tonic responses of muscle strips from the distal pyloric loop, in response to motilin stimulation. Bombesin has been reported to induce excitation of the pylorus and antrum both in vitro (Mayer et al 1982) and in vivo (Bertraccini and Impicciatore 1975). There is almost no information about the physiological role of gastric inhibitory polypeptide (GIP) on pyloric motility. GIP is considered inhibitory as it reduced motilin-induced spike potentials in the distal stomach of the dog (Castresana et al 1978). A mainly inhibitory effect of glucagon on antro-duodenal motility has been demonstrated (Kowalewski and Kolodej 1975, Bortolotti et al 1975). However the true hormonal status of these and other compounds in the control of pyloric motility are yet to be established.

SECTION 3

METHODS

3.1 Establishment of the Animal Preparation

- 3.1.1 The Animal Preparation Previously Established
- 3.1.2 Choice of Unsedated Kangaroo Island Pigs
- 3.1.3 Development of Gastro-Intestinal Cannulae
  - (i) Duodenal Cannula
  - ii) Gastric and Oesophageal Cannulae

3.2 Stimulation of Pyloric Motility

- 3.2.1 Intestinal Stimulation of Pyloric Motility
- 3.2.2 Gastric Stimulation of Pyloric Motility

3.3 Application of Manometric Techniques to the Pig Preparation

- 3.3.1 Profile of Trans-Mucosal Potential Difference across the Pig Pylorus
- 3.3.2 Intraluminal Pressure Measurement of Pyloric Motor Function in the Unsedated Pig

3.4 Liquid Gastric Emptying Studies

3.5 Gastric Emptying of a Digestible Solid

- 3.5.1 Simultaneous Manometry - Emptying Studies
- 3.5.2 Particle Size Measurements
- 3.5.3 External Gamma Camera Studies

3.6 Surgical Interventions

- 3.6.1 Excision of the Pylorus
- 3.6.2 Transection of the Duodenum
- 3.6.3 Vagus Nerve Cooling

ETHICAL APPROVAL

All work undertaken in this thesis conformed with the guidelines of the National Health and Medical Research Council of Australia's Statement on Animal Experimentation and was approved by the Animal Ethics Committees of the University of Adelaide and the Institute of Medical and Veterinary Science, South Australia.

STATISTICAL ANALYSES

All data were assessed for normal and homogenous variance, by a plot of residuals versus fitted values. When indicated from this assessment, data were normalised by either weighting each group by the inverse of the standard deviation of that group (liquid gastric emptying data) or by $\log_e$ transformation of the data (solid gastric emptying data). Data were analysed by paired and unpaired T-test, analysis of variance with Fisher's LSD (least significant difference) and simple regression analysis, as appropriate. Data are expressed as mean and standard deviation. Statistical significance was set at $p < 0.05$.

3.1 ESTABLISHMENT OF THE ANIMAL PREPARATION

3.1.1 THE ANIMAL PREPARATION PREVIOUSLY ESTABLISHED

The work presented in this thesis is in part a continuation of work undertaken by Dr. Brian Landers, as Research Associate in the Department of Surgery, University of Adelaide. Those aspects which were developed by Dr. Landers and incorporated into the research presented in this thesis include the decision to use unsedated Kangaroo Island pigs as the animal preparation (Section 3.1.2), the use of an indwelling duodenal cannula (Landers et al 1988), (Section 3.1.3), the protocols for nutrient and hyperosmolar control of liquid gastric emptying (Section 3.2.1), as well as the protocol for measurement of particle sizes emptied during solid gastric emptying (Landers et al 1990), (Section 3.5.2). Each aspect developed by Dr. Landers has been modified and applied to the study of pyloric motility.

3.1.2 CHOICE OF UNSEDATED KANGAROO ISLAND PIGS

Historically the dog has been the animal preparation most widely used in the study of gastric emptying and pyloric motility (Thomas 1957, Kelly 1981, Meyer 1987). Throughout the world the pig has been used increasingly in place of the dog for biomedical research (McIntosh and Pointon 1981). A variety of financial, physiological, practical and social reasons led to the use of the Kangaroo Island pig in the Department of Surgery. By 1986 the cost of purchase of one dog for biomedical research was five hundred dollars, compared to fifty dollars for one Kangaroo Island pig. The Kangaroo Island pig was also more readily available than the dog, there being two centres in South Australia breeding the pigs. The Kangaroo Island pig was known to undergo a growth cycle such that, following an initial growth spurt over four to five months, growth temporarily halted at the "manageable" size of between thirty and fifty kilograms. The Kangaroo Island pig is known to be relatively disease free, adapted to intensive piggery conditions, relatively docile and known to breed true to type and smaller litter size, consistent with it being "inbred" (McIntosh and Pointon 1981, Esminger 1961). In biochemical and haematological terms, the Kangaroo Island pig is similar to man (Mount and Ingram 1971, McIntosh and Pointon 1981, Pond and Houpt 1979). The anatomy of the pylorus and gastro-duodenal junction of the pig has been precisely documented (Torgersen 1942). Finally, pigs are more socially accepted for research, by the staff that maintain the animals as well as by society as a whole.

3.1.3 DEVELOPMENT OF GASTRO-INTESTINAL CANNULAE

(i) DUODENAL CANNULA

Introduction

The indwelling duodenal cannula was first developed and used in dogs by Thomas in 1941 (Thomas 1941) and subsequently modified (Jones et al 1971). Although the duodenum of the pig is mobile on a mesentry like that of the dog, it is of smaller calibre, so that a cannula of new dimensions had to be developed. The modified Thomas cannula used in the pigs was of single piece construction, with a secure central plug. The cannula allowed prolonged access to the duodenum, without interfering with normal behaviour, feeding or growth of the animals. Use of duodenal cannulae in the Kangaroo Island pig has been reported previously (Landers et al 1988).

Methods

Kangaroo Island pigs ranging in body weight from 34 to 55 kilograms underwent operation at 5 months of age, under general anaesthesia of halothane and nitrous oxide. A modified Thomas cannula (Jones et al 1971) was inserted into the duodenum 5 centimetres distal to the pylorus, via a 4 centimetre longitudinal incision. Each animal was allowed 4 weeks to recover before studies commenced.

Results

Cannulae were inserted into 24 pigs over the duration of the research project.

In all studies of the 24 animals, no motor activity was recorded from the duodenum, beyond the duodenal bulb. This is probably due to drainage of this part of the duodenum by the duodenal cannula. As a result duodenal resistances were minimal (Parr et al 1987, Shirazi et al 1988). It was anticipated that exclusion of duodenal factors would allow more conclusive demonstration of the role of the pylorus in gastric emptying.

(ii) GASTRIC AND OESOPHAGEAL CANNULAE

Introduction

Gastric and oesophageal cannulae, first introduced by Pavlov in 1890 (Pavlov and Shumivo-Somanovski 1890), have been used extensively in the experimental study of gastro-intestinal physiology in the dog (Jones et al 1971, Parr et al 1987, Shirazi et al 1988), cat (Svensson et al 1971), rat (Borrella and Herr 1971) and guinea pig (Batzri et al 1987). As far as was known, no cannula had been developed for used in the pig. It was necessary to develop a cannula for access to the gastro-intestinal tract proximal to the pylorus, in order to position a manometric assembly. A gastric cannula was believed easier to apply and use for manometric studies, but in theory a gastric cannula could influence both gastric emptying and pyloric motility. It was thus necessary to develop cannulae at both the oesophagus and stomach and compare motility and gastric emptying patterns between the two.

Methods

Gastric cannulae used were identical to those positioned at the duodenum. Under general anaesthesia and through a midline incision, a cannula was inserted at the gastric corpus, ten to fifteen centimetres proximal to the pylorus and secured with an inverting purse string suture. The cannula was exteriorised through a separate stab wound in the abdominal wall.

The oesophageal cannulae were constructed from five separate part (Figure 3.1), glued together with cyano-acrylate glue ("Superglue"). Under general anaesthesia a longitudinal neck incision was made, to the left of the midline below the level of the pharynx. Dissection was deepened and the oesophagus exposed after retraction laterally of the recurrent laryngeal nerve, neck strap muscles and carotid sheath. At this stage the silastic component of the cannula destined to lie within the oesophagus (Figure 3.1) was cut to the appropriate length for each pig, usually three to four centimetres oral and eight to ten centimetres caudal in length. The 'T' portion of the cannula was inserted through a longitudinal incision in the oesophagus and the wall of the oesophagus closed with inverting Connell sutures. The neck was closed in layers. Each pig was allowed four weeks recovery before studies commenced.

Pyloric manometric studies were performed and analysed as described in Section 3.3.2.

Results

(i) Gastric Cannula

Gastric cannulae were successfully used in research presented in this thesis, in 21 pigs, with minimal morbidity to each animal. Towards the end of the working life, a few

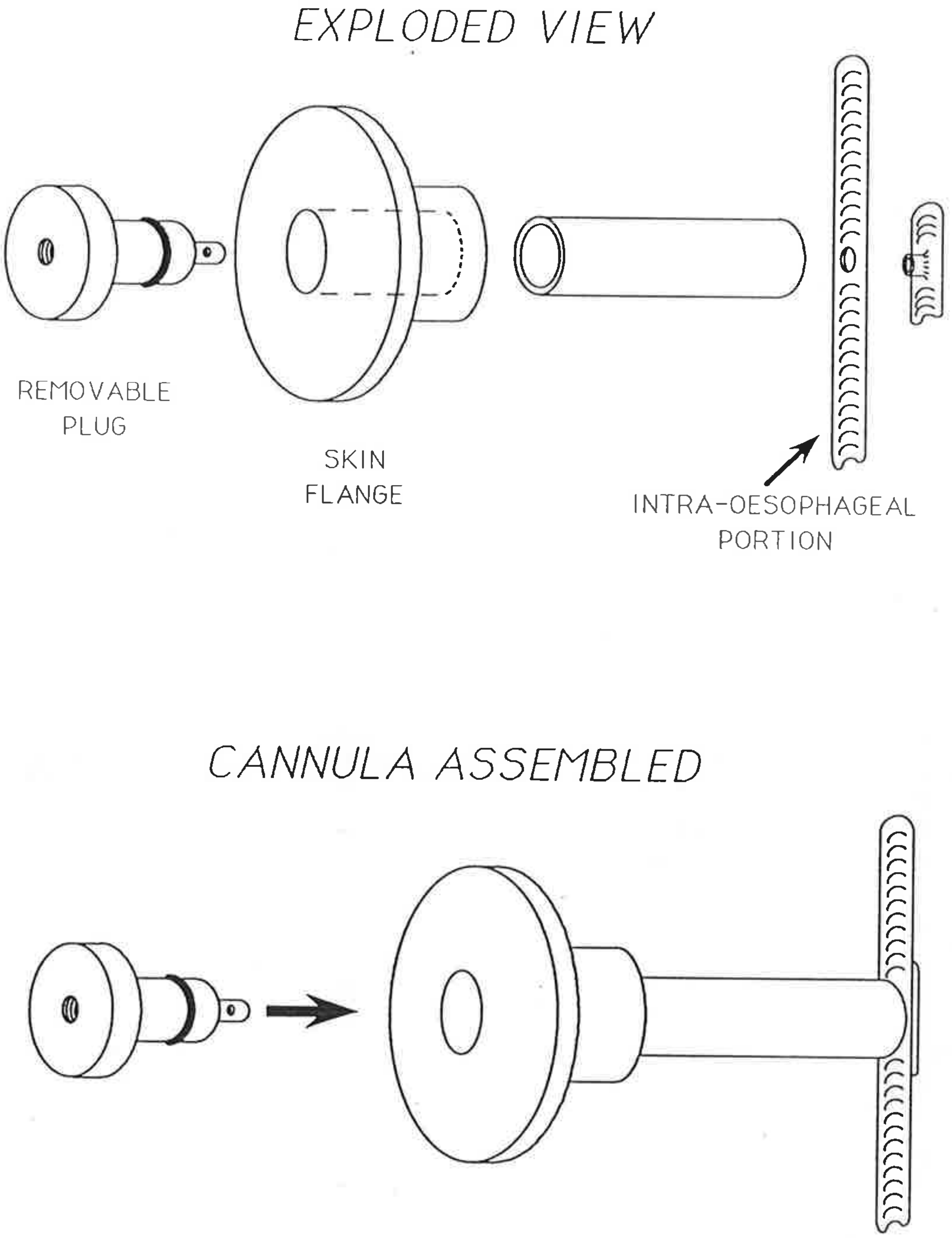


Figure 3.1: Oesophageal cannula.

cannulae began to migrate out from the wall of the stomach, creating a fistula with leakage of gastric chyme. It was possible to control leakage for up to four weeks by a deep purse string suture placed in the skin around the cannula. Occasionally the cannula migrated inwards, with inversion of the skin over the outer flange.

(ii) Oesophageal Cannula

Oesophageal cannulae were maintained successfully in three pigs for up to ten months. All animals suffered noticeable dysphagia during the first two weeks following surgery, which apparently resolved. As the oesophageal cannulae were a significant distance from the pylorus, position and maintenance of position of a manometric assembly was more difficult than in those animals with gastric cannulae. The end of the working life of each cannula was heralded by the leakage of foodstuffs out around the cannula, during feeding.

(iii) Comparison of Gastric and Oesophageal Cannulae

The patterns of pyloric motility were comparable between pigs with oesophageal cannulae and pigs with gastric cannulae (Figure 3.2).

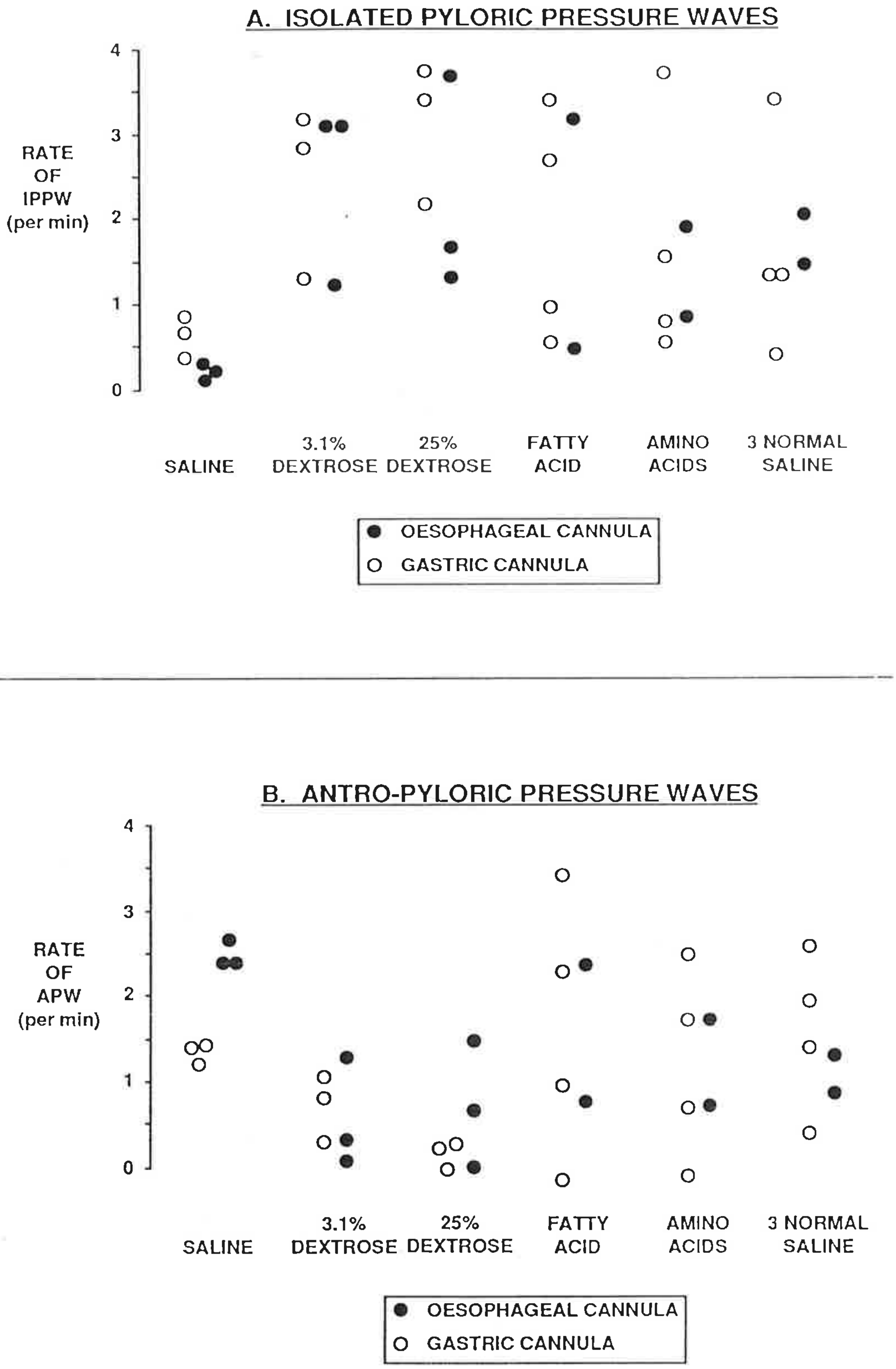


Figure 3.2: Rates of isolated pyloric pressure waves and antro-pyloric pressure waves in pigs with oesophageal or gastric cannulae.

Conclusion

The manufacture and surgical placement of cannulae at the gastric corpus and cervical oesophagus, for access to the upper gastro-intestinal tract proximal to the pylorus, have been described. Both cannulae were lightweight, easy to manufacture and had a useful working life with minimal morbidity. The Komorov type oesophagostomy has been used in dogs (Komorov and Marks 1958), but is technically not feasible in the pig due to the pig's very thick neck. The oesophageal cannula described above is flexible enough to move with the oesophagus on swallowing while maintaining a relatively constant secure position of the flange at the skin level. Migration of the cannula from the oesophagus is minimized due to the long intra-oesophageal portion of silastic tubing. Both cannulae lie flush with the skin to avoid being scratched or being caught on a cage wall.

No significant differences of antro-pyloric motility were demonstrated between pigs with a gastric cannula and with an oesophageal cannula. Subsequent studies demonstrated no alterations to the rates of gastric emptying between pigs with gastric or oesophageal cannulae (Section 5.1). These findings support the view that the presence of a gastric cannula does not affect gastric emptying. The use of the oesophageal cannula has demonstrated that they can be placed, but as they require more operating, are more complication prone and make manometric assembly placement more difficult, they were not applied to more than three pigs.

3.2 STIMULATION OF PYLORIC MOTILITY

Study Protocol

All studies were performed in unsedated pigs. Each pig was trained to stand quietly in loose fitting slings. Animals were fasted from solids for 20 hours and from liquids for 3 hours prior to each study. Prior to the commencement of studies, the stomach of pigs with gastric cannulae were washed with water at body temperature until the effluent was clear.

A manometric assembly (Section 3.3.2) was passed through the oesophageal or gastric cannula, to lie at the antro-duodenal region. A 16 gauge Foley catheter was passed through the duodenal cannula and its balloon inflated with 6 millilitres of water. This prevented the passage of gastric effluent into the second part of the duodenum, directing the effluent instead through the duodenal cannula. The lumen of the Foley catheter was used for infusion of various test solutions (see below) into the duodenum beyond the Foley balloon (Figure 3.3).

3.2.1 INTESTINAL STIMULATION OF PYLORIC MOTILITY

After passage of the manometric assembly and Foley catheter, manometric recordings started, concurrent with intestinal stimulation. Ten minutes following the start of stimulation, the pig was given a 1000 millilitre drink (Section 3.4). This was completely drunk by 4 of the 6 animals within two minutes. In the remaining two animals, both ingested just over half the drink and the remainder was infused within the first two minutes

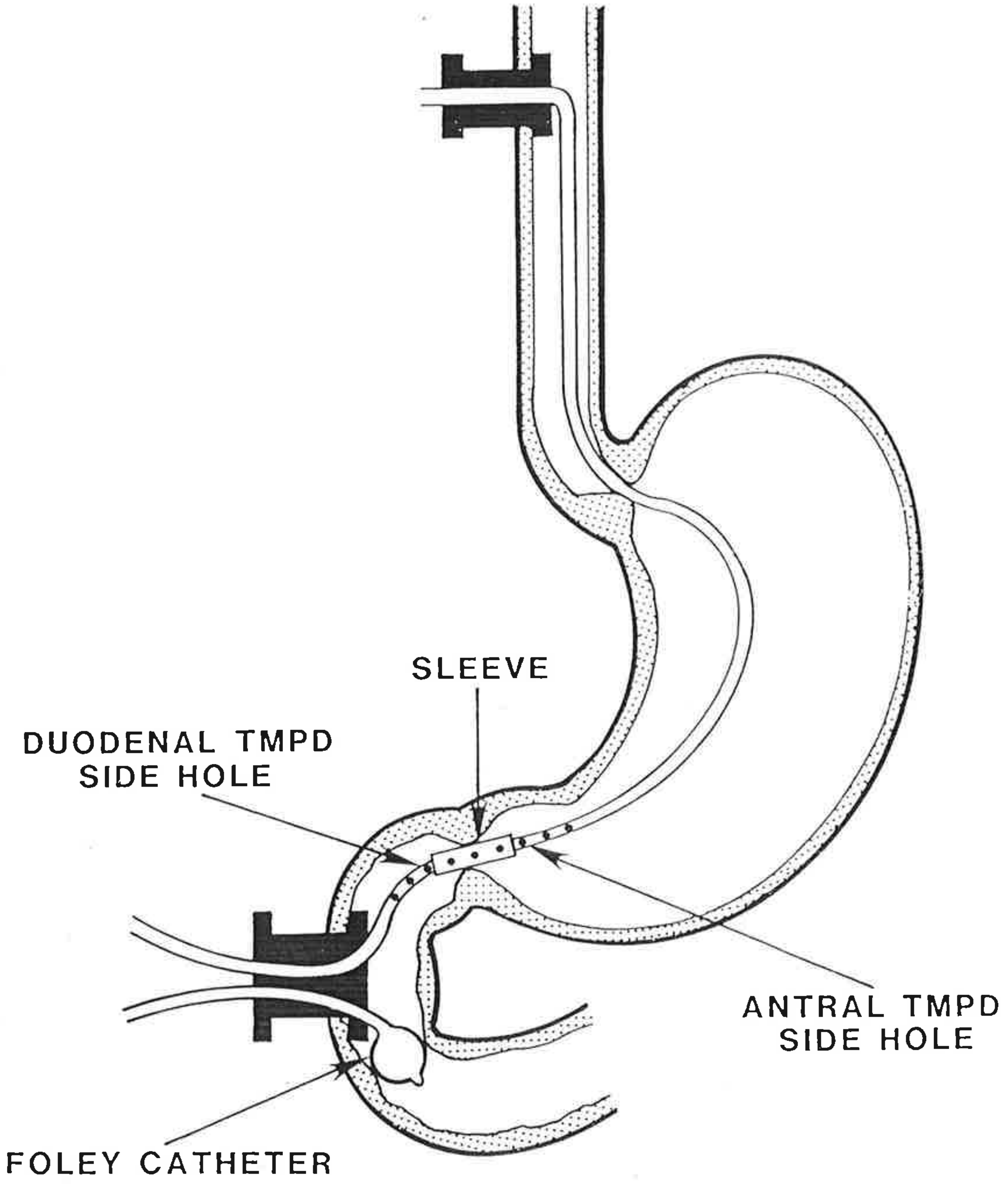


Figure 3.3: Manometric technique in the pig.

via a 16 gauge Foley catheter passed through the duodenal cannula into the stomach. Once all the drink was infused, this Foley catheter was removed.

Duodenal Nutrient and Hyperosmolar Stimuli

Stimulation was by infusion into the duodenum beyond the balloon of the Foley catheter of various test solutions. One test solution was infused continuously for the duration of each study, that is, for 10 minutes prior and for 30 minutes following ingestion. Test solutions included (i) normal saline as control, (ii) isosmolar nutrient solutions of dextrose, fatty acid, amino acids and (iii) hyperosmolar solutions of 3 normal saline and 25% dextrose (Table 1). The solutions were chosen to provide a dose-dependent manipulation of the rate of liquid gastric emptying (Landers et al 1986).

Stimulation by Duodenal Distension

These studies evaluated the effect of proximal duodenal distension by inflation of the Foley catheter balloon. Normal saline, 20 millilitres per minute, was infused into the lumen of the duodenum distal to the Foley balloon for the duration of the study. Following 10 minutes infusion, the Foley balloon was inflated from 6 millilitres (diameter 22 millimetres) to the test volume, either 15 (diameter 31 millimetres) or 25 millilitres (diameter 36 millimetres). After a further 10 minutes each pig was offered the drink. Measures of motility continued for 30 minutes following ingestion.

3.2.2 GASTRIC STIMULATION OF PYLORIC MOTILITY

Water Barostat System

The barostat consisted of a water reservoir with a fluid level maintained constant by an overflow. Tap water flowed continuously into the reservoir. A wide bore tube (internal diameter 10 millimetres, length 1 meter) connected from the barostat reservoir to the gastric cannula (Figure 3.4). Water at body temperature flowed freely from the reservoir, through the wide bore tube into the lumen of the stomach, across the pylorus and was diverted by the balloon of the Foley catheter out the duodenal cannula. No intragastric balloon was used. Intragastric pressure was adjusted by alteration of the height of the barostat referenced to the level of the gastric cannula of the pig. The level of the pylorus referenced to the level of the gastric cannula was determined in two animals by radiological contrast studies, in which barium filled the upright pig's stomach. The height of the water-level of the barostat system referenced to the level of the pylorus was determined. By the free flow of water from the barostat to the pig's stomach or vice versa, intragastric pressure was held constant.

Elevation of the height of the barostat produced a predictable increase in intragastric pressure ($r = 0.82$, $p = 0.0001$), from a mean of 0 mm Hg intragastric pressure with the barostat at 5 centimetres to 11 mm Hg with the barostat at 35 centimetres height. Intragastric pressures generated with the barostat set at 15 centimetres and 25 centimetres were

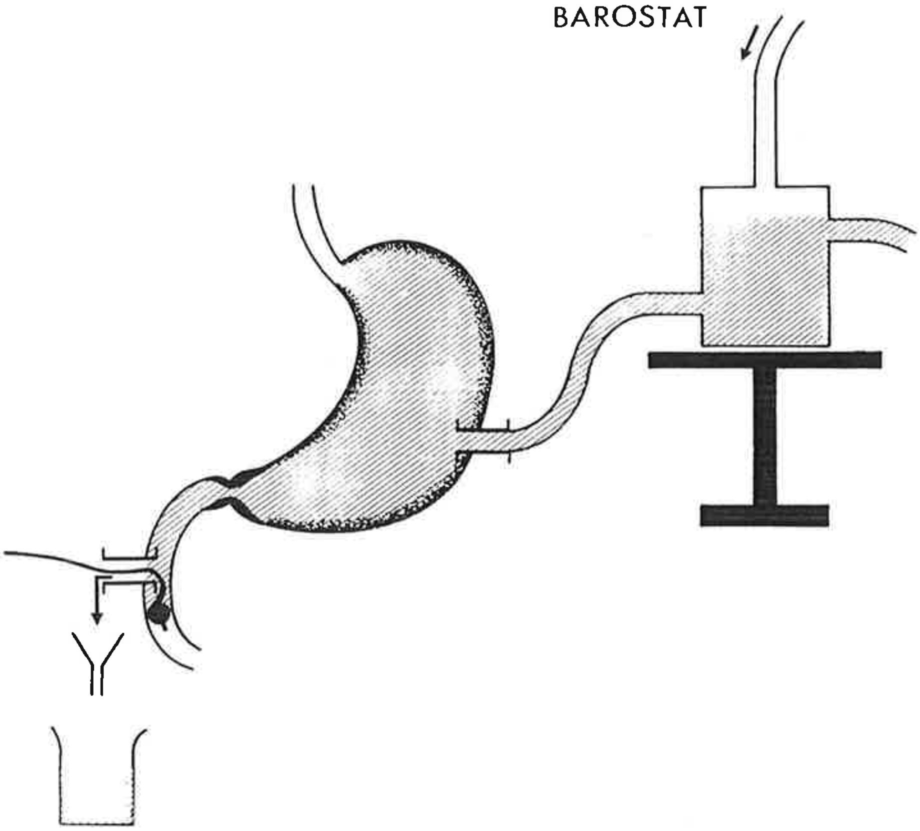


Figure 3.4: Diagrammatic representation of the barostat system.

comparable to those following ingestion, in the Kangaroo Island pig (Section 4.2).

Study Protocol

For each study the barostat system, Foley catheter and sleeve manometric assembly (Section 3.3.2) were positioned. The barostat fluid level was set initially at 5 centimetres above the gastric cannula. After 10 minutes, infusion of one of the intraduodenal test solutions, motility was recorded at progressively increasing barostat pressures of 5 centimetres, 15 centimetres, 25 centimetres and 35 centimetres above the gastric cannula. Recordings of motility and transpyloric flow were made for 15 minutes at each level.

Two studies were performed on each animal, on separate days, during intraduodenal infusion of either (i) normal saline, 20 millilitres per minute or (ii) 3.1% dextrose-saline solution, 20 millilitres per minute.

Discussion

The barostat presented here provides a cheap, easily manufactured means to manipulate intragastric pressures. The barostat creates an artificial situation, which may be unphysiological at high pressures. In comparison, the electronic air-barostat system utilised by Malagelada and co-workers (Azpiroz and Malagelada 1984) is expensive and complicated to manufacture, but does provide a measure of the motor activity of the proximal stomach.

3.3 APPLICATION OF MANOMETRIC TECHNIQUES TO THE PIG PREPARATION

3.3.1 PROFILE OF TRANS-MUCOSAL POTENTIAL DIFFERENCE ACROSS THE PIG PYLORUS

INTRODUCTION

Measurement of pyloric motility with stationary or pull through side hole manometry has provided conflicting results as to the motor activity of the pyloric region (Section 2.2). This controversy has developed in part because of the inability to confirm the position of sensors at the pylorus. This has been successfully overcome by the application of dual point trans-mucosal potential difference (TMPD) measurements, to confirm position of a sensor at the pylorus (Section 2.2). In order to apply the technique, it was necessary to define the the profile of TMPD across the gastro-duodenal junction, in the unsedated Kangaroo Island pig.

METHODS

Measurement of Trans-Mucosal Potential Difference

Trans-mucosal potential difference (TMPD) was recorded at two TMPD side holes, referred to as antral and duodenal TMPD side holes, on a multiple side hole manometric assembly (Section 3.3.2). These TMPD side holes were 55 millimetres apart. TMPD side holes were continuously perfused by a low compliance pneumo-hydraulic capillary infusion system (Arndorfer et al 1977), from separate and electrically isolated saline reservoirs. TMPD was measured through the perfusing saline column, connected via potassium chloride in agar bridges to silver-silver chloride electrodes, interfaced to high impedance purpose built millivoltmeters (model 1201, Biomedical Engineering, Flinders Medical Centre, South Australia), (Geall et al 1970). A potassium chloride in agar filled needle acted as subcutaneous reference. TMPD was monitored on the Grass polygraph. At the start of each study full scale pen deflection (5 centimetres) was set at -50 to +50 millivolts.

Study Protocol

At the start of each study the TMPD side holes were both positioned outside the duodenal cannula. The assembly was then withdrawn at 1 centimetre interval each 30 seconds, into and through the duodenum, to the antrum. As the pylorus lay 5 centimetres proximal to the duodenal cannula (Section 3.1.3), position of the TMPD side holes in relation to the gastro-duodenal junction was determined from the position of the manometric assembly relative to the duodenal cannula. TMPD was recorded continuously through all studies.

RESULTS

5 unsedated Kangaroo Island pigs were studied. With the TMPD side hole located at the duodenum, median TMPD recorded was

-2 millivolts (range +1 to -4 millivolts). TMPD at the duodenum was always less negative than -5 millivolts. When the TMPD side hole was located at the antrum, median TMPD recorded was -23 millivolts (range -18 millivolts to -28 millivolts). TMPD at the stomach was always more negative than -15 millivolts.

A sharp gradient of TMPD was confirmed to lie across the gastro-duodenal junction in each pig, of a median of 21 millivolts (range 16 to 26 millivolts). This gradient occurred across a median distance of 30 millimetres (range 24 to 32 millimetres).

In each animal, it was possible to position the manometric assembly with the antral TMPD side hole registering TMPD more negative than -15 millivolts and the duodenal TMPD side hole registering TMPD less negative than -5 millivolts. With the manometric assembly so positioned, the point of the manometric assembly midway between the two TMPD side holes lay on average 5 centimetres from the duodenal cannula, that is, at the gastro-duodenal junction.

CONCLUSION

This study has demonstrated that a gradient of TMPD exists across the gastro-duodenal junction in pigs. With the use of dual point TMPD measurements, it has been possible to position a manometric assembly, with TMPD side holes either side of the gastro-duodenal junction. These findings have been used to establish criteria of TMPD to position an array of side holes or a sleeve sensor across the gastro-duodenal junction during later studies. These TMPD criteria are: (1). The side hole at the antral end of either an array of side holes or a sleeve sensor records TMPD more negative that -15 millivolts. (2). The side hole at the duodenal end of either an array of side holes or a sleeve sensor records TMPD less negative than -5 millivolts.

The 21 millivolts gradient of TMPD across the gastro-duodenal junction of the pig is suitable for precise, continuous positioning of a manometric assembly at the pylorus and enabled accurate editing of manometric traces so that data could be obtained only during those intervals when then assembly was correctly positioned across the gastro-duodenal junction.

The existence of a gradient of TMPD across the gastro-duodenal junction has been well documented in man (Blackwood 1969, Anderson and Grossman 1965). TMPD recorded from the pig does differ in that TMPD recorded at both the antrum and duodenum were approximately 10 millivolts less negative than in man (Heddle et al 1988b). Different TMPD criteria are thus necessary to position a manometric assembly in the pig.

3.3.2 INTRALUMINAL PRESSURE MEASUREMENT OF PYLORIC MOTOR FUNCTION IN THE UNSEDATED PIG

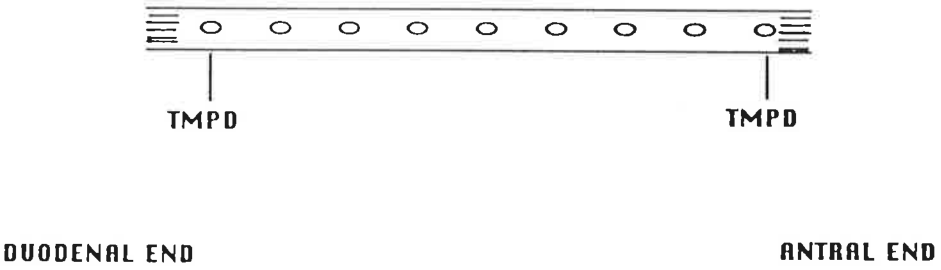
Manometric Assemblies

Two manometric assemblies were used. A multiple side hole manometric assembly incorporated 10 side holes at 6 millimetre intervals (Figure 3.5a). The assembly had a maximal external diameter of 4.5 millimetres. A sleeve manometric assembly incorporated a 5.5 centimetre long sleeve sensor for pyloric manometry and 8 side holes spaced at 1.5 centimetre intervals on either side of the sleeve as well as along the back of the sleeve, for recording antral, pyloric and duodenal motility (Figure 3.5b). The assembly had a maximal external diameter of 5.5 millimetres.

Manometric Technique

Each manometric assembly was continuously perfused by a low compliance pneumo-hydraulic capillary infusion system, at 0.6 millilitres per minute for the sleeve sensor and side holes at either end of the sleeve, the antral and duodenal TMPD side holes (Figure 3.5), and at 0.3 millilitres per minute for all other side holes. The pressure rise rate on occlusion at mid sleeve was 36 mm Hg per second and a each side hole occlusion was at least 270 mm Hg per second. Pressures were measured by external transducers (2 of Gould Statham model P23 1D, Hato Rey, Puerto Rico and 8 of Code model 01N 4655, Lakewood, Colorado, USA) with output to a 12 channel pen chart polygraph (Grass

A: MULTIPLE SIDE HOLE MANOMETRIC ASSEMBLY



B: SLEEVE MANOMETRIC ASSEMBLY

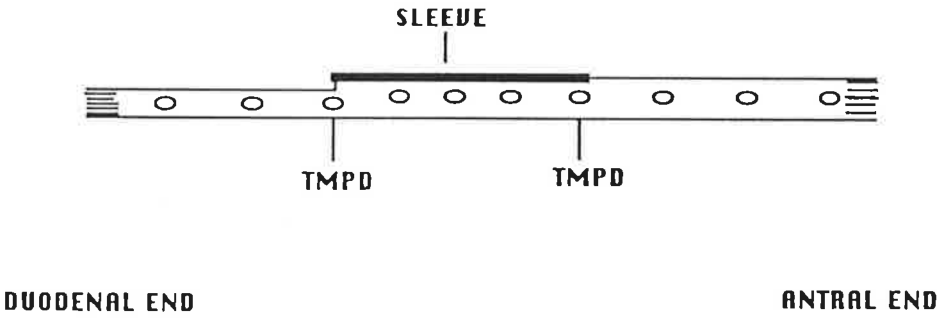


Figure 3.5: Manometric assemblies:

A: Multiple side hole assembly.

B: Sleeve assembly.

model 7D, Quincy, Massachusetts, USA), chart speed 100 millimetres per minute. At the start of each study full scale pen deflection (5 centimetres) was calibrated at 0 to 50 mm Hg pressure.

Analysis of Manometric Recordings

Manometric analyses used in this thesis have been drawn directly from those established by Heddle et al (1988b).

Analysis of motility during stationary side hole studies was performed only on those segments of a trace in which TMPD criteria confirmed that the array of side holes were correctly positioned astride the gastro-duodenal junction (Section 3.3.1). Phasic pressure waves were defined as rises in pressure equal to or greater than 10 mm Hg, which lasted for less than 20 seconds. Pressure waves were classified as associated when the major pressure rise recorded by a side hole had its onset within 5 seconds of the onset of the major pressure rise recorded by the most proximal (antral) side hole. A 'typical sequence' of pressure waves was defined as an episode of three or more of one type of pressure wave, in which the time from onset of any pressure wave to onset of the following pressure wave in that sequence occurred within 20 seconds.

In studies of intestinal stimulation of motility, basal pyloric pressure each 5 minute interval was derived from a planimetric measure of the area under the curve of the manometric trace. In studies of gastric stimulation of motility, basal pressures at the pylorus, antrum and duodenum were determined by direct measurement of basal pressure each half minute and the mean pressure each five minute intervals then calculated. Pyloric pressure, recorded by the sleeve, was referenced to antral pressure, recorded by the antral side hole 3 centimetres proximal to the sleeve sensor. Sustained pyloric tone was defined as basal pyloric pressure greater than or equal to 3 mm Hg above antral basal pressure, for at least 5 minutes. Pressure waves were edited by drawing a line from their onset to offset. Abrupt elevation of intra-abdominal pressure, caused by grunting or body movement, were recognised as they produced identical pressure changes in all manometric channels. Such changes were excluded from analysis.

3.4 LIQUID GASTRIC EMPTYING STUDIES

Measurement of Gastric Emptying

Measurement of emptying of an ingested liquid was performed simultaneously with manometry, during intestinal stimulation of pyloric motility. The liquid meal consisted of 1000 millilitres of 5% dextrose, labelled with 100 microCuries (3.7 megaBequerels) of ^{113m}Indium-DTPA (diethylenetriamine pentaacetate). Prior to each study a 1 millilitre sample was taken from the 1000 millilitre liquid to be drunk by the pig. This was used to determine the total counts ingested by the pig. Drainage from the duodenal cannula was collected over 5 minute intervals, the volume noted and a sample stored for subsequent radio-isotopic counting. The relative volumes of the radio-labelled drink emptied from the duodenal cannula were calculated for each 5 minute interval, for 30 minutes following ingestion.

Continuous Record of Flow

With the aim of measurement of pyloric motility simultaneously with the measurement of gastric emptying, it was appreciated that a continuous permanent record of transpyloric flow associated with recordings of motility was necessary. This was achieved by draining the effluent from the duodenal cannula into a funnel and, with suction, drawing the chyme to a balance. By interfacing the output from the balance to a polygraph, it was possible to continuously collect, weigh and record gastric outflow. This setup provided a measure of rates of flow as well as precise temporal correlation of episodes of flow with patterns of motility.

An episode of pulsatile flow was defined as an increase in flow out the cannula of greater than 6 millilitres per second within a two second interval, with a return to the previous rate of flow within the following 20 seconds. An episode of pulsatile flow was classified as related to a pressure wave when the onset of flow occurred either 8 seconds before or after onset of a pressure waves recorded by the sleeve sensor (see below). This analysis included an allowance for delay due to the passage of fluid from the duodenal bulb to the cannula and into the collection chamber. This correction factor was determined in each pig by injection of a bolus of fluid into the duodenal bulb.

3.5 GASTRIC EMPTYING OF A DIGESTIBLE SOLID

Three different solid gastric emptying studies were undertaken. No intestinal or gastric stimulation of pyloric motility was undertaken during solid emptying studies.

3.5.1 SIMULTANEOUS MANOMETRY - EMPTYING STUDIES

Measurement of solid gastric emptying during these studies was performed simultaneously with the measurement of antro-pyloric motility, recorded by the sleeve manometric assembly.

The meal consisted of a 400 gram hamburger radio-labelled with 400 microCuries (15 megaBequerels) of ^{99m}Technecium sulphur colloid in a median weight of 21.2 grams (range 12.8 to 32.6 grams) of chicken liver (Meyer et al 1976). A sample of the radio-labelled liver was taken prior to ingestion for subsequent counting.

Study Protocol

The Foley catheter and manometric assembly were positioned (see above). Following ingestion of the 400 gram meat meal, drainage from the duodenal cannula was collected in 10 minute periods for the 120 minute duration of each study. The duration of lag period and the linear rate of emptying following the lag period were determined for each study from a line of best fit of the data (Collins et al 1983).

3.5.2 PARTICLE SIZE MEASUREMENTS

The protocol for measurement of particle sizes that empty from the stomach of the Kangaroo Island pig has been reported previously (Landers et al 1990). For logistic reasons it was necessary to perform measurements of particle size separately from manometric studies. The solid meal for particle size measurements consisted of a 400 gram meal of 1 centimetres cubed liver, radio-labelled with 400 microCuries (15 megaBequerels) of ^{99m}Technecium sulphur colloid in a median of 45.3 grams (range 19.7 to 65.7 grams) of chicken liver. A sample of the radio-labelled liver was taken prior to ingestion for subsequent counting. Drainage from the duodenal cannula was collected over 30 minute intervals, for the 120 minute duration of each study and passed through a series of 4 woven wire mesh sieves with apertures of 1.00 millimetre, 0.50 millimetres, 0.25 millimetres and 0.15 millimetres (Endecotts Ltd, Lombard Road, Morden Factory Estate, London). Material retained by each sieve was harvested and its radioactivity counted.

3.5.3 EXTERNAL GAMMA CAMERA STUDIES

Introduction

The pig preparation has enabled correlation of gastric emptying with antral, pyloric and duodenal motility. The pig preparation is limited in that the movement of solids and liquids within the stomach cannot be measured. The external gamma camera provides information on the movement of radio-labelled foodstuffs both within the stomach, across a postulated mid-gastric band (Moore et al 1987, Collins et al 1988) and from the stomach to the intestine.

Technique

The solid meal consisted of 300 grams of mince, radio-labelled with 2.5 milliCuries (94 megaBequerels) of ^{99m}Technecium sulphur colloid in chicken liver.

Neither a manometric assembly nor Foley catheter were positioned. Plugs from the intestinal cannulae were left closed. Measures of gastric emptying were recorded each 10 minute interval for 120 minutes, with the camera positioned lateral to the pig. Position of the stomach was confirmed by reference to the position of a radio-active skin marker (Collins et al 1988).

3.6 SURGICAL INTERVENTIONS

3.6.1 EXCISION OF THE PYLORUS

Introduction

The aim was to investigate the role of the pylorus in the control of gastric emptying by removal of pyloric motor function. Results from animals with the pylorus excised were compared to results from animals with the pylorus intact.

Animal Preparation

Six Kangaroo Island pigs aged 5 months and weighing between 30 and 55 kilograms underwent surgery under general anaesthesia. Each animal had cannulae inserted into the duodenum and stomach. At the same operation, in 3 of the 6 animals, the pylorus was excised and continuity restored by a standard Billroth I antroduodenal anastomosis. Inversion of bowel ends was avoided. Three animals initially prepared with only insertion of cannulae underwent pylorus excision at a second operation, 3 to 6 months after the first surgery and following physiological studies. At the completion of all experiments the animals were killed and the site of anastomosis examined. Median luminal diameter at the site of anastomosis was 13 millimetres, compared to a median luminal diameter 1 centimetres distal to the anastomosis of 15.5 millimetres. This minor degree of narrowing was thought to be of no significance for effects on gastric emptying.

As the proximal margin of the pylorus varies and cannot be recognised macroscopically (Torgersen 1942), the length of the pylorus to be excised was determined in each animal by mapping with the multiple side hole manometric assembly positioned astride the pylorus (Section 3.3.2). The length of excision, as determined manometrically, was referenced from the anatomically distinct gastroduodenal junction. Pylorus-mapping manometry was performed intra-operatively in 3 animals, during stimulation of localised pyloric contractions (Section 4.1) by the intravenous bolus injection of 0.7 micrograms of cholecystokinin octapeptide (Kinevac, Squibb Diagnostic, New Jersey) repeated 3 times, and prior to a second operation in 3 animals, during stimulation of localised pyloric contractions by the intraduodenal infusion of dextrose solution, while conscious (Section 4.1). Overall, a pylorus of between 24 and 36 millimetres length was mapped, and a median length of 35 millimetres of pylorus excised.

Each animal was allowed 4 weeks recovery following operation before studies commenced.

3.6.2 TRANSECTION OF THE DUODENUM

Introduction

The aim was to investigate the role of ascending duodenal intramural nerves in the control of pyloric motility and gastric emptying. Nerves travelling within the wall of the duodenum just distal to the pylorus were interrupted by transection of the duodenum. Results from animals with the duodenum transected were compared to results from animals with the duodenum intact.

Surgical Preparation

Six Kangaroo Island pigs ranging in body weight from 34 to 55 kilograms, with duodenal and gastric cannulae underwent operation under general anaesthesia. Duodenal cannulae were inserted via a 4 centimetres longitudinal incision. At the same operation, the duodenum was divided transversely and re-anastomosed end-to-end, 1 to 2 centimetres distal to the pylorus. At the completion of all experiments all animals were killed and the site of anastomosis examined, to ensure that surgery had not produced significant stenosis. Luminal diameter at the site of anastomosis was 24% less than the luminal diameter 1 centimetres distal to the anastomosis (diameter at anastomosis: 11-14 millimetres; diameter distally: 14-18 millimetres). This degree of narrowing was thought not to influence liquid transpyloric flow.

Each animal was allowed 4 weeks recovery following operation before studies commenced.

3.6.3 VAGUS NERVE COOLING

Introduction

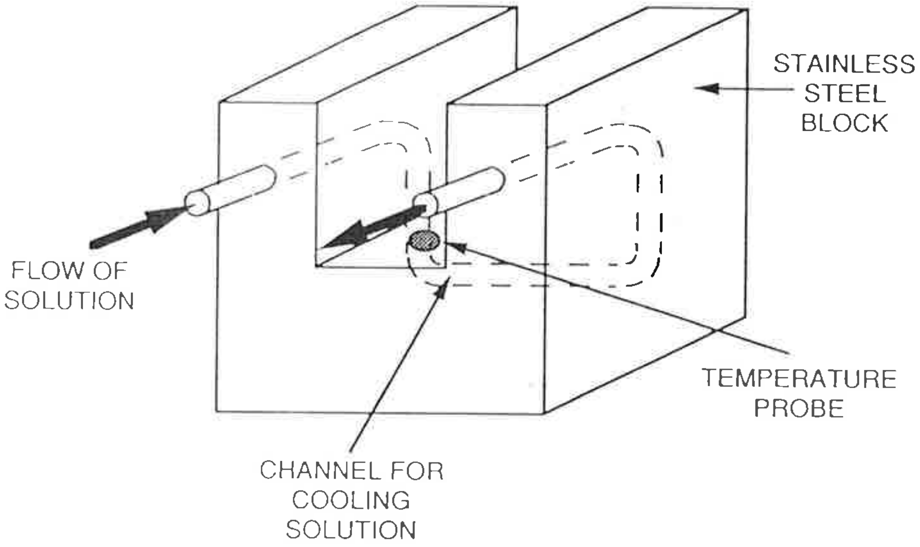
The aim was to investigate the role of the vagus nerve in the control of pyloric motility and gastric emptying, by acute reversible vagal blockade, achieved by cooling the vagus nerve trunks.

Vagus Nerve Cooling Device

Three identical cooling devices were manufactured, by Mr. Gary Hallas, technical assistant to the project. Each cooling device consisted of a one centimetre cube of stainless steel, with a slit along one side, 3 millimetres wide and 5 millimetres deep, through which the vagus nerve trunks would be positioned. A temperature probe was attached to the device, with the sensing surface aligned to be in contact with the vagal trunks. A convoluted tunnel passed through the block, through which a cooling solution could be pumped. The steel block acted as a heat sink. Silastic tubing connected to each end of the tunnel. The whole assembly was coated in a 3 millimetre thickness of silastic sheeting for insulation (Figure 3.6).

Bench Testing

Preliminary testing of each devices was performed. Each assembly was placed in a water bath at 38 °C. A cooling



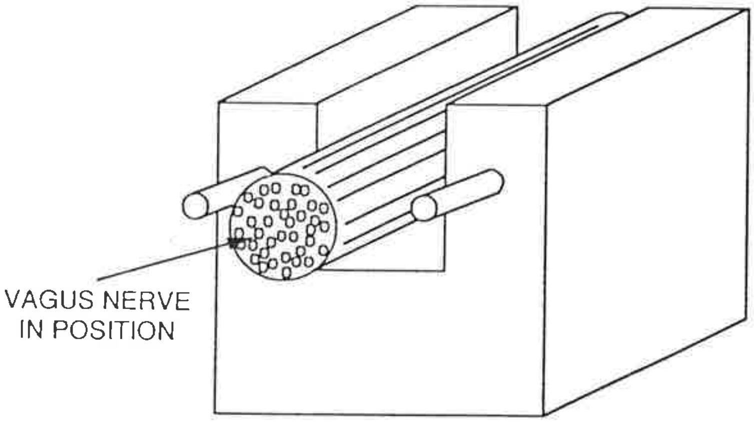


Figure 3.6: Vagal cooling device.

solution of absolute alcohol was pumped through a blood warmer coil, placed within a slurry of dry ice/ethanol (-70 ^{o}C). Temperature of the assembly, recorded by the enclosed thermistor, could be precisely adjusted to 4 ^{o}C by alteration of the rate of flow of the cooling solution.

Device Implantation

Under general anaesthesia of halothane/nitrous oxide, and through a mid-line laparotomy, the left lobe of the liver was mobilized so as to expose the abdominal vagal trunks. In each animals operated upon, the trunks were anatomically comparable to that found in humans, in size and location. The anterior and posterior vagal trunks were mobilized over 5 centimetres and placed within the slit of the cooling device. In two animals both vagal trunks were positioned within a single device. In one animal the vagal trunks were positioned in two separate devices, one for each trunk. Gastric and duodenal cannulae were inserted at the same operation.

Each animal was allowed 4 weeks recovery before studies commenced.

SECTION 4

STIMULATION OF PYLORIC MOTILITY

4.1 Patterns of Motility in the Pig Pylorus

4.2 Intestinal Stimulation of Pyloric Motility

4.3 Cephalic Stimulation of Pyloric Motility

4.4 Gastric Stimulation of Pyloric Motility

4.1 PATTERNS OF MOTILITY OF THE PIG PYLORUS

INTRODUCTION

Measurement of pyloric motility with stationary or pull through side hole manometry have provided conflicting results as to the motor activity of the pyloric region (Section 2.2). This controversy has probably developed due to both the inability of single or widely spaced side holes to accurately record pressure from the narrow and mobile pylorus (Heddle et al 1988b), as well as the inability to confirm the position of sensors at the pylorus.

The aim of this study was to define the topography of contractions of the pig pylorus, as recorded by the multiple side hole manometric assembly, and apply these results to characterise and define the patterns of motility of the pylorus recorded by the sleeve manometric assembly.

METHODS

Multiple Side Hole Manometric Assembly Studies

Five animals were studied. For each study the multiple side hole manometric assembly was positioned with the array of side holes across the gastro-duodenal junction. Correct position was confirmed by dual point measurement of trans-mucosal potential difference (Section 3.3.1). After positioning both the manometric assembly and Foley catheter, manometric recordings started, concurrent with distal duodenal infusions. Normal saline was infused into the duodenum at 20 millilitres per minute for 15 minutes. The intraduodenal infusion was then changed to isosmolar 3.1% dextrose-saline solution, 20 millilitres per minute (Table 1) and continued for the remaining 15 minutes of each stationary side hole study.

Sleeve Manometric Assembly Studies

Six animals were studied. The sleeve manometric assembly was positioned at the antro-duodenal region, with the sleeve sensor astride the pylorus, as confirmed by dual point measurements of TMPD (Section 3.3.1). After positioning both the manometric assembly and Foley catheter, manometric recordings commenced, concurrent with distal duodenal infusions. Studies were performed during intraduodenal infusion of either normal saline, 20 millilitres per minute, or isosmolar 3.1% dextrose-saline solution, 20 millilitres per minute.

Manometric definitions used in this thesis have been derived directly from those established by Heddle et al (1988b), and applied to the pig preparation.

RESULTS

Two patterns of associated pressure waves were recorded with the multiple side hole manometric assembly. This classification of pressure waves led to the definitions of antro-pyloric pressure waves and isolated pyloric pressure waves.

During intraduodenal infusion of normal saline, 20 millilitres per minute, 55 pressure waves were recorded by the multiple side hole manometric assembly. Of these, 89% were recorded by 7 or more side holes and thus occurred over a length greater than 42 millimetres. All waves were recorded by the two most proximal side holes of the assembly (at the antrum) and none by the most distal side holes of the assembly (at the duodenum). These waves were classified as antro-pyloric pressure waves (APWs). Based on these results, pressure waves recorded with the sleeve manometric assembly were defined as APWs when registered by the sleeve sensor plus 1 or more side holes proximal to the antral trans-mucosal potential difference side hole (Figure 4.1a).

The intraduodenal infusion of 3.1% dextrose-saline at 20 millilitres per minute was associated with a second pattern of pressure waves, recorded over a narrow zone at the pylorus alone. Of the 131 pressure waves recorded with the manometric assembly, 84% were recorded by 3 to 6 contiguous side holes and all were recorded by 2 to 7 side holes, that is, the width of the pylorus generating the wave was from a minimum of 12 to a maximum of 42 millimetres in length (Figure 4.2). These waves had a synchronous onset across the pylorus and were classified as isolated pyloric pressure waves (IPPWs). Based on this multiple side hole analysis, pressure waves recorded with the sleeve manometric assembly were defined as IPPWs when registered by the sleeve sensor and two side holes along the back of the sleeve, in the absence of an associated wave of any amplitude at

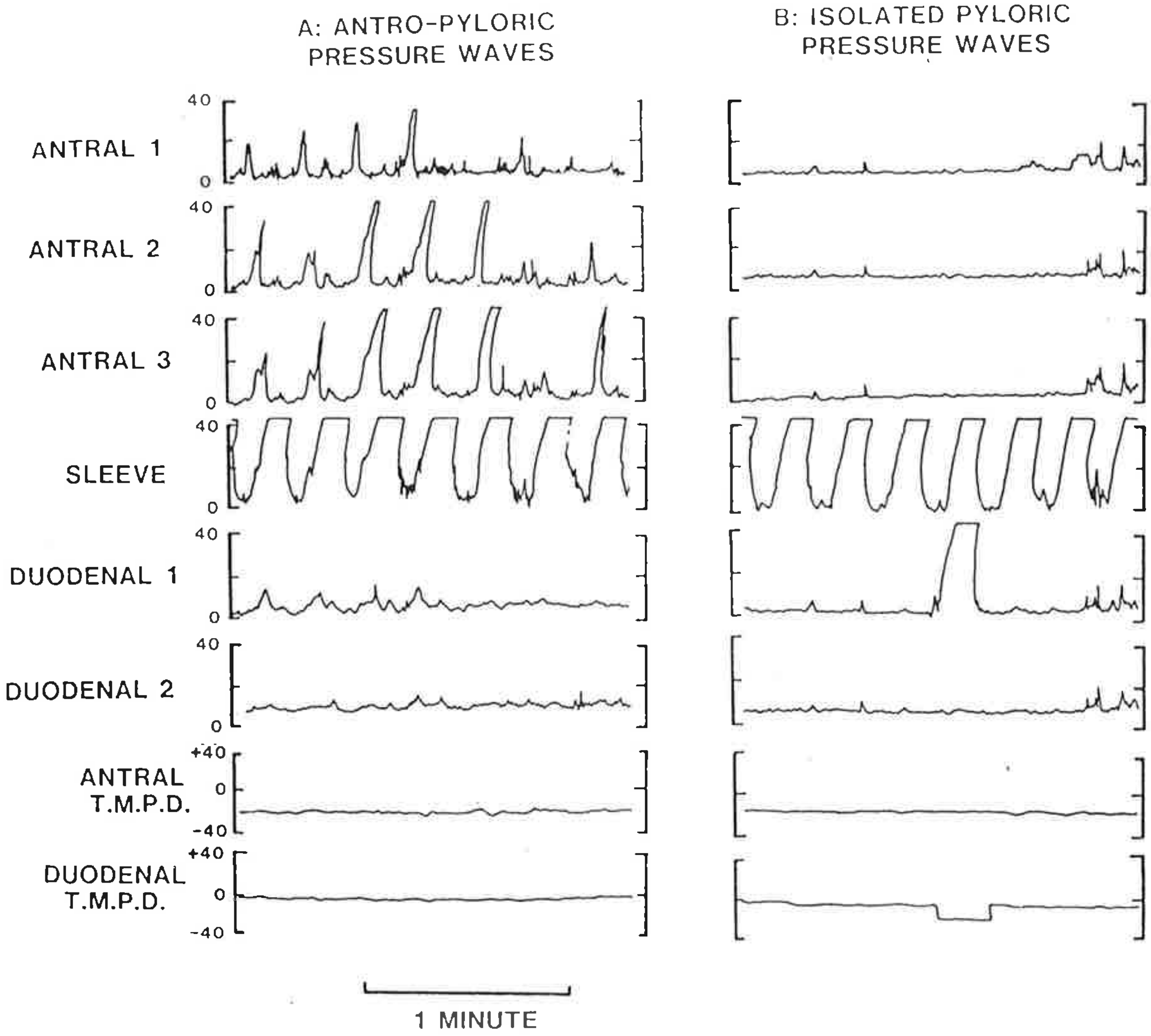


Figure 4.1: Characteristic recordings for:

A: Antro-pyloric pressure waves.

B: Isolated pyloric pressure waves.

Recordings from one pig during two separate studies. Antral 1, 2 and 3 refers to pressure recordings from the three separate antral side holes. Duodenal 1 and 2 refers to pressure recordings from the two separate duodenal side holes. TMPD refers to trans-mucosal potential difference recordings. N.B. At one point during the recording of isolated pyloric pressure waves (B), the manometric assembly slipped proximally into the stomach and thus out of position, as registered by the duodenal trans-mucosal potential difference recording. This portion of the recording was edited out.

NUMBER OF SIDE HOLES	WIDTH OF PHASICALLY ACTIVE ZONE (mm)
2	6 - 18
3	12 - 24
4	18 - 30
5	24 - 36
6	30 - 42
7	36 - 48

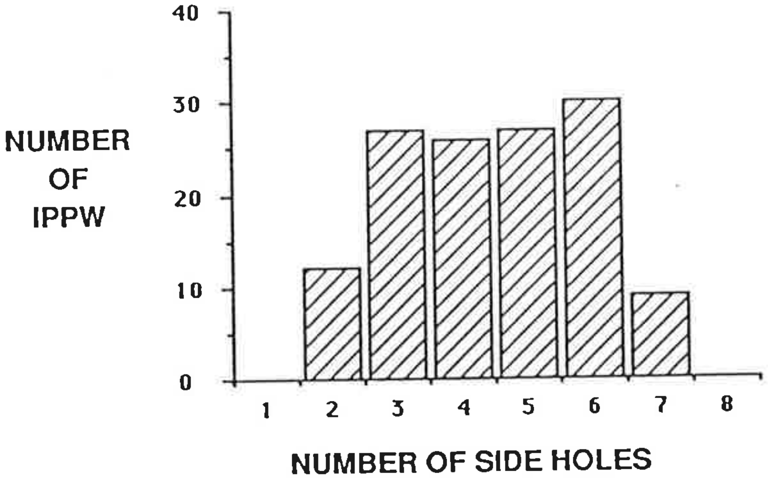


Figure 4.2: Width of pyloric phasically active zone. Results from 131 pressure waves recorded by the multiple side hole manometric assembly during intraduodenal infusion of 3.1% dextrose-saline solution at 20 ml/min. Results from 5 pigs, one study per pig.

any of the side holes proximal or distal to the sleeve, including the trans-mucosal potential difference side holes (Figure 4.1b).

The protocol of studies permitted examination of the time course of alteration of motility resulting from alteration of the duodenal infusate. Conversion from predominantly an APW pattern to a predominantly IPPW pattern occurred 110 seconds following the change of intraduodenal infusion from saline to dextrose (mean of 4 pigs, range 40 to 195 seconds).

Neither the multiple side hole nor the sleeve manometric assemblies indicated any sustained elevation in pyloric pressure (pyloric tone) during any study.

CONCLUSIONS

Results from this study have demonstrated that pyloric manometric studies in awake unsedated pigs are feasible, and have helped define the topography of motor activity of the pig pylorus.

The pyloric region of the pig has been demonstrated to undergo at least two distinct patterns of motility. These patterns are phasic pressure waves localised or isolated to the pylorus, classified as IPPWs, and localised phasic pressure waves, classified as APWs. In all studies, no consistent elevation of basal pyloric pressure, or pyloric tone, was recorded.

STIMULATION OF PYLORIC MOTILITY

The stimulation of pyloric motility can categorized into three basic components : cephalic, gastric and intestinal.

4.2 INTESTINAL STIMULATION OF PYLORIC MOTILITY

INTRODUCTION

The stomach acts to store food, slowly passing chyme into the small intestine at rates that are closely modulated by the nutrient, osmolar or pH content of the chyme leaving the stomach (Meyer 1987). The stimulation of receptors at the duodenum and upper small bowel by this chyme provides feedback to the motor mechanisms that control gastric emptying (Meyer 1987). The aim of this study was to investigate and characterise the effects on pyloric motility of stimulation of the upper small bowel by a variety of nutrient and osmolar solutions and by distension of the mid-duodenum.

METHODS

6 Kangaroo Island pigs (weights 34 to 55 kilograms) with duodenal and either oesophageal (3 pigs) or gastric (3 pigs) cannulae were studied (Table 1). Pyloric motility was recorded as described previously (Section 3.3.2), during intestinal stimulation of pyloric motility (Section 3.2.1), for the 30 minutes following ingestion of a 1000 millilitre drink.

TABLE 1

SOLUTIONS INFUSED INTO THE DUODENUM

Duodenal Infusate (ml/min)	Rate of Infusion (kcal/min)	Calorie Load (kcal/min)	Number of Pigs
Normal Saline	20	0	6
3.1% Dextrose	5	0.62	5
3.1% Dextrose	10	1.24	6
3.1% Dextrose	20	2.48	6
Fatty Acid	5	0.62	5
Amino Acids	30	3.72	5
3 Normal Saline	10	0	5
25% Dextrose	4	4.00	6

Statistical Analysis

Data were analysed by analysis of variance with Fisher's LSD (least significant difference) and simple regression analysis, as appropriate.

RESULTS

1. Nutrient and Hyperosmolar Studies

Following ingestion of the radio-labelled drink, intraduodenal infusion of saline was associated primarily with the occurrence of APWs at 0.81 per minute and relative absence of IPPWs at 0.43 per minute (Figure 4.3). Duodenal infusion of dextrose, amino acids, fatty acid and hyperosmolar saline solutions resulted in a markedly different pattern of antro-pyloric motility: IPPWs occurred significantly more frequently (Figure 4.3a); APWs occurred significantly less frequently (Figure 4.3b).

A dose-response relationship was investigated, using differing rates of 3.1% dextrose-saline infusion (Table 1). An increase in the dextrose load infused intraduodenally throughout each study resulted in a significant increase in the rate of IPPWs ($r = 0.70$, $p = 0.0002$) and a decrease in the rate of APWs ($r = 0.32$, $p = 0.14$), although this did not reach statistical significance (Figure 4.4).

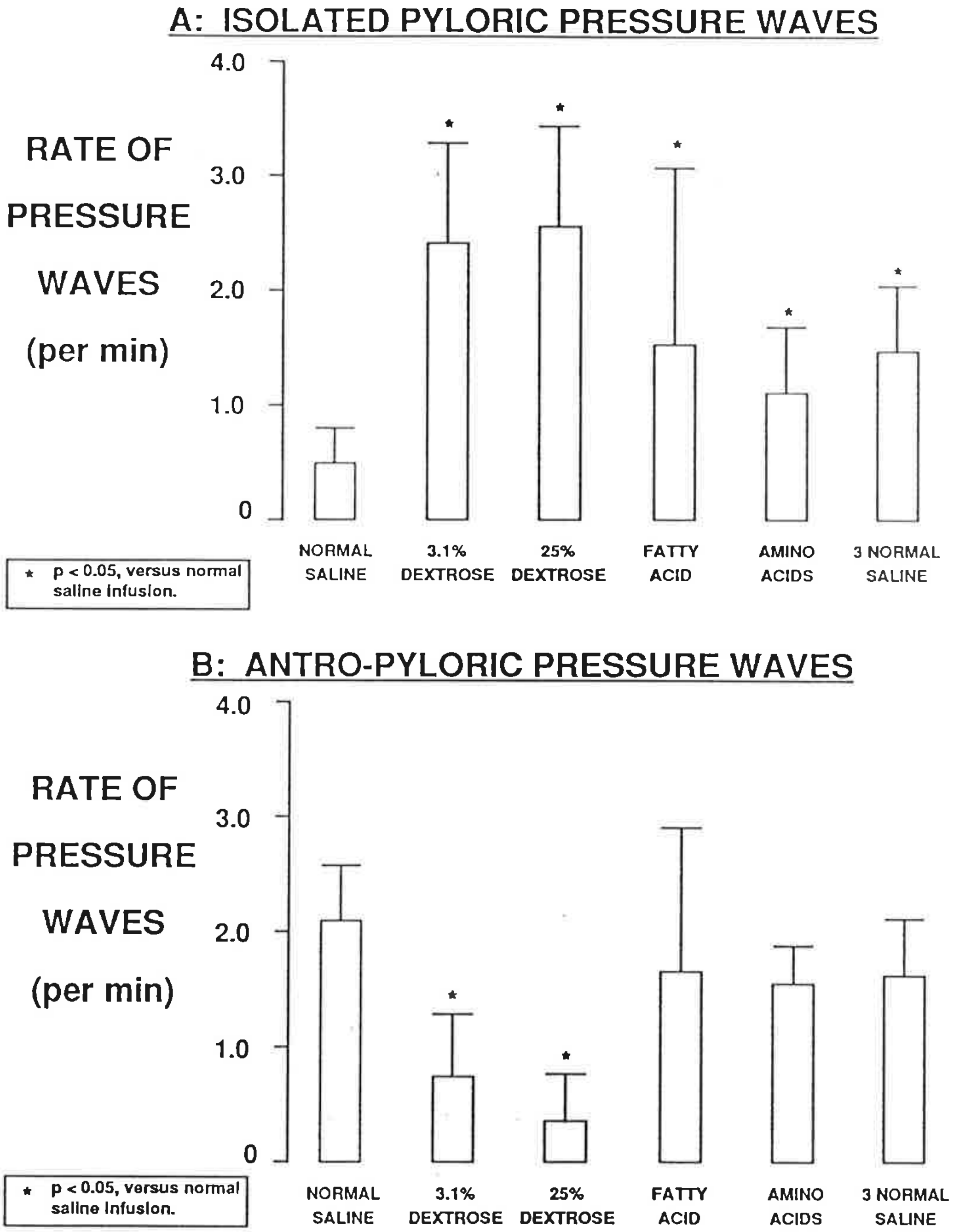


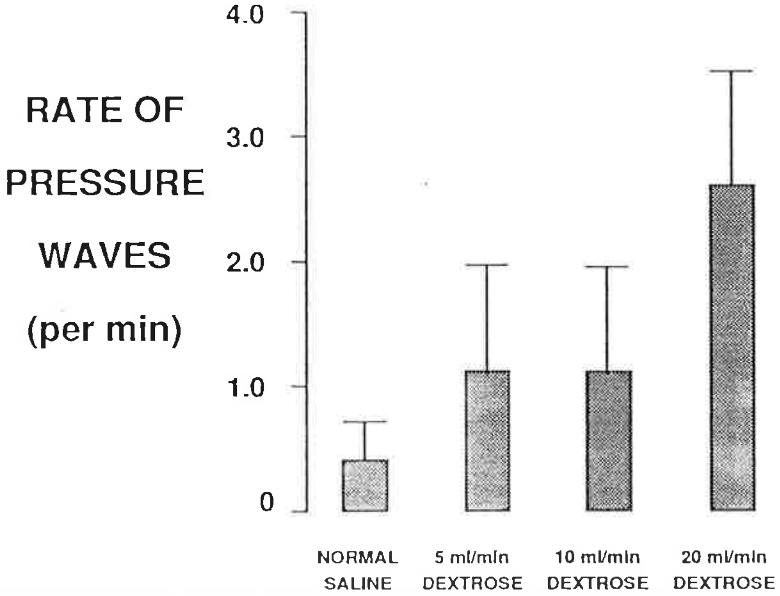
Figure 4.3: Rates of

A: isolated pyloric pressure waves,

B: antro-pyloric pressure waves,

during duodenal infusions of nutrient or hyperosmolar solutions. Results from 6 pigs, one study per pig.

A: ISOLATED PYLORIC PRESSURE WAVES



B: ANTRO-PYLORIC PRESSURE WAVES

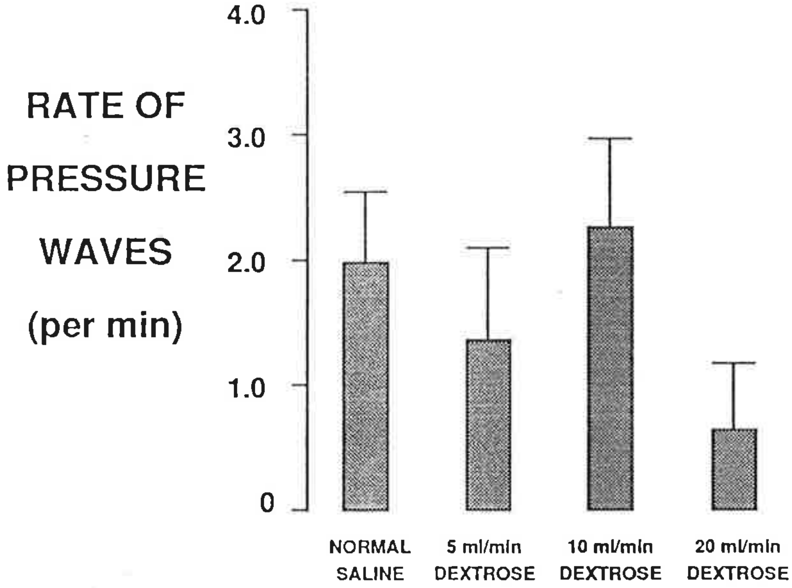


Figure 4.4: Rates of

A: isolated pyloric pressure waves,

B: antro-pyloric pressure waves,

during increase in the dextrose load infused intraduodenally throughout each study. Results from 6 pigs (5 pigs only during dextrose-saline infusion at 10 ml/min), one study per pig.

In all studies, side holes distal to the sleeve, that is, within the duodenum beyond the duodenal cap, did not record any pressure rise, phasic or tonic, except for those due to straining.

2. Duodenal Distension Studies

A total of 14 studies were performed, on five animals: 5 studies with the Foley balloon at 6 and 15 millilitres and 4 studies with the Foley balloon at 25 millilitres volume.

Distension of the duodenum by the Foley balloon was associated with a significant stimulation of IPPWs ($r = 0.53$, $p = 0.04$) (Figure 4.5a) and inhibition of APWs ($r = -0.48$, $p = 0.05$) (Figure 4.5b), in proportion to the volume of the Foley balloon.

CONCLUSIONS

This study gives new information about the intestinal control of pyloric motility. The major findings are that IPPWs are stimulated and APWs are inhibited by both the intraduodenal infusion of a range of nutrient and hyperosmolar solutions, as well as by distension of the duodenum. In the cases of both intraduodenal dextrose infusion and duodenal distension, a dose-response relationship was investigated and demonstrated.

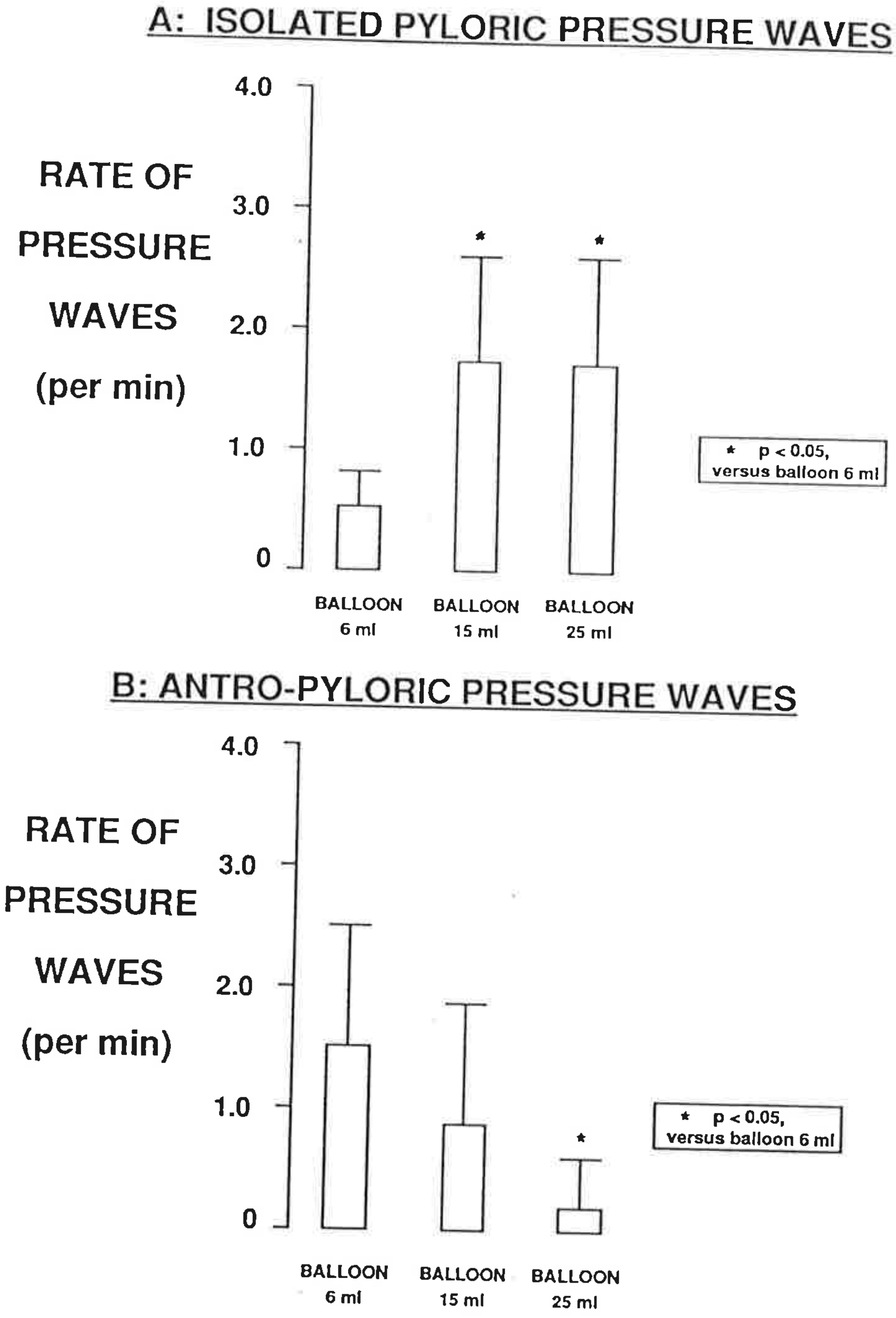


Figure 4.5: Rates of

A: isolated pyloric pressure waves,

B: antro-pyloric pressure waves,

during duodenal distension. Results from 6 pigs with duodenal balloon 6ml, 5 pigs with balloon 15 ml, 4 pigs with balloon 25 ml, one study per pig.

4.3 CEPHALIC STIMULATION OF PYLORIC MOTILITY

INTRODUCTION

Stimulation of gastric motility and emptying following ingestion may occur in response to the cephalic stimuli of sight, smell and taste of food. These stimuli can be assessed by the measurement of gastric motility before and following presentation of a meal. The aim of this study was to examine the effect of such cephalic stimulation of pyloric motility patterns recorded, during modulation of motility by a variety of intestinal stimuli.

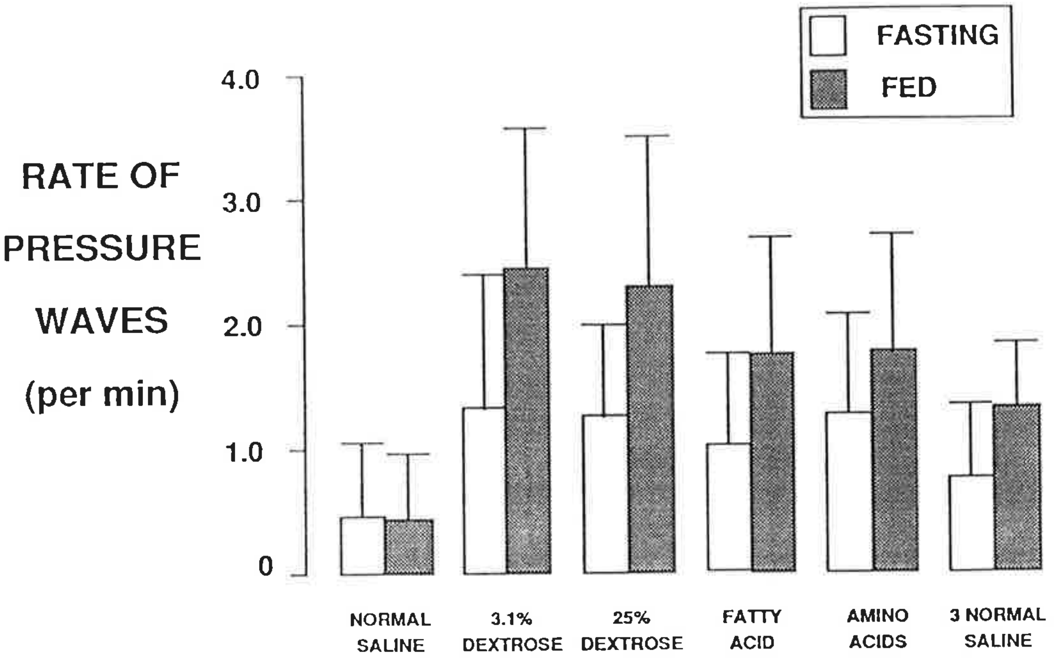
METHODS

Studies with the sleeve manometric assembly (Section 3.3.2) were undertaken in 6 pigs. Intestinal stimulation of motility was by the intraduodenal infusion of nutrient or hyperosmolar stimuli (Section 3.2.1). Data was analysed from the ten minute interval prior to and following ingestion of the 1000 millilitre drink.

RESULTS

Prior to ingestion of the drink, pressure waves at the pylorus and antrum occurred infrequently (Figure 4.6). Ingestion of the drink stimulated the occurrence of regularly occurring pressure waves in all studies, immediately upon

A: ISOLATED PYLORIC PRESSURE WAVES



B: ANTRO-PYLORIC PRESSURE WAVES

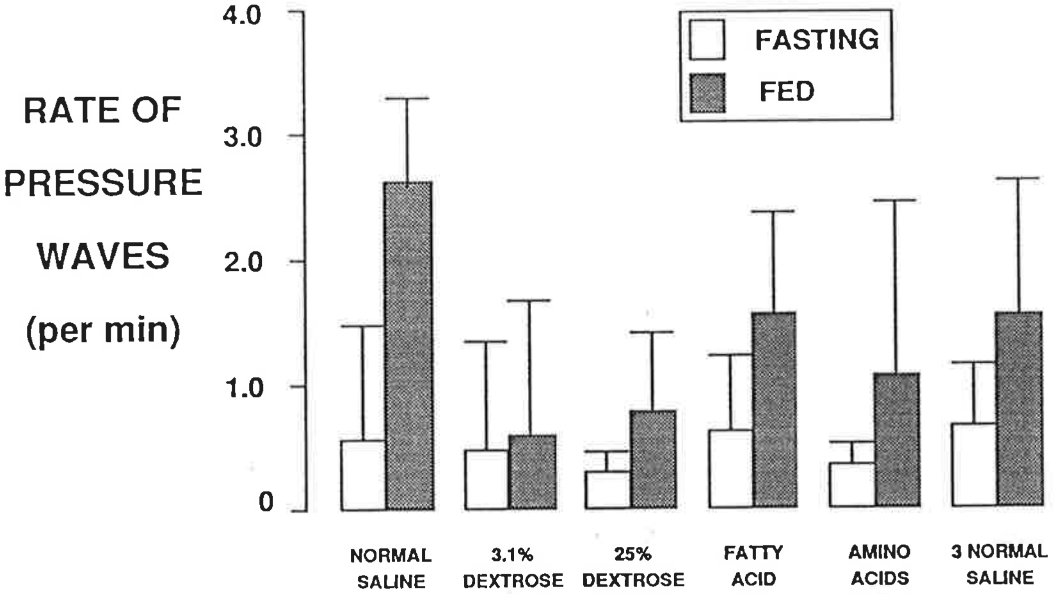


Figure 4.6: Rates of:

A: isolated pyloric pressure waves,

B: antro-pyloric pressure waves,

for the 10 minute intervals prior to (fasting) and following (fed) ingestion of the 1000 ml radio-labelled drink, during duodenal infusions of nutrient or hyperosmolar solutions. Results from 6 pigs, one study per pig.

presentation of the drink, usually before ingestion had begun (Figure 4.7). This stimulation of pressure waves was observed for both IPPWs and APWs (Figure 4.6).

CONCLUSIONS

This study has demonstrated a cephalic stimulation of pyloric motility. Regular unrelenting pressure waves commenced within seconds of presentation of the meal to the animal, often before drinking had begun and always before any significant volume of the drink had entered the stomach.

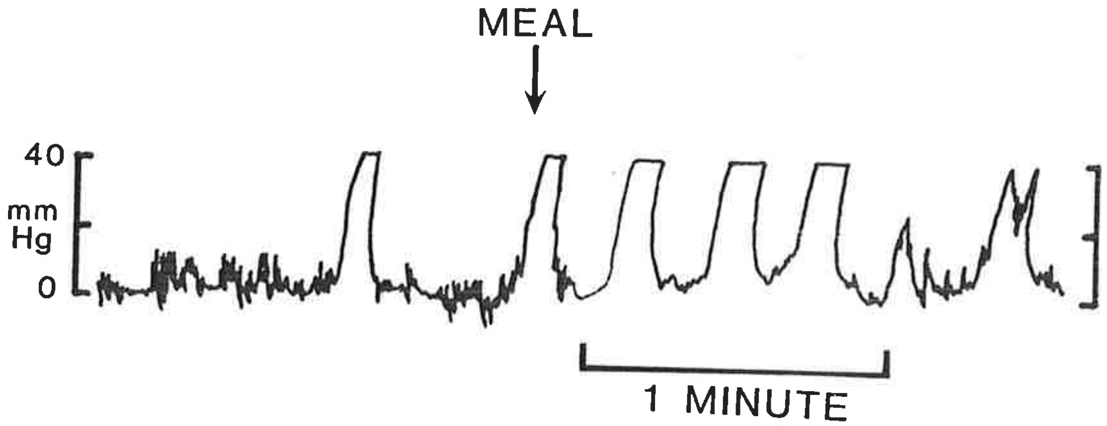


Figure 4.7: Stimulation of pyloric motility with ingestion of the 1000 ml radio-labelled drink. Recording from sleeve sensor, during intraduodenal infusion of 3.1% dextrose-saline solution at 20 ml/min.

4.4 GASTRIC STIMULATION OF PYLORIC MOTILITY

INTRODUCTION

Little is known about the role of gastric stimulatory mechanisms in the control of pyloric motility. Distension of the stomach has been proposed as one major stimulus of gastric motor activity (Azpiroz and Malagelada 1984), through such reflexes as the "antral reflex" (Andrews et al 1980a).

The aim of this study was to investigate the effects of distension of the stomach upon pyloric motor activity. A water barostat has been developed and applied to the pig preparation, to control intragastric pressures.

METHODS

Pyloric motility was recorded in 6 Kangaroo Island pigs, during gastric stimulation of motility (Section 3.2.2). Data were analysed by two way analysis of variance, using Fisher's LSD and simple regression analysis, as appropriate.

RESULTS

Duodenal infusion of dextrose stimulated IPPWs (Figure 4.8). The level of stimulation of IPPWs was influenced by the barostat, being near maximal with the barostat set at or above 15 centimetres, at an overall mean of 2.6 waves per minute for

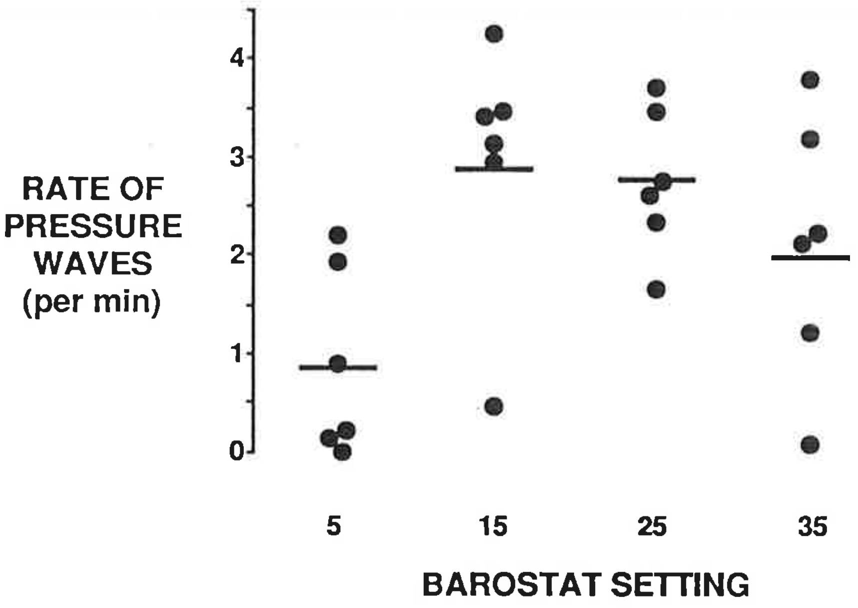


Figure 4.8: Rates of isolated pyloric pressure waves during intraduodenal dextrose infusion, at each barostat setting. Results from 6 pigs, one study per pig.

the barostat at 15, 25 and 35 centimetres, and unrelated to intragastric pressure (r = -0.31, p = 0.22), (Figure 4.8). Below this setting, IPPWs occurred infrequently, at 0.9 waves per minute.

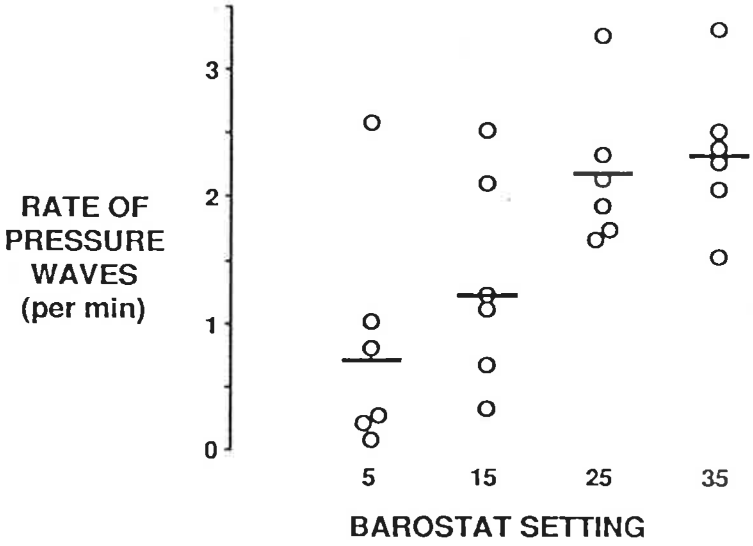
The rate of APWs was directly dependent upon intragastric pressure, during duodenal saline infusion (r = 0.66, p = 0.0005). No threshold for stimulation was seen (Figure 4.9a). Intraduodenal infusion of dextrose inhibited APWs (Figure 4.9b).

A sub-category of APWs was observed and classified during these studies: pressure waves lasting less than 20 seconds which were greater than or equal to 5 mm Hg pressure, which had an identical pressure pattern at all side holes proximal to the sleeve sensor (Figure 4.10). These pressure waves were classified as "non-lumen occluding antro-pyloric pressure waves". In practise such pressure waves were readily distinguished from other APWs due to their lower amplitude.

Non-lumen occluding APWs were seen virtually only at high barostat settings, that is at barostat setting of 25 and 35 centimetres (Figure 4.11).

No sustained pyloric tone was recorded at any stage in any study. Although elevations of baseline pressure was recorded, they were always less than 3 mm Hg.

A: INTRADUODENAL SALINE INFUSION



B: INTRADUODENAL DEXTROSE INFUSION

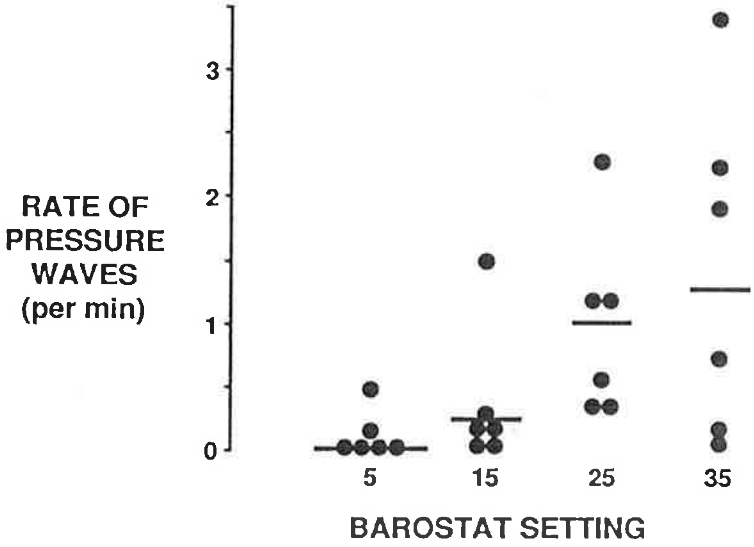


Figure 4.9: Rates of antro-pyloric pressure waves at each barostat setting, during

A: Intraduodenal saline infusion.

B: Intraduodenal dextrose infusion.

Results from 6 pigs, one study per pig.

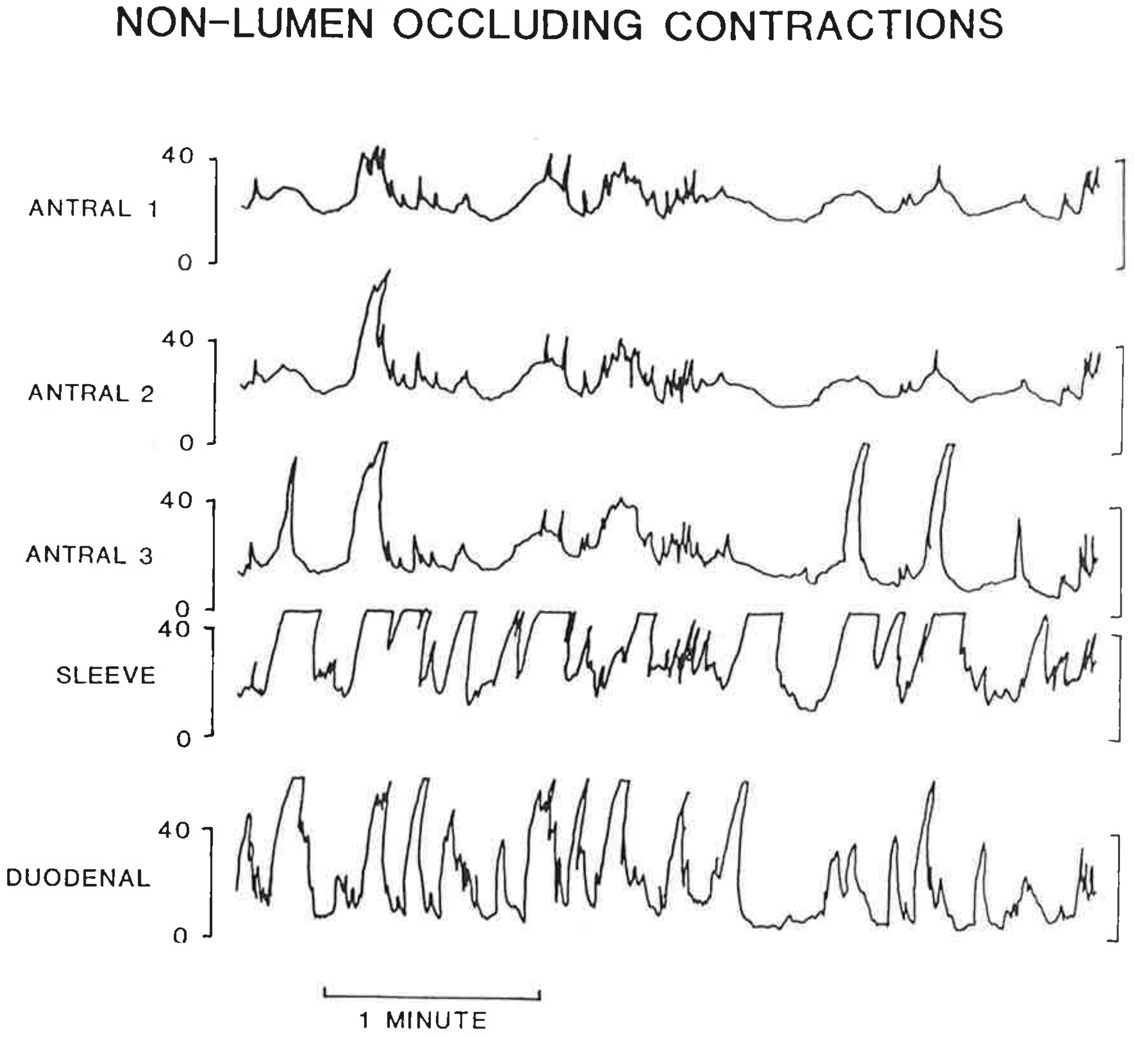


Figure 4.10: Characteristic recording of non-lumen occluding antro-pyloric pressure waves. Antral 1, 2 and 3 refers to pressure recordings from the three separate antral side holes.

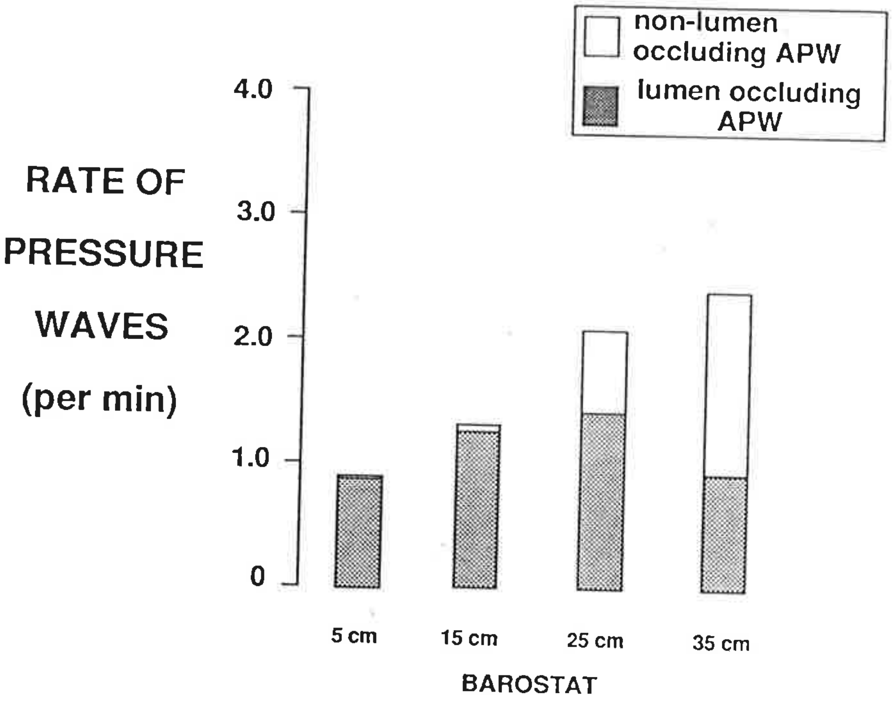


Figure 4.11: Rates of antro-pyloric pressure waves and non-lumen occluding antro-pyloric pressure waves during duodenal saline infusion, at each barostat setting. Results from 6 pigs, one study per pig.

CONCLUSIONS

Studies undertaken with the water barostat system permitted assessment of gastric stimulatory mechanisms, in the virtual absence of both cephalic and intestinal mechanisms. Cephalic mechanisms were excluded, as at no stage during any study was an animal presented with the sight, smell or taste of food, and swallowing, with the associated distension of the pharynx and oesophagus, did not occur. During duodenal infusion of saline, the only intestinal stimulation that may have occurred was that due to the volume of the infusate passing into the duodenum and beyond. Work previously undertaken with the pig preparation has demonstrated that infusion of saline at rates from 0 to 30 millilitres per minute does not influence gastric emptying rates (Landers et al 1986). It seems justified to assume that during those barostat studies with duodenal infusion of saline, the only stimulatory mechanisms involved were gastric.

The main findings from this study were: (1). The intestinal stimulation of IPPWs was most marked when intragastric pressure exceeded a threshold. (2). The rate of APWs was directly dependent upon intragastric pressure.

SECTION 5

THE PYLORUS AND LIQUID GASTRIC EMPTYING

5.1 LIQUID GASTRIC EMPTYING STUDIES

INTRODUCTION

The control of gastric emptying has been ascribed primarily to feedback from luminal receptors of the proximal small intestine, following stimulation by gastric effluent (Meyer 1987). A variety of stimuli to the small intestine have been proposed to control emptying, including nutrients, osmolarity, acidity and distension (Kelly 1981, Meyer 1987).

The aim of this study was to identify and investigate those factors that promote the entero-gastric retardation of liquid gastric emptying in the Kangaroo Island pig.

METHODS

Six Kangaroo Island pigs (weights 34 to 55 kilograms) were studied. Liquid gastric emptying was measured as described previously (Section 3.4), during the intraduodenal infusion of a variety of nutrient or osmolar solutions, or by distension of the duodenum (Section 3.2).

To normalise the data, data were weighted by the inverse of the standard deviation of each group. Statistical analysis was by analysis of variance with Fisher's LSD and simple regression analysis, as appropriate.

RESULTS

1. Nutrient and Osmolar Stimulation Studies

The intraduodenal infusion of saline was associated with rapid gastric emptying over the 30 minutes in each pig. In contrast the intraduodenal infusion of each of dextrose, amino acids, fatty acid and 3 normal saline was associated with a significant retardation of gastric emptying (Figure 5.1).

A dose-response relationship was investigated, using differing rates of infusion of 3.1% dextrose-saline. The volume of the radio-labelled 5% dextrose emptied at 30 minutes decreased in a dose-response relationship with delivery of an increasing dextrose calorie load to the duodenum ($r = -0.76$, $p = 0.0001$), (Figure 5.2).

2. Duodenal Distension Studies

Distension of the duodenum by inflation of the Foley catheter was associated with significant retardation of gastric emptying, the degree of retardation correlating with the volume of the Foley balloon ($r = -0.54$, $p = 0.038$), (Figure 5.3).

3. Differences Between Animals

The patterns of gastric emptying were comparable between animals with gastric cannulae, that had prior washout of the

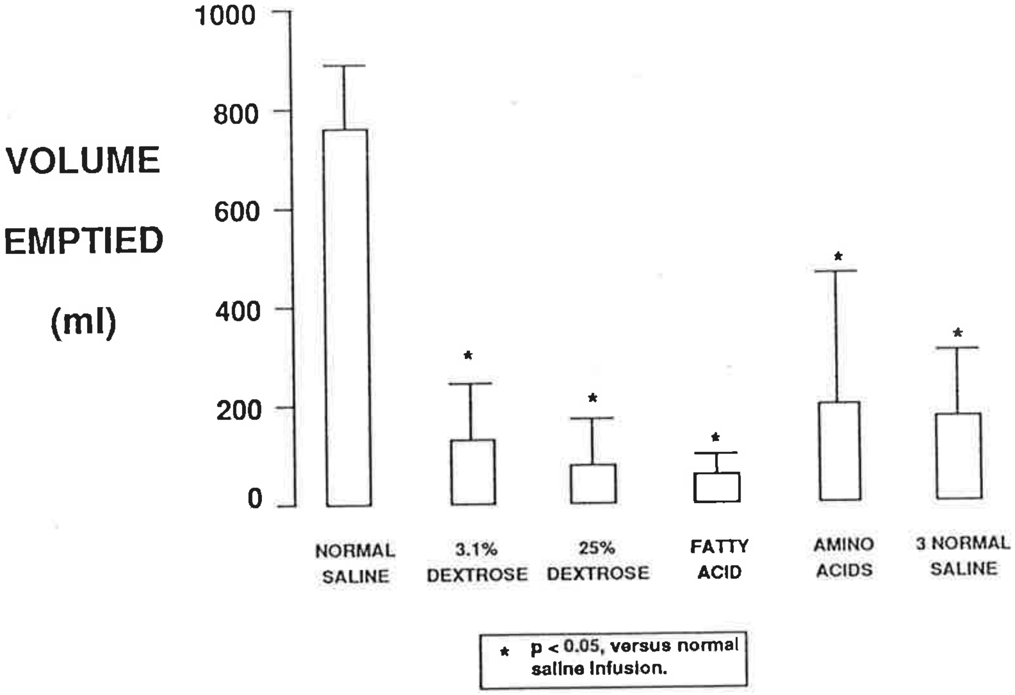


Figure 5.1: Rates of gastric emptying during duodenal infusion of nutrient or hyperosmolar solutions. Results from 6 pigs, one study per pig.

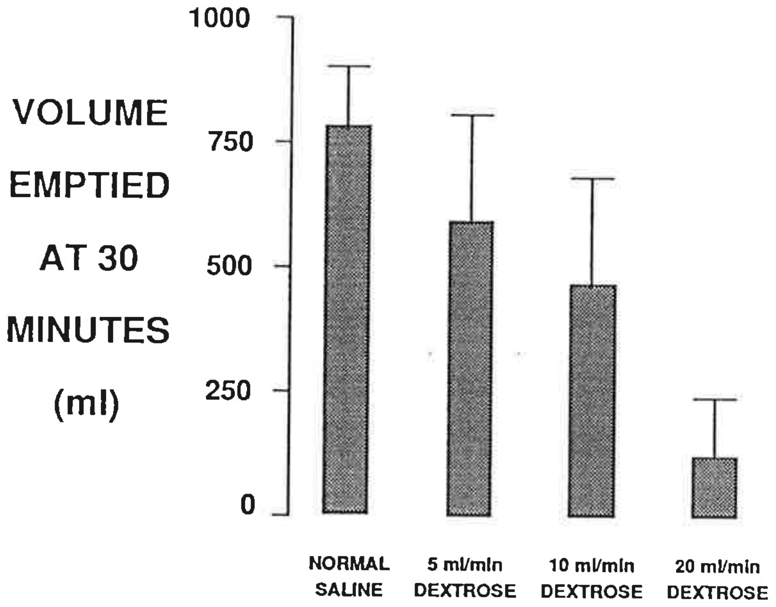


Figure 5.2: Rates of gastric emptying during an increase in the dextrose load infused intraduodenally throughout each study. Results from 6 pigs (5 pigs only during dextrose-saline infusion at 10 ml/min), one study per pig.

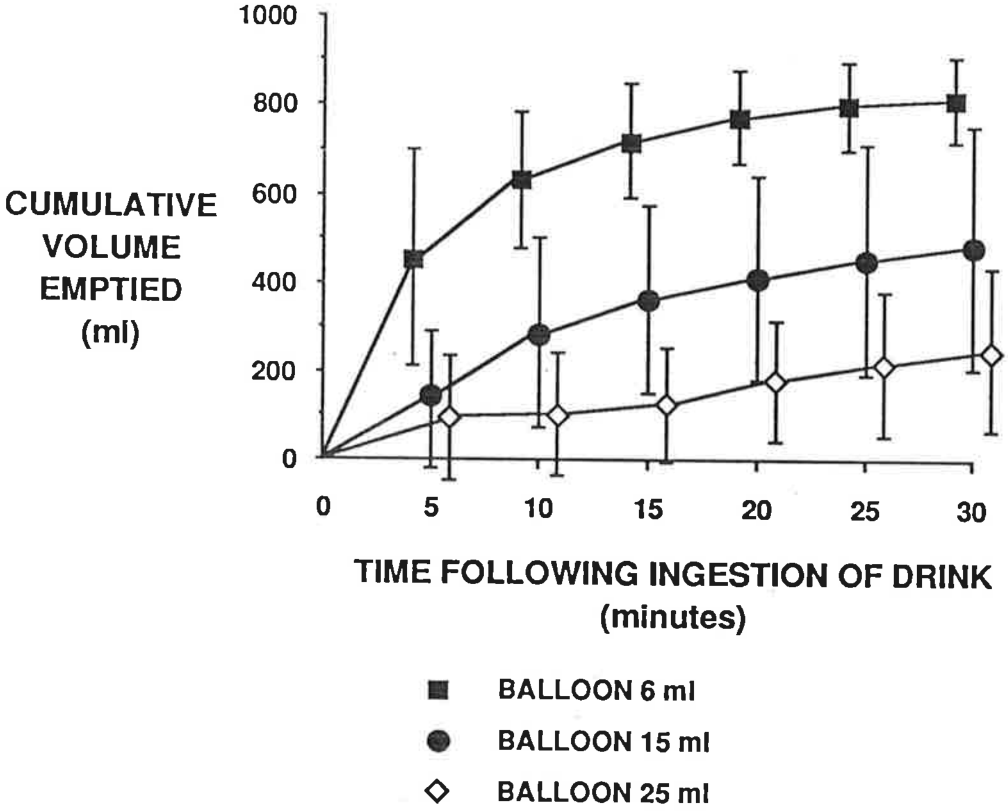


Figure 5.3: Time course of gastric emptying during duodenal distension. Results from 6 pigs with duodenal balloon 6ml, 5 pigs with balloon 15 ml, 4 pigs with balloon 25 ml, one study per pig.

stomach, versus oesophageal cannulae, that had no washout of the stomach prior to each study (Figure 5.4).

CONCLUSIONS

This study has confirmed the existence of a very potent entero-gastric feedback control of liquid gastric emptying in the Kangaroo Island pig, that responds to a variety of nutrient, osmolar and mechanical stimuli in a dose-dependent manner.

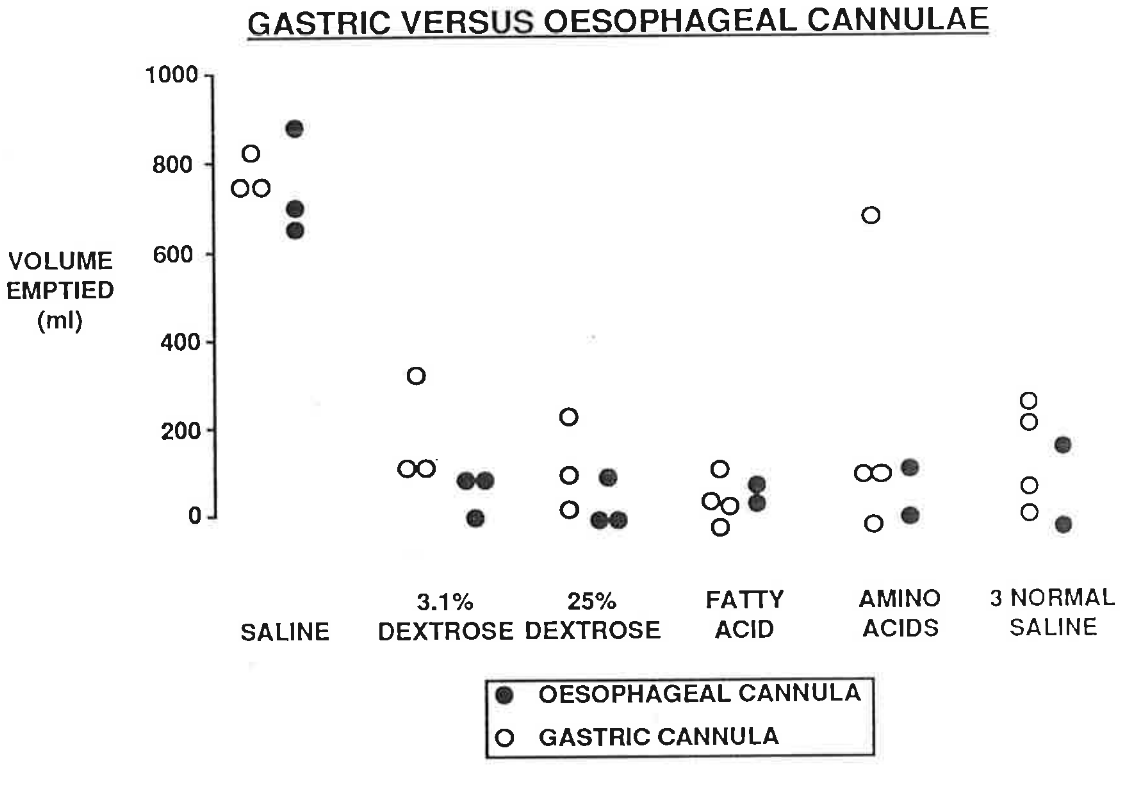


Figure 5.4: Rates of gastric emptying for animals with a gastric cannula (stomach washout prior to study) or an oesophageal cannula (no stomach washout prior to study).

5.2 THE ASSOCIATION BETWEEN PYLORIC MOTOR FUNCTION AND LIQUID GASTRIC EMPTYING

INTRODUCTION

The aim of this study was to examine the relationship between pyloric motility and gastric emptying of liquids, in order to investigate the importance of pyloric motor function in the control of liquid gastric emptying.

METHODS

Six Kangaroo Island pigs (weights 34 to 55 kilograms), with a duodenal and either a gastric or oesophageal cannula were studied. Liquid gastric emptying studies (Section 3.4) were performed simultaneously with measures of pyloric motility, recorded by the sleeve manometric assembly (Section 3.3.2), during intestinal stimulation (Section 3.2).

The analysis of pulsatile flow was restricted to sleeve catheter studies which tested the effect of intraduodenal infusion of either normal saline, 20 millilitres per minute or of 3.1% dextrose-saline, 5 millilitres per minute.

To normalise the data, emptying data were weighted by the inverse of the standard deviation of each group. Statistical analysis was by analysis of variance with Fisher's LSD and simple regression analysis, as appropriate.

RESULTS

1. Nutrient and Osmolar Stimulation Studies

53 typical sequences of IPPWs were recorded. Transpyloric flow occurred during these sequences at a median of 4.7 millilitres per minute (range 0 to 35 millilitres per minute).

Episodes of strictly defined pulsatile flow accounted for 52% of the total volume emptied from the stomach, with a mean volume of each episode of 16.2 millilitres (range 4 to 70 millilitres). Of the 150 episodes of pulsatile flow, 91% (137) were related to an APW, occurring 0.9 seconds +/-4.9 seconds prior to the onset of a sleeve recorded pressure wave (Figure 5.5). Only 31% (137 out of 435) of the APWs recorded were associated with a clearly defined episode of pulsatile flow. Pulsatile flow associated with APWs occurred at 57 millilitres per minute (range 14 to 240 millilitres per minute). The rate of APWs paralleled the rate of gastric emptying of the radio-labelled drink over each 5 minute interval of each study, whether emptying occurred exponentially as during normal saline infusion (Figure 5.6a), or more linearly as during 3.1% dextrose-saline infusions at 5 and 10 millilitres per minute (Figure 5.6b). The volume of each episode of pulsatile flow related to an APW correlated with the extent of the antro-pyloric segment over which the APW occurred, as measured by the number of antro-pyloric side holes that registered the pressure wave ($r = 0.31$, $p = 0.0003$).

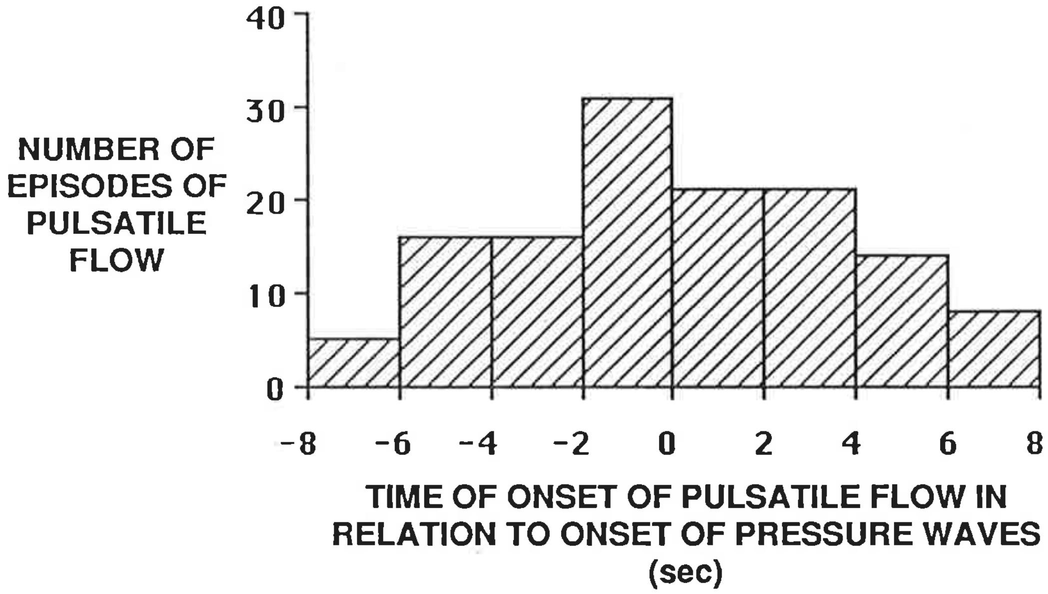
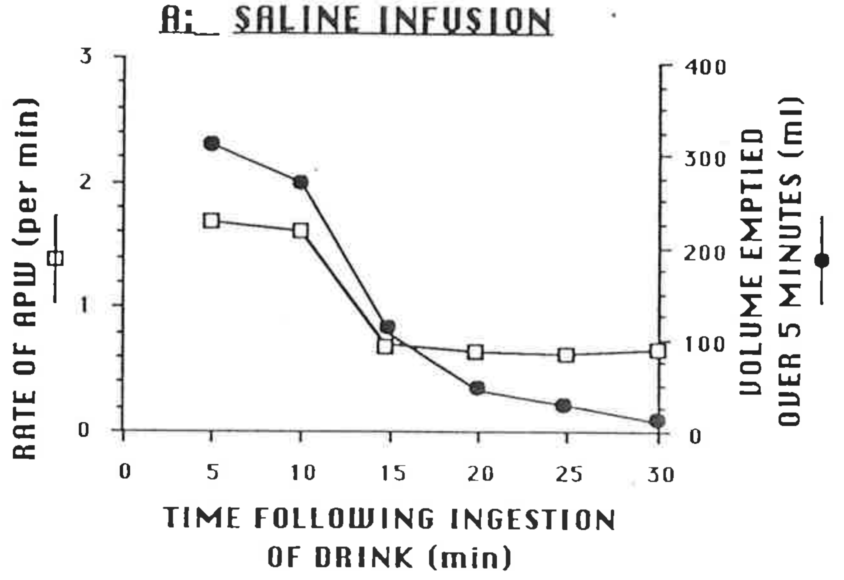


Figure 5.5: Timing of episodes of pulsatile flow in relation to antro-pyloric pressure waves. Results from 137 pressure waves recorded by the sleeve sensor in six pigs. Negative value means flow occurred before onset of pressure wave at sleeve sensor.



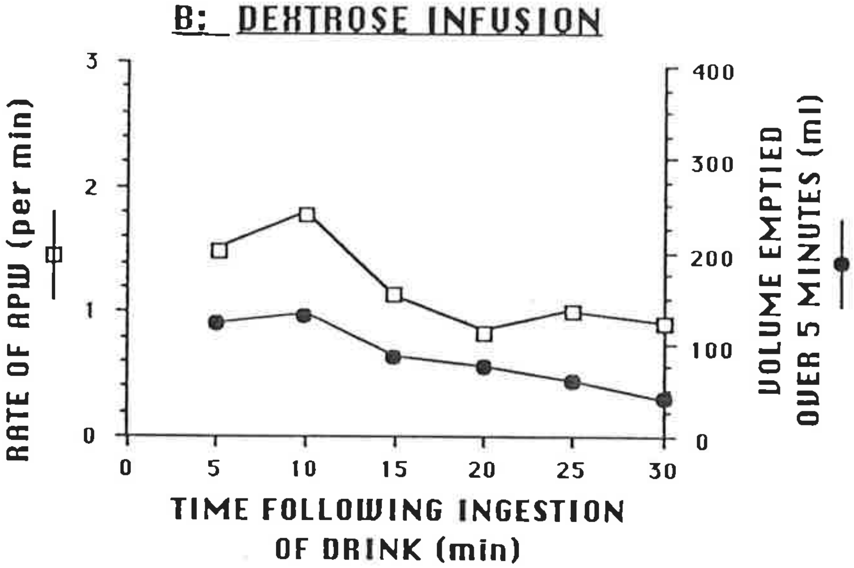


Figure 5.6: Relationship between rate of antro-pyloric pressure waves and volume of drink emptied, each 5 minute interval of a study, during intraduodenal infusion of

A: Normal saline.

B: 3.1% dextrose-saline solution, 5 & 10 ml/min.

Results from 6 pigs (5 pigs only during dextrose-saline at 10 ml/min), one study per pig.

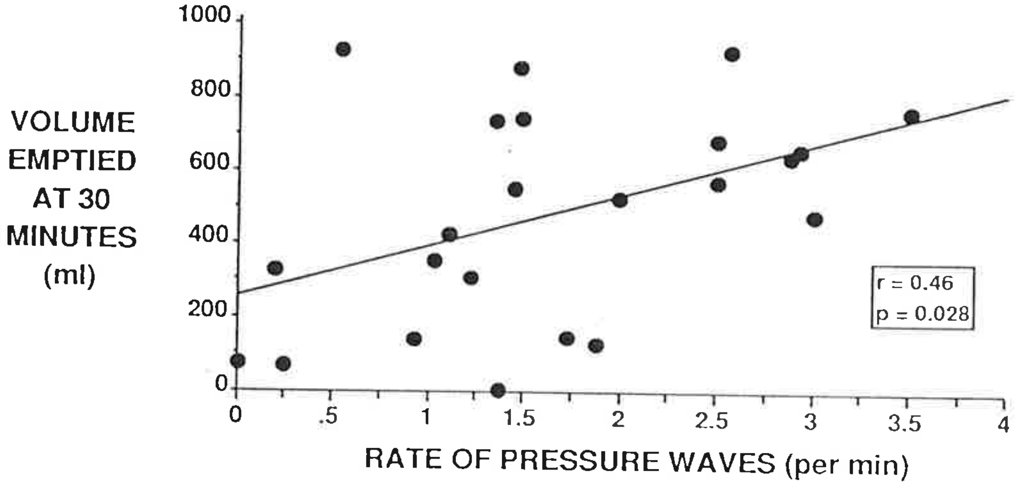
During the post-prandial interval, periods of motor quiescence of greater than one minute duration were recorded only 8% of the time in total. This absence of activity was seen in only 22 out of the total 44 studies. During these periods, flow occurred at a median rate of 20.1 millilitres per minute (range 2.5 to 46.0 millilitres per minute). No relationship was demonstrated between emptying and type of infusate during these periods of quiescence (p = 0.21). During these periods of motor quiescence no pulsatile flow was recorded.

In studies with intraduodenal infusion of 3.1% dextrose-saline, there was a statistically significant positive correlation between emptying of the radio-labelled drink and the rate of APWs (Figure 5.7a) and a significant negative correlation between emptying of the radio-labelled drink and the rate of IPPWs (Figure 5.7b).

2. Duodenal Distension Studies

The volume of the radio-labelled drink that emptied during duodenal distension was negatively correlated with the rates of IPPWs (r = -0.66, p = 0.008), (Figure 5.8a). No significant correlation was demonstrated between the rates of APWs and the volume of the radio-labelled drink that emptied during duodenal distension (r = 0.40, p = 0.14), (Figure 5.8b).

A: ANTRO-PYLORIC PRESSURE WAVES



B: ISOLATED PYLORIC PRESSURE WAVES

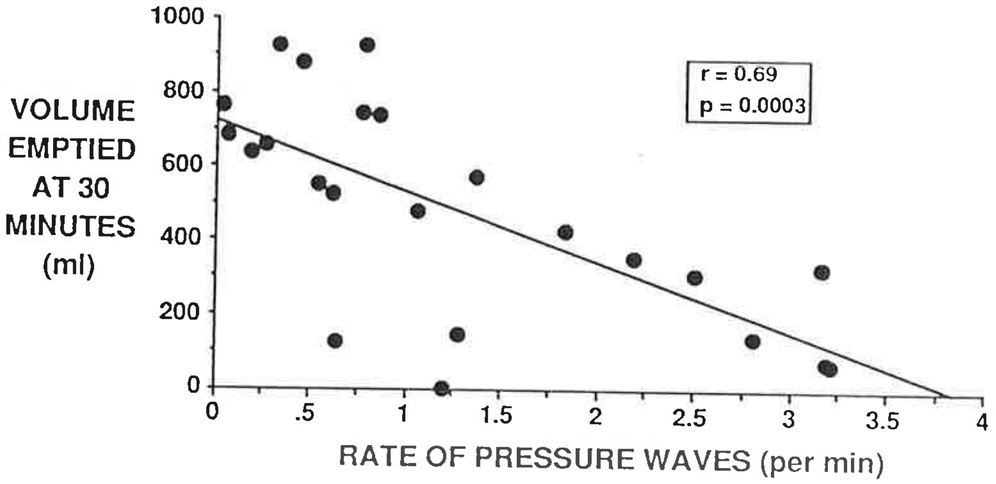
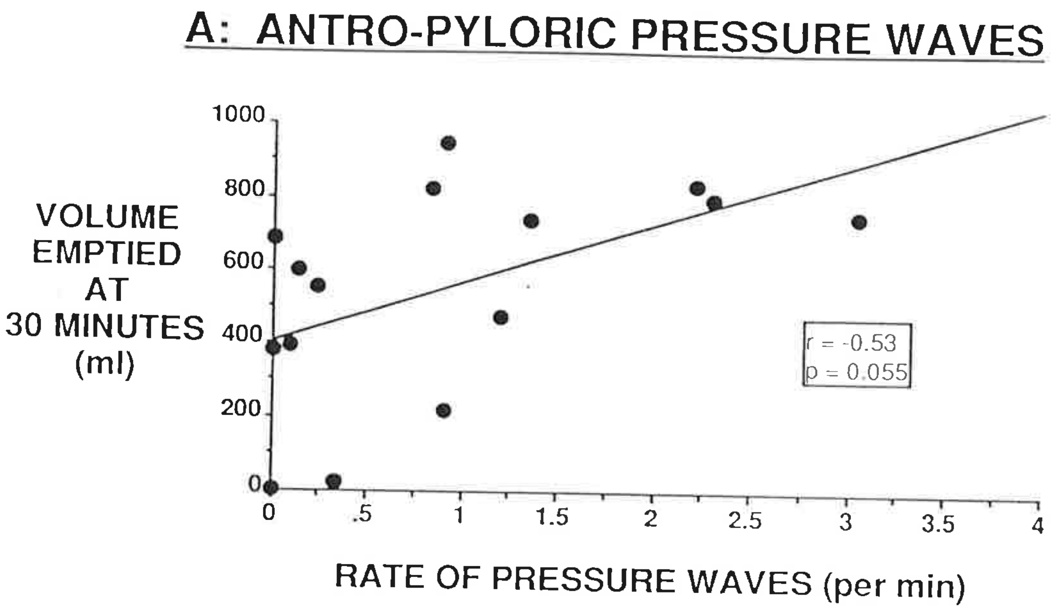


Figure 5.7: Correlation between gastric emptying and rate of

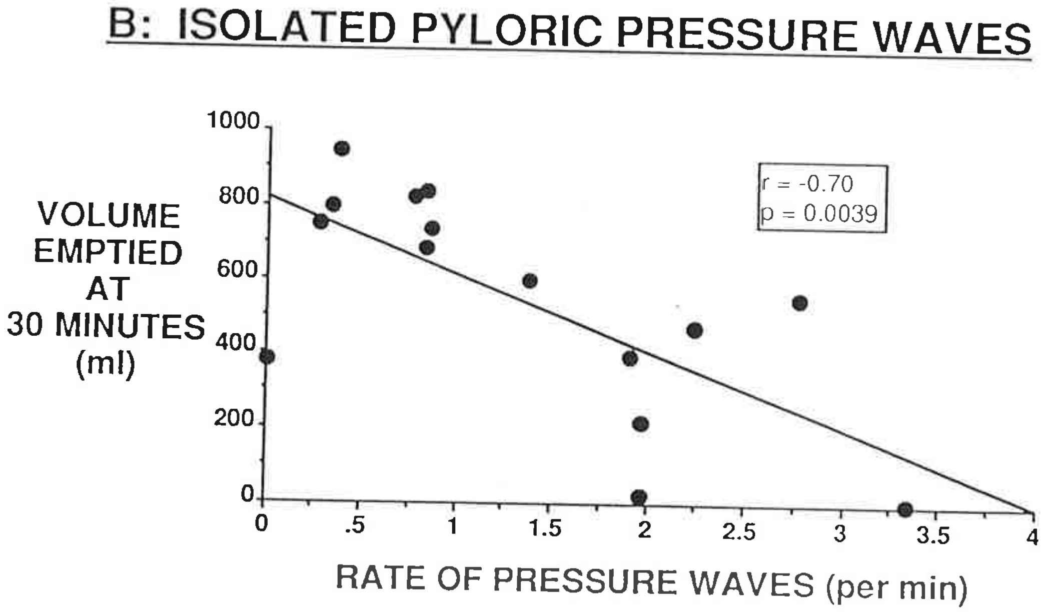
A: antro-pyloric pressure waves,

B: isolated pyloric pressure waves,

during intraduodenal infusion of saline and 3.1% dextrose-saline solutions. Results from 6 pigs, four studies each pig (three only in one pig).



A: ANTRO-PYLORIC PRESSURE WAVES



B: ISOLATED PYLORIC PRESSURE WAVES

Figure 5.8: Correlation between gastric emptying and rate of:

A: isolated pyloric pressure waves,

B: antro-pyloric pressure waves,

during duodenal distension. Results from 6 pigs with duodenal balloon 6 ml, 5 pigs with balloon 15 ml and 4 pigs with balloon 25ml, one study per pig.

CONCLUSIONS

The direct measurement of gastric emptying in the pig preparation, combined with a record of this emptying on the manometric tracing, has enabled close temporal correlations between patterns of pyloric motility and episodes of transpyloric flow. The major findings are: (1) That IPPWs were closely associated with cessation of transpyloric flow of liquids. (2) That more than half of liquid emptying occurred as episodes of pulsatile flow, which were intimately associated in time with APWs. (3) That alterations of motility were closely associated in time with alterations of liquid gastric emptying.

5.3 THE EFFECT OF PYLORUS EXCISION ON LIQUID GASTRIC EMPTYING

INTRODUCTION

The aim of this study was to investigate the role of the pylorus in the control of gastric emptying of liquids, by excision of the pylorus with end-to-end anastomosis. Gastric emptying was assessed simultaneously with measures of antral, pyloric and duodenal motility.

METHODS

Twelve Kangaroo Island pigs ranging in body weight from 30 to 55 kilograms, with duodenal and gastric (9 animals) or oesophageal (3 animals) cannulae were studied. In six of the twelve animals the pylorus was excised (Section 3.6.1) and in the remaining six the pylorus was left intact.

Liquid gastric emptying studies were performed with the sleeve manometric assembly during intestinal stimulation (Sections 3.2.1, 3.3 & 3.4).

To normalise the data, liquid gastric emptying data were weighted by the inverse of the standard deviation of each group. Data were analysed by analysis of variance with Fisher's LSD and simple regression analysis, as appropriate.

RESULTS

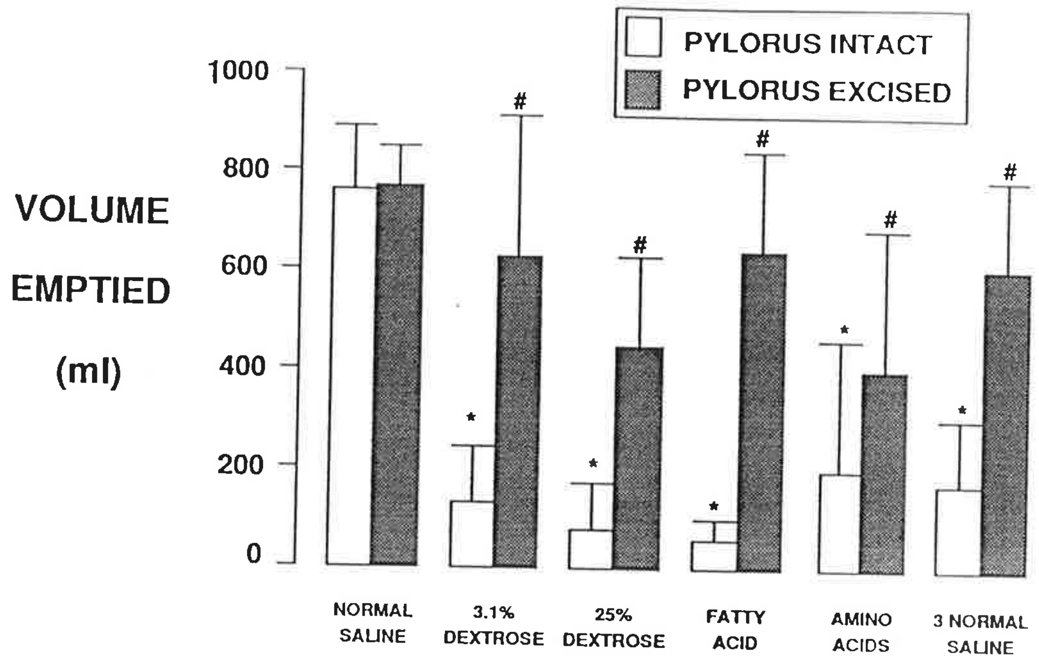
Data were analysed from one technically successful study of each experiment in each animal, making a total of 36 liquid emptying studies of pylorus excised animals.

Gastric Emptying

In pylorus excised animals, the intraduodenal infusion of each of isosmolar dextrose, fatty acid, amino acids, 25% dextrose and 3 normal saline solutions failed to slow gastric emptying (Figure 5.9a). In these animals, the time course of emptying during intraduodenal infusion of each nutrient and hyperosmolar solution was similar to that found during intraduodenal infusion of normal saline (Figure 5.10).

Distension of the duodenum by the Foley balloon produced a significant retardation of gastric emptying in pylorus excised animals ($p = 0.0048$). This retardation was comparable to that recorded in pylorus intact animals ($p = 0.927$), (Figure 5.9b). The degree of retardation of gastric emptying was in proportion to the degree of duodenal distension (pylorus intact animals: $r = 0.54$, $p = 0.0377$; pylorus excised animals: $r = 0.578$, $p = 0.0119$).

A: DUODENAL NUTRIENT OR OSMOLAR SOLUTIONS



B: DUODENAL DISTENSION

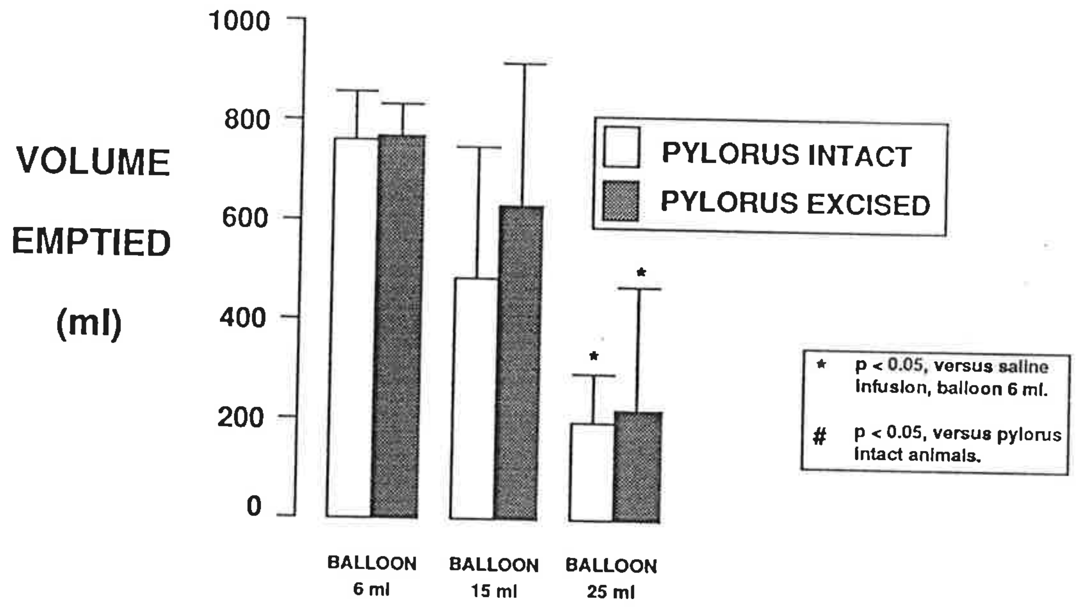


Figure 5.9: Rates of gastric emptying in pylorus intact and excised animals, during:

A: Duodenal nutrient and hyperosmolar stimulation.

B: Duodenal distension.

Results from 6 pylorus intact and 6 pylorus excised pigs (5 pylorus intact pigs with balloon 15 ml, 4 pylorus intact pigs with balloon 25 ml), one study per pig.

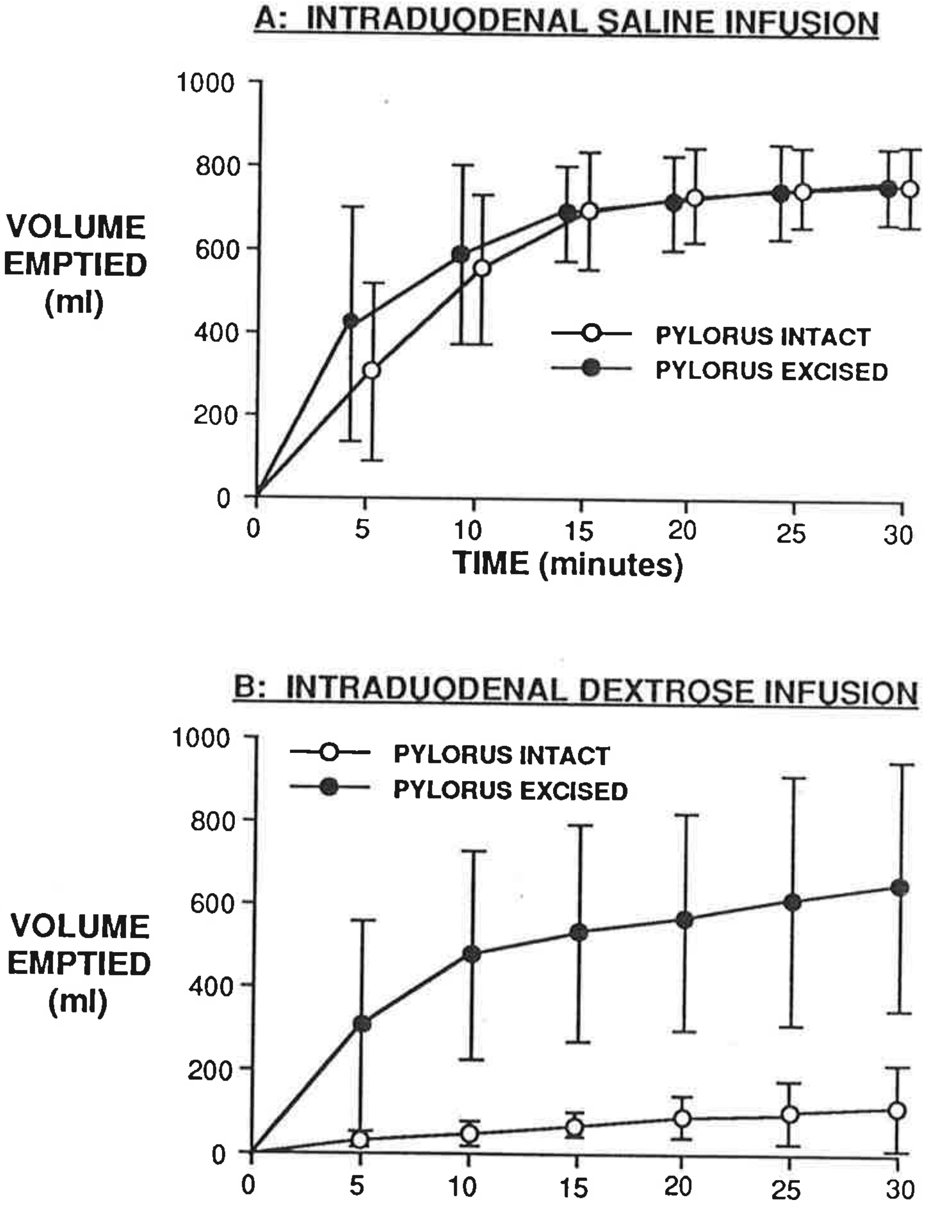


Figure 5.10: Time course of emptying in pylorus intact and excised animals during duodenal infusion of:

A: Normal saline.

B: 3.1% dextrose-saline solution, 20 ml/min.

Results from 6 pylorus intact and 6 pylorus excised pigs, one study per pig.

Antro-Pyloro-Duodenal Motility

In pylorus excised animals, as expected very few pressure waves satisfying our criteria for IPPWs were seen in any study (Figure 5.11).

During intraduodenal infusion of normal saline there was a predominance of pressure waves that satisfied our criteria for APWs (Figure 5.12). These APWs were significantly ($p < 0.05$) inhibited by the intraduodenal infusion of 3.1% dextrose-saline and 25% dextrose (Figure 5.12a), as well as by distension of the duodenum (Figure 5.12b).

CONCLUSIONS

This study provides new information about the consequences of pylorus excision. The major findings are that pylorus excision results in loss of the retardation of liquid emptying that is normally produced by entry of nutrient or hyperosmolar solutions into the duodenum, but does not result in any alteration of liquid emptying rates produced by duodenal distension.

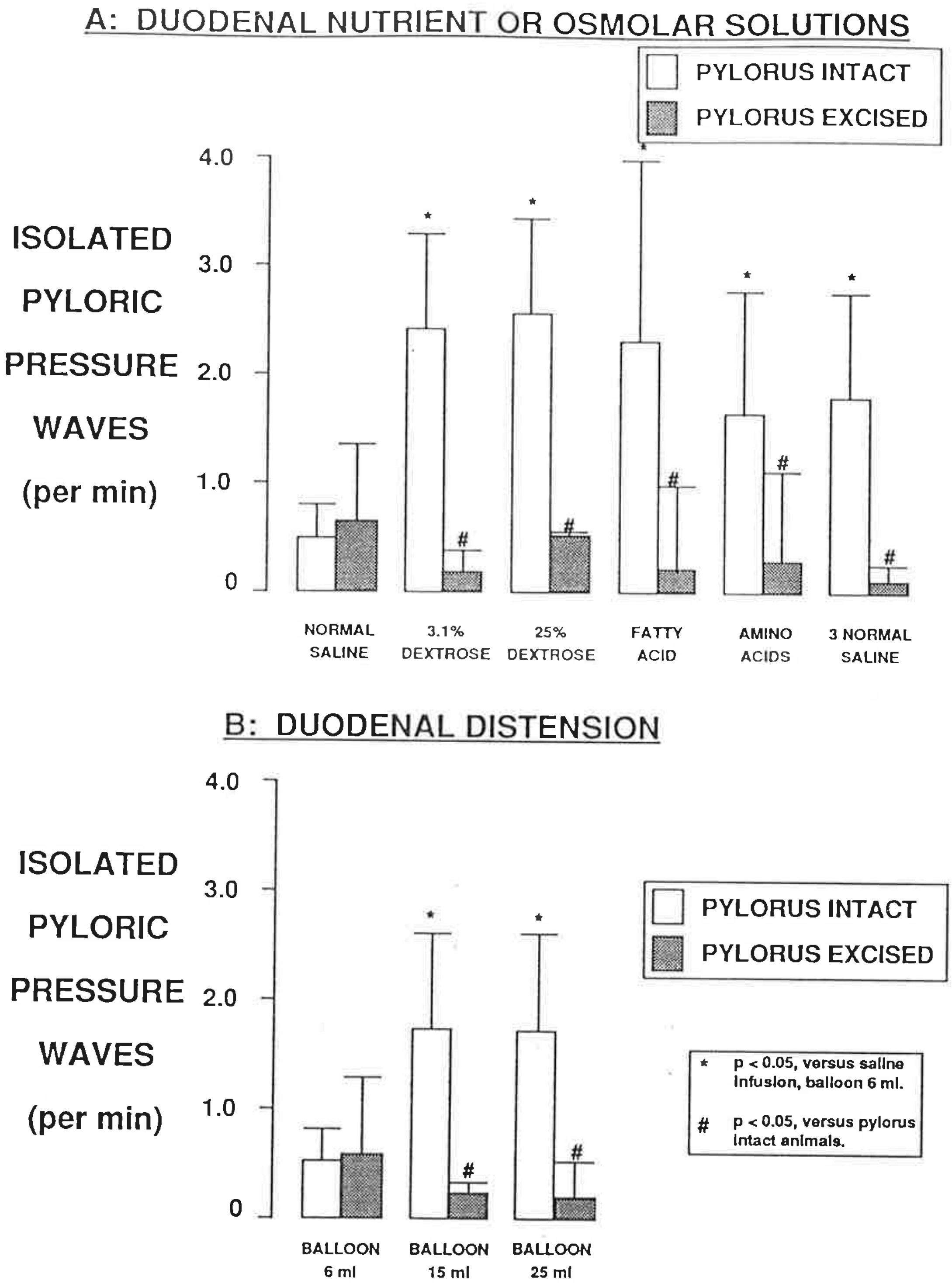


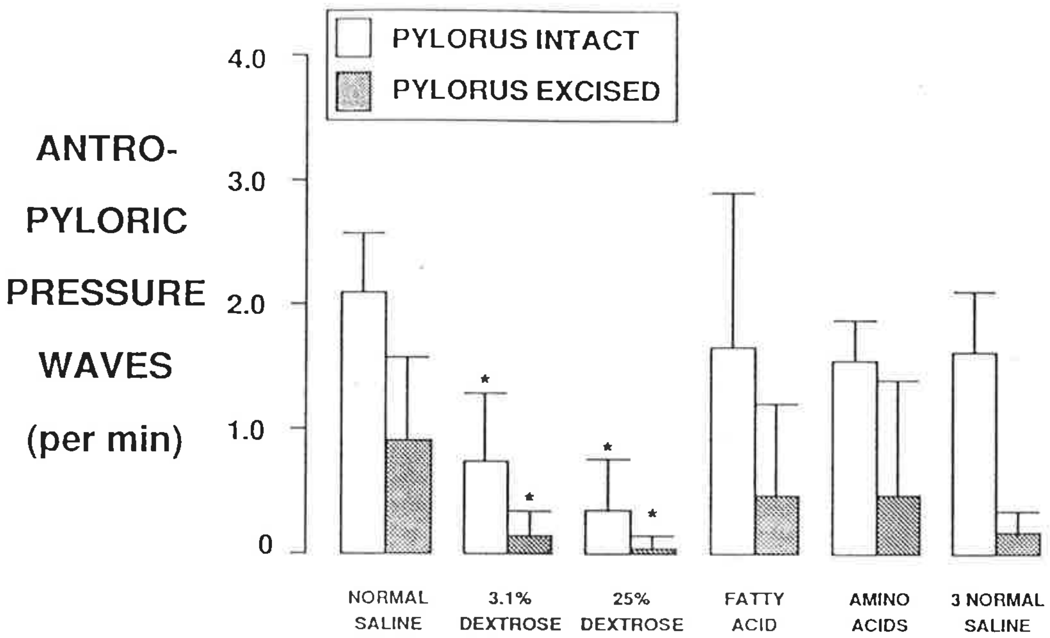
Figure 5.11: Rates of isolated pyloric pressure waves in pylorus intact and excised animals during

A: Duodenal nutrient and hyperosmolar stimulation.

B: Duodenal distension.

Results from 6 pylorus intact and 6 pylorus excised pigs (5 pylorus intact pigs with balloon 15 ml, 4 pylorus intact pigs with balloon 25 ml), one study per pig.

A: DUODENAL NUTRIENT OR OSMOLAR SOLUTIONS



B: DUODENAL DISTENSION

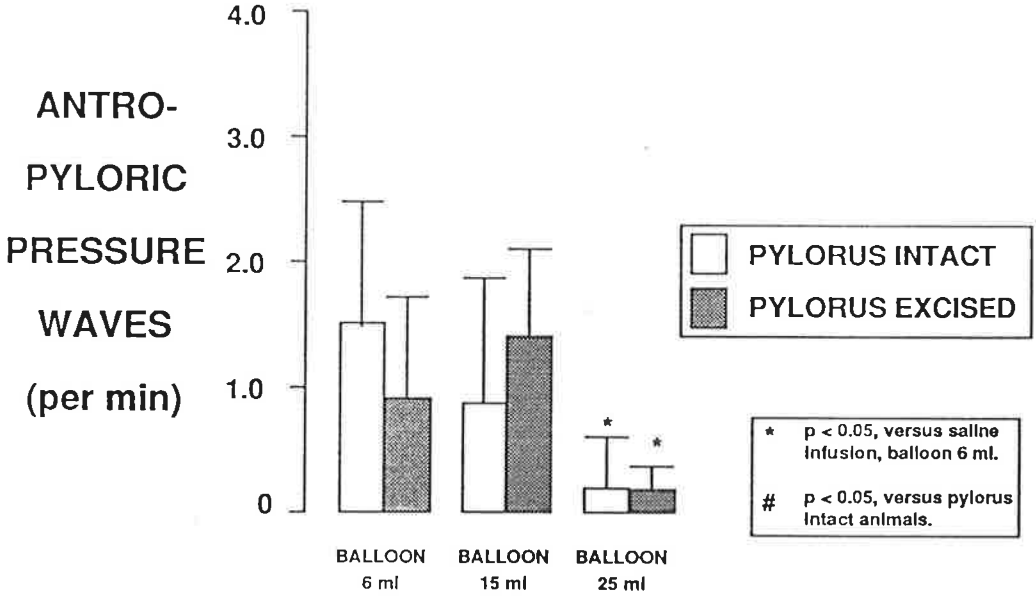


Figure 5.12: Rates of antro-pyloric pressure waves in pylorus intact and excised animals during

A: Duodenal nutrient and hyperosmolar stimulation.

B: Duodenal distension.

Results from 6 pylorus intact and 6 pylorus excised pigs (5 pylorus intact pigs with balloon 15 ml, 4 pylorus intact pigs with balloon 25 ml), one study per pig.

5.4 PYLORIC MOTILITY AND LIQUID GASTRIC EMPTYING DURING BAROSTATIC CONTROL OF GASTRIC PRESSURE

INTRODUCTION

The aim of this study was to investigate the role of the pylorus in the regulation of liquid gastric emptying, in the absence of influence of the proximal stomach. A gastric water barostat system has been used to control intragastric pressures and thus minimise the influence of the proximal stomach. Gastric emptying rates were assessed simultaneously with measures of antral, pyloric and duodenal motility.

METHODS

Gastric barostat studies were performed as described previously (Section 3.2.2). Twelve Kangaroo Island pigs were studied. Six of the animals underwent pylorus excision (Section 3.6.1) and in the remaining 6 animals the pylorus was left intact.

Two studies were performed on each animal, on separate days, during intraduodenal infusion of either saline or 3.1% dextrose-saline solution, 20 millilitres per minute.

To normalise the data, gastric emptying data were transformed to $\log_e$ values. Data were analysed by unpaired T-test, analysis of variance, using Fisher's LSD and simple regression analysis, as appropriate.

RESULTS

1. Effects of Intragastric Pressure on Transpyloric Flow

Pylorus Intact Animals The rate of transpyloric flow was directly dependent upon intragastric pressure, during duodenal infusion of both saline ($r = 0.75$, $p = 0.0001$) and dextrose ($r = 0.537$, $p = 0.0068$), (Figure 5.13). Transpyloric flow was significantly slower during intraduodenal infusion of dextrose than of saline ($p = 0.0006$).

Pylorus Excised Animals At each setting of the barostat, pylorus excision did not influence rates of transpyloric flow during intraduodenal infusion of saline, although there was a trend towards more rapid emptying in pylorus excised animals ($p = 0.27$). By contrast, during intraduodenal infusion of dextrose, excision of the pylorus was associated with a significant alteration of transpyloric flow, being faster compared to pylorus intact animals ($p = 0.0179$), (Figure 5.14). This difference was most marked at barostat settings of 25 and 35 centimetres. In pylorus excised animals, intraduodenal infusion of dextrose was still associated with significant slowing of transpyloric flow, compared to duodenal saline infusion.

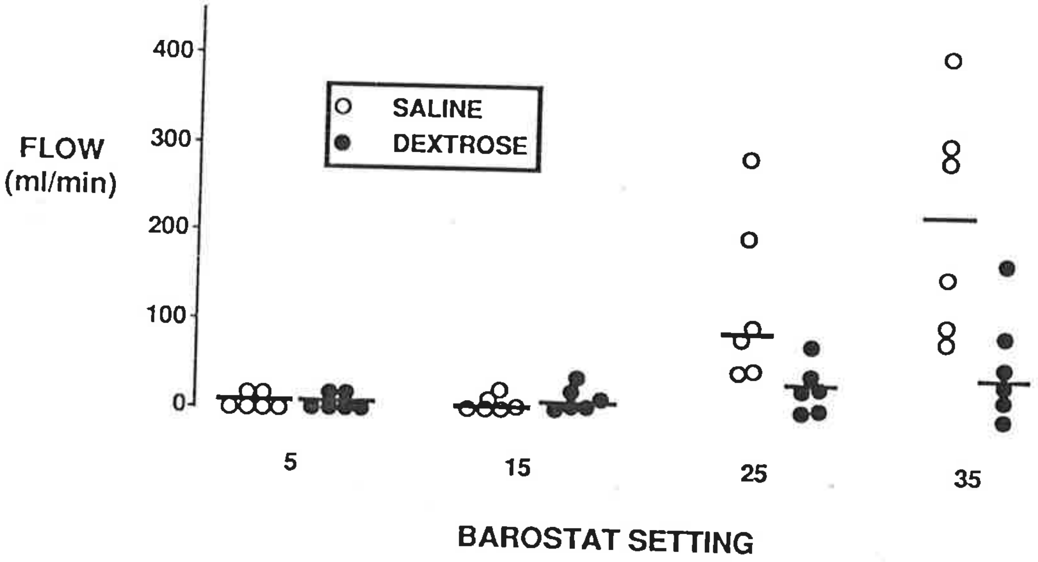


Figure 5.13: Rates of transpyloric flow at each barostat setting in pylorus intact animals.

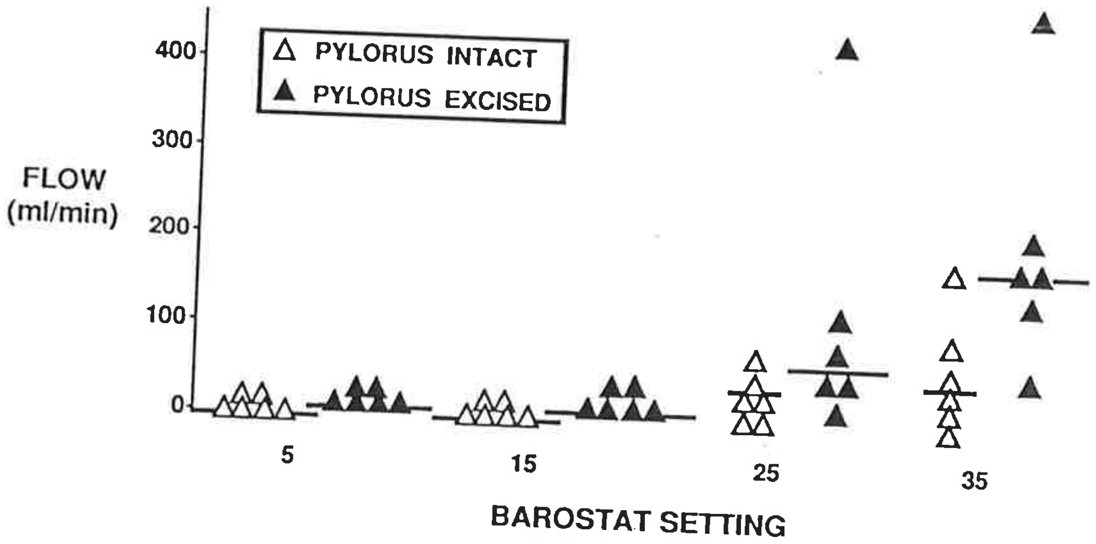


Figure 5.14: Rates of transpyloric flow at each barostat setting during duodenal infusion of dextrose, in pylorus intact and pylorus excised animals. Results from 6 pylorus intact and 6 pylorus excised pigs, one study per pig.

2. Differences in Flow Related to Motility

With the barostat set at 25 centimetres, so that intragastric pressure most closely simulated physiological pressure following a drink (mean 7 mm Hg, range 1 - 10 mm Hg) and the gastro-duodenal pressure gradient always positive (mean 3 mm Hg, range 1 - 8 mm Hg), duodenal dextrose infusion stimulated IPPWs to 2.8 per minute, compared to duodenal saline infusion (0.8 per minute, $p < 0.05$) and retarded transpyloric flow to 28 millilitres per minute (range 3 - 76 millilitres per minute), from 130 millilitres per minute with saline infusion (range 49 - 292 millilitres per minute), ($p < 0.05$). In pylorus excised animals, virtually no pressure waves that satisfied our criteria for IPPWs were seen ($p < 0.05$) and flow was significantly more rapid during duodenal dextrose infusion, at 121 millilitres per minute (range 15 - 425 millilitres per minute), compared to pylorus intact animals ($p < 0.05$).

In pylorus intact animals, an increased in the rate of APWs was associated with an increase in transpyloric flow ($r = 0.74$, $p = 0.0001$). Following pylorus excision, the positive correlation between flow and APWs was maintained, during duodenal saline infusion ($r = 0.62$, $p = 0.0012$).

In pylorus intact animals, at all settings of the barostat, the occurrence of 10 or more IPPWs per five minute interval (more than 2 IPPWs per minute) was associated with a flow rate of 28 +/- 58 millilitres per minute during that five minute interval. Such 5 minute intervals of IPPWs were recorded 40% of the time overall. In contrast, the occurrence of 10 or more

APWs per five minute interval was associated with more rapid gastric emptying, at 137 +/- 125 millilitres per minute. Such 5 minute intervals of APWs were recorded 34% of the time overall.

CONCLUSIONS

The main findings from this study were: (1) IPPWs are closely associated with retardation of transpyloric flow, even in the face of a range of relatively high gastroduodenal pressure gradients. (2) This retardation of flow associated with IPPWs was significantly reduced following excision of the pylorus. (3) Across a wide range of intragastric pressures, a close correlation was demonstrated between APWs and gastric emptying rates, that seen also in pylorus excised animals.

SECTION 6

THE PYLORUS AND SOLID GASTRIC EMPTYING

6.1 GASTRIC EMPTYING OF A DIGESTIBLE SOLID

INTRODUCTION

One of the major roles of the stomach is to disperse solid food into tiny particles, before their passage into the small intestine (Meyer 1987). The precise motor mechanisms that perform this task have not been completely defined. In particular, the association between antral contractions and gastric emptying is poorly defined.

The aims of this study were (1) To establish a protocol for solid gastric emptying in the pig preparation. (2) To investigate the relationship between solid gastric emptying and pyloric motility.

METHODS

6 Kangaroo Island pigs were studied. Solid gastric emptying studies were performed simultaneously with manometry and also during measurement of particle sizes emptied from the stomach (Sections 3.5.1 & 3.5.2).

To normalise the data, emptying data were transformed to $\log_e$ values. Data were analysed by simple regression.

RESULTS

Simultaneous Manometry - Emptying Studies

The radio-labelled hamburger mince emptied at a linear rate of 7.1 +/- 6.1 grams per 10 minute interval, following a lag period of 12.6 +/- 10.8 minutes (Figure 6.1). A total of 81 +/- 51 grams emptied over the two hours.

Antral pressure waves occurred at a near constant rate throughout the studies, at 1.6 +/- 1.2 waves per minute (Figure 6.2). The rate of emptying of the mince each 10 minute interval correlated with the rate of APWs each 10 minutes ($r = 0.28$, $p = 0.0159$).

Particle Size Measurements

The radio-labelled liver was ground to fine particles in each animal: 55% of the liver cubes emptied as particles less than 1 millimetre size and 38% emptied as particles less than 0.15 millimetres size.

CONCLUSIONS

This study has demonstrated that gastric emptying of a digestible solid in the pig occurs at a near constant linear rate, following an initial lag phase. The ingested solid meal empties as fine particles, 69% of which are less than 1 millimetre in size. This emptying is associated with a near constant rate of APWs.

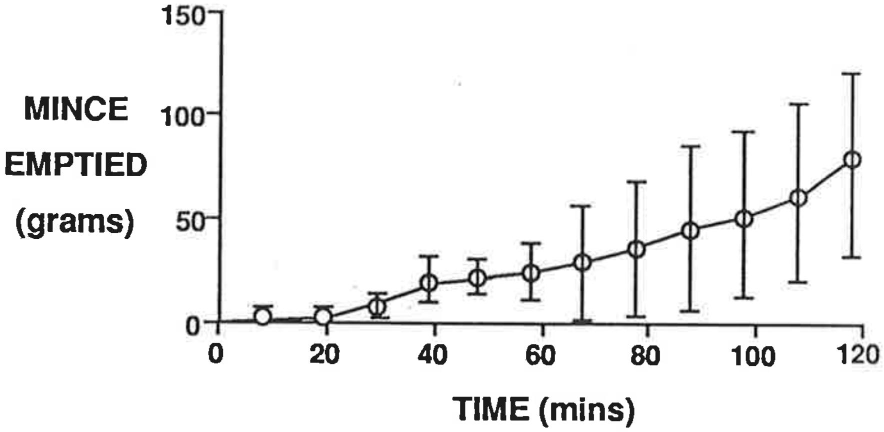


Figure 6.1: Time course of emptying of mince, pylorus intact animals. Results from 6 pigs, one study per pig.

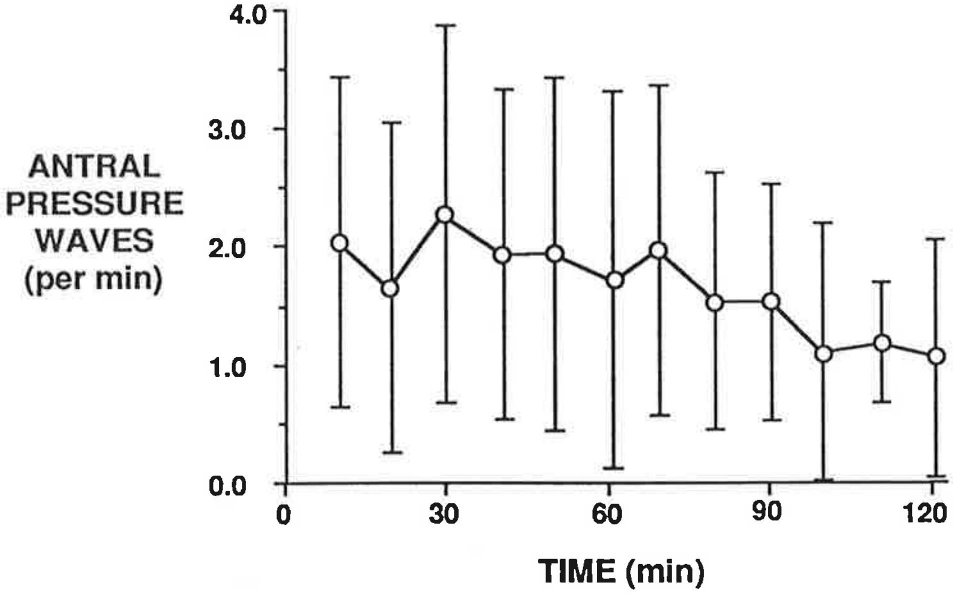


Figure 6.2: Time course of rates of antro-pyloric pressure waves during solid gastric emptying, pylorus intact animals. Results from 6 pigs, one study per pig.

6.2 THE EFFECT OF PYLORUS EXCISION ON THE GASTRIC EMPTYING OF A DIGESTIBLE SOLID

INTRODUCTION

One of the main functions of the stomach is to disperse solid food into tiny particles, before their passage into the small intestine (Meyer 1987). The motor mechanisms that perform these tasks have not been completely defined. In particular, the role of the pylorus remains controversial.

The aim of this study was to investigate the role of the pylorus in the control of gastric emptying of digestible solids, by excision of the pylorus. Gastric emptying was assessed simultaneously with measures of antral, pyloric and duodenal motility.

METHODS

Six animals underwent pylorus excision (Section 3.6.1) and a further six animals acted as controls. Solid gastric emptying studies were performed simultaneously with antro-pyloro-duodenal manometry, and also during measurement of particle sizes emptied from the stomach (Sections 3.5.1 & 3.5.2).

To normalise the data, gastric emptying data were transformed to $\log_e$ values. Data were analysed by unpaired T-test, analysis of variance and simple regression analysis, as appropriate.

RESULTS

Simultaneous Manometry - Emptying Studies

The linear rate of emptying was significantly faster in pylorus excised animals, at 25.8 +/- 20.6 grams per 10 minutes compared to pylorus intact animals, at 7.1 grams per 10 minute interval ($p = 0.048$). Correspondingly, the total solid emptied over two hours was greater in pylorus excised animals (181 +/- 91 grams) than in pylorus intact animals (80 grams), ($p = 0.046$), (Figure 6.3).

Although the lag period before emptying commenced was longer in pylorus excised animals, at 26.7 +/- 17.4 minutes, than in pylorus intact animals, at 12.6 minutes, this did not reach statistical significance ($p = 0.12$).

Similarly, although the overall rate of APWs was greater in pylorus excised animals (2.31 per minute) than in pylorus intact animals (1.61 per minute), there was no statistically significant difference between the two ($p = 0.31$). In pylorus excised animals, the rate of APWs tended to decline towards the end of the study (Figure 6.4). In pylorus excised animals, there was no correlation between rate of APWs and meat emptied each 10 minutes ($p = 0.76$), in contrast to pylorus intact animals.

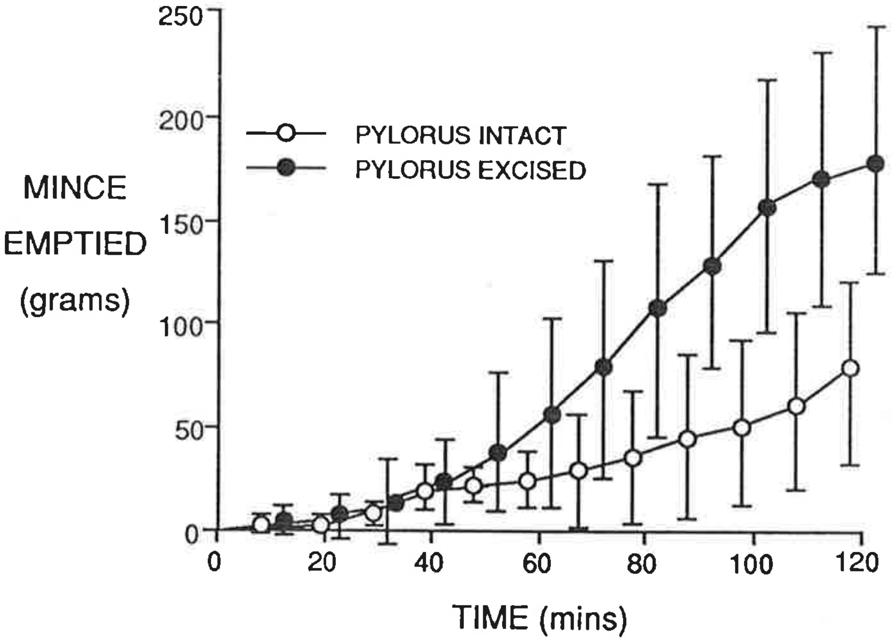


Figure 6.3: Time course of emptying of mince, pylorus intact and excised animals. Results from 6 pylorus intact and 6 pylorus excised pigs, one study per pig.

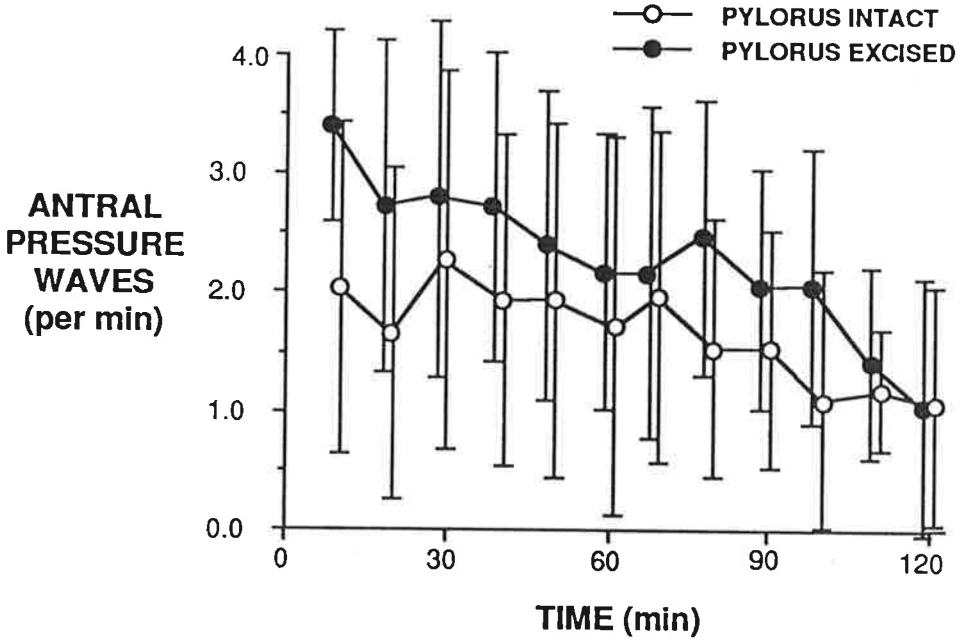


Figure 6.4: Time course of rates of antro-pyloric pressure waves during solid gastric emptying, pylorus intact and excised animals. Results from 6 pylorus intact and 6 pylorus excised pigs, one study per pig.

Particle Size Measurements

In pylorus intact animals, 55% of the liver cubes emptied as particles less than 1 millimetre and 38% emptied as particles less than 0.15 millimetres. In pylorus excised animals, the distribution of particle sizes that emptied was comparable to that in pylorus intact animals (p = 0.39), with 69% less than 1 millimetre size and 43% less than 0.15 millimetres size (Figure 6.5). A total of 110 +/- 42 grams of the cubed liver emptied at two hours in pylorus intact animals and 161 +/- 56 grams emptied in pylorus excised animals (p = 0.10).

CONCLUSIONS

The significant findings from this study were that pylorus excision did not alter the range of particle size in the gastric chyme emptied, nor abolish antral motility, but that the solid meal emptied more rapidly.

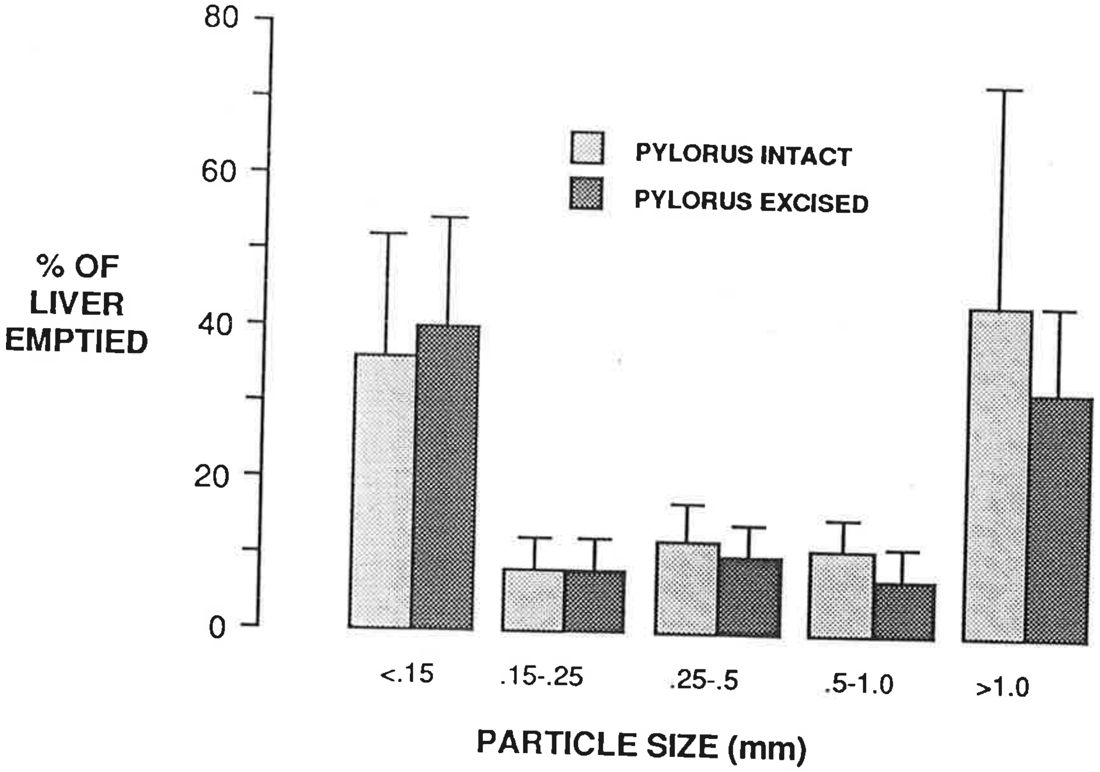


Figure 6.5: Distribution of particle sizes, pylorus intact and excised animals. Results from 6 pylorus intact and 6 pylorus excised pigs, one study per pig.

6.3 EXTERNAL GAMMA CAMERA STUDIES

INTRODUCTION

The aim of this study was to use an external gamma camera in the pig preparation, in order to measure the movement of a solid meal within and from the regions of the stomach. In the event only one study was performed (see below), but the method has been described (Section 3.5.3) and the difficulties of carrying out such studies are discussed.

RESULTS

One study was performed on one pig only. The solid meal was observed to lie at one region, considered the distal stomach, and recorded to pass on to another region, considered the small bowel (Figure 6.6). No distribution of food across the stomach was observed. Following a 30 minute lag period, emptying occurred linearly and ceased at 70 minutes (Figure 6.7).

CONCLUSIONS

One study was performed on one pig only, due to limitations of availability of equipment and the demands on numbers of staff to perform the study. The one study required 4 persons - 2 to position and maintain the pig in front of the camera and 2 to operate the gamma camera, including collecting photographic images plus measurements of radio-activity in the field of

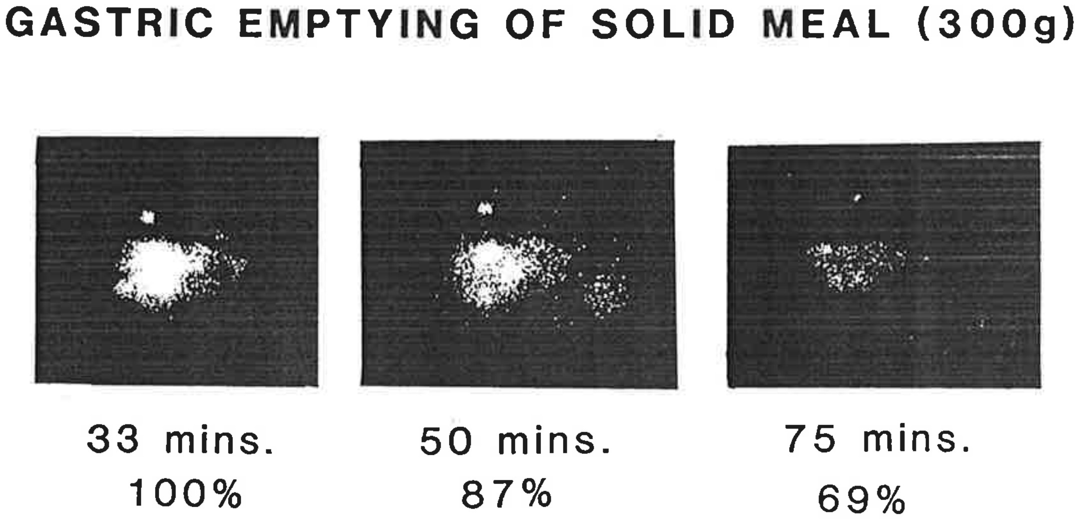


Figure 6.6: Gastric emptying recorded by external gamma camera.

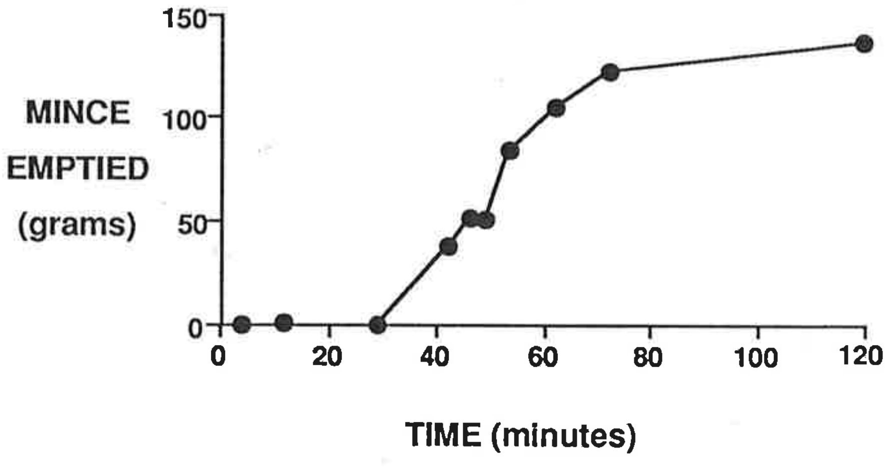


Figure 6.7: Time course of emptying of mince measured by external gamma camera. Result from one pig.

interest. The addition of manometry plus measurements of emptying from the duodenal cannula was well beyond the resources of staff available.

That no redistribution of food across the stomach was observed is at odds with comparable studies in humans (Collins et al 1988). It is possible that the solid meal was so small that the meat fell immediately to the distal stomach region. The only conclusion that can be drawn from this one study is that external gamma camera studies are feasible in pigs, albeit demanding a lot of technical resources.

SECTION 7

MEDIATION OF CONTROL OF PYLORIC MOTILITY

7.1 Intrinsic Neural Control: Control of Pyloric Motility and Liquid Gastric Emptying by Ascending Duodenal Intramural Nerves

7.2 Extrinsic Neural Control: Control of Pyloric Motility and Liquid Gastric Emptying by the Vagus Nerves

7.1 INTRINSIC NEURAL CONTROL: CONTROL OF PYLORIC MOTILITY AND LIQUID GASTRIC EMPTYING BY ASCENDING DUODENAL INTRAMURAL NERVES

INTRODUCTION

The stimulation of duodenal and upper small bowel receptors by chyme that empties from the stomach provides feedback to the motor mechanisms that control gastric emptying (Meyer 1987). The mediation of this feedback control remain poorly defined. Pathways known to influence gastric motility and emptying include extrinsic nerves of the autonomic nervous system (Roman and Gonella 1987), intramural neurones of the enteric nervous system (Wood 1984) and endocrine mechanisms (Valenzuela 1976).

The aim of this study was to investigate the role of ascending duodenal intramural neurones in the regulation of pyloric motility and gastric emptying, by interruption of these nerves through transection of the duodenum.

METHODS

Twelve Kangaroo Island pigs ranging in body weight from 34 to 55 kilograms, with duodenal and gastric (9 animals) or oesophageal (3 animals) cannulae were studied. In six of the twelve animals the duodenum was transected (Section 3.6.2) and in the remaining six the duodenum was left intact. Studies were performed in the 1 to 3 months after surgery.

Manometry and liquid gastric emptying studies were performed during intestinal stimulation of pyloric motility (Sections 3.2.1, 3.3 & 3.4).

Statistical Analysis

To normalise the data, gastric emptying data were transformed to $\log_e$ values. Data were analysed by analysis of variance with Fisher's LSD and simple regression analysis, as appropriate.

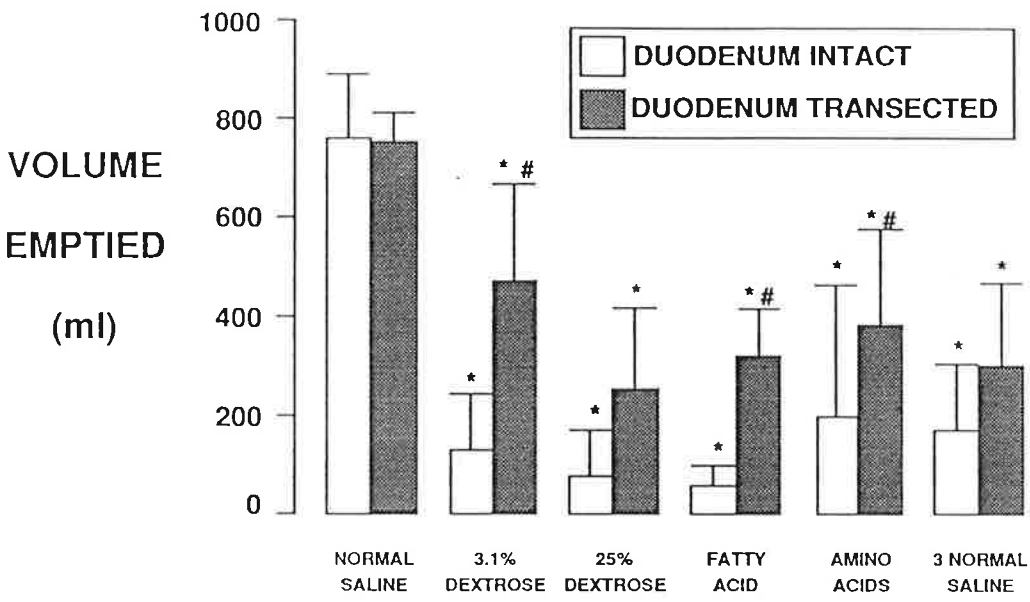
RESULTS

Gastric Emptying

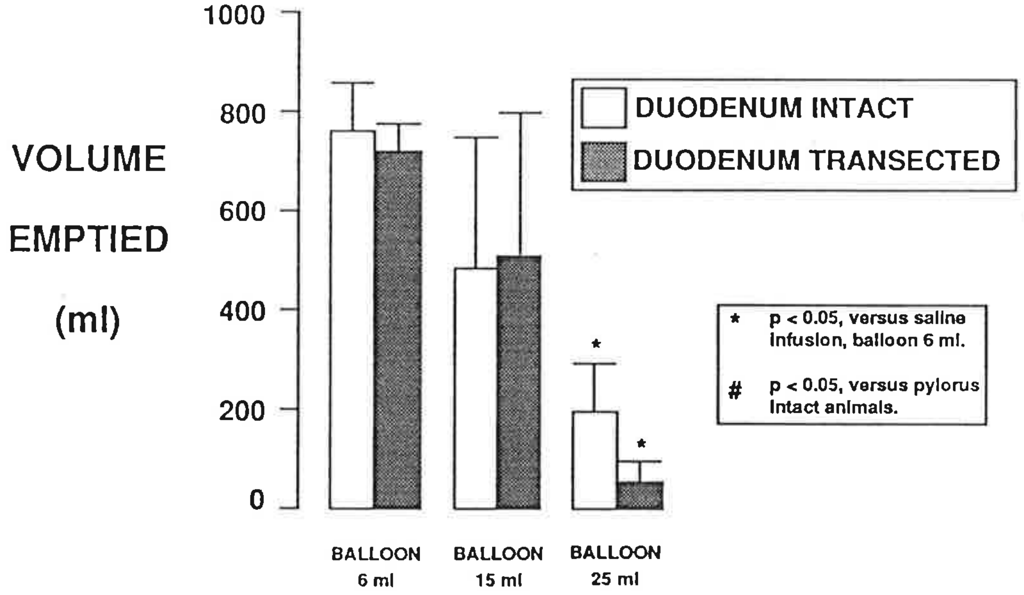
1. Duodenal Nutrient and Osmolar Solutions

Gastric emptying was relatively rapid during intraduodenal infusion of normal saline. Duodenal transection did not alter the rate of gastric emptying during duodenal saline infusion, compared to duodenum intact animals (Figure 7.1).

In contrast, when solutions that are known to alter gastric emptying rates (Section 4.2) were infused into the duodenum, emptying rates differed significantly between duodenum intact and transected animals. In transection animals, intraduodenal infusion of each isosmolar solution of 3.1% dextrose-saline, fatty acid and amino acids was associated with significantly



A: DUODENAL NUTRIENT OR OSMOLAR SOLUTIONS



B: DUODENAL DISTENSION

Figure 7.1: Rates of gastric emptying in duodenum intact and transected animals, during

A: Duodenal nutrient and hyperosmolar stimulation.

B: Duodenal distension.

Results from 6 duodenum intact and 6 duodenum transected pigs, one study per pig.

more rapid emptying than in duodenum intact animals (p = 0.0001), (Figure 7.1a). A significant difference was not demonstrated during intraduodenal infusions of the hyperosmolar solutions of 25% dextrose and 3 normal saline (Figure 7.1a). Emptying occurred evenly throughout the 30 minute duration of each study (Figure 7.2).

Transection did not completely abolish the retardant effect of duodenal infusates, as in the transected animals gastric emptying rates were significantly slower during infusion of each nutrient and hyperosmolar solution tested, when compared to normal saline infusion (p = 0.0001), (Figure 7.1a).

2. Duodenal Distension

In both groups of animals, distension of the duodenum by inflation of the Foley balloon was associated with a significant retardation of gastric emptying (p = 0.0001), the effect being greater with greater distension of the duodenum (Figure 7.1b). Gastric emptying rates were comparable between duodenum intact and duodenum transected animals, at each degree of duodenal distension (p = 0.263). The volume emptied correlated with the volume of the Foley balloon, in both groups of animals (control: r = -0.54, p = 0.0377; transect: r = -0.78, p = 0.0001).

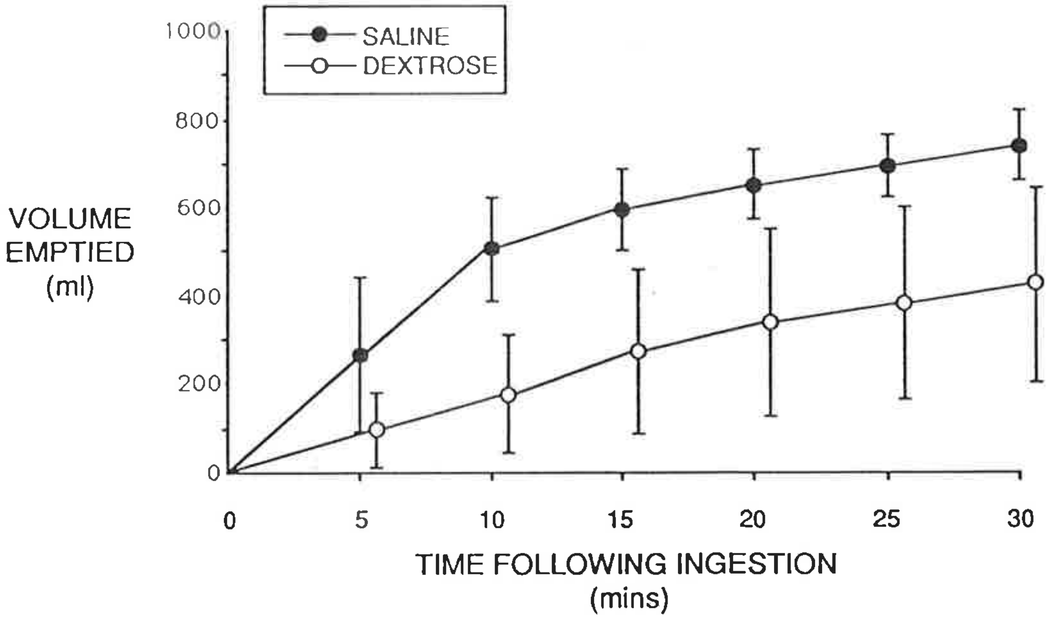


Figure 7.2: Time course of emptying in duodenum transected animals during duodenal infusion of normal saline and 3.1% dextrose-saline solutions. Results from 6 pigs, one study per pig.

Antro-Pyloro-Duodenal Motility

1. Duodenal Nutrient and Osmolar Solutions

The intraduodenal infusion of normal saline was associated with a predominance of APWs for both duodenum intact and transected animals, the rates for this wave pattern not differing significantly.

In contrast, a difference was demonstrated between duodenum intact and transected animals, during duodenal infusion of nutrient or hyperosmolar solutions ($p = 0.03$). In duodenum transected animals infusion of each of 3.1% dextrose-saline, fatty acid, amino acids and 3 normal saline failed to stimulate IPPWs. Only infusion of 25% dextrose produced a significant stimulation of IPPWs (Figure 7.3a).

In duodenum intact animals, intraduodenal infusion of 3.1% dextrose-saline and 25% dextrose was associated with a significant inhibition of APWs, compared to duodenal saline infusion ($p = 0.0044$), (Figure 7.4a). In duodenum transected animals, APWs decreased significantly only during duodenal infusion of 25% dextrose (Figure 7.4a).

2. Duodenal Distension

The stimulation of IPPWs by distension of the duodenum, seen in duodenum intact animals, was absent in duodenum transected animals ($p = 0.03$), (Figure 7.3b).

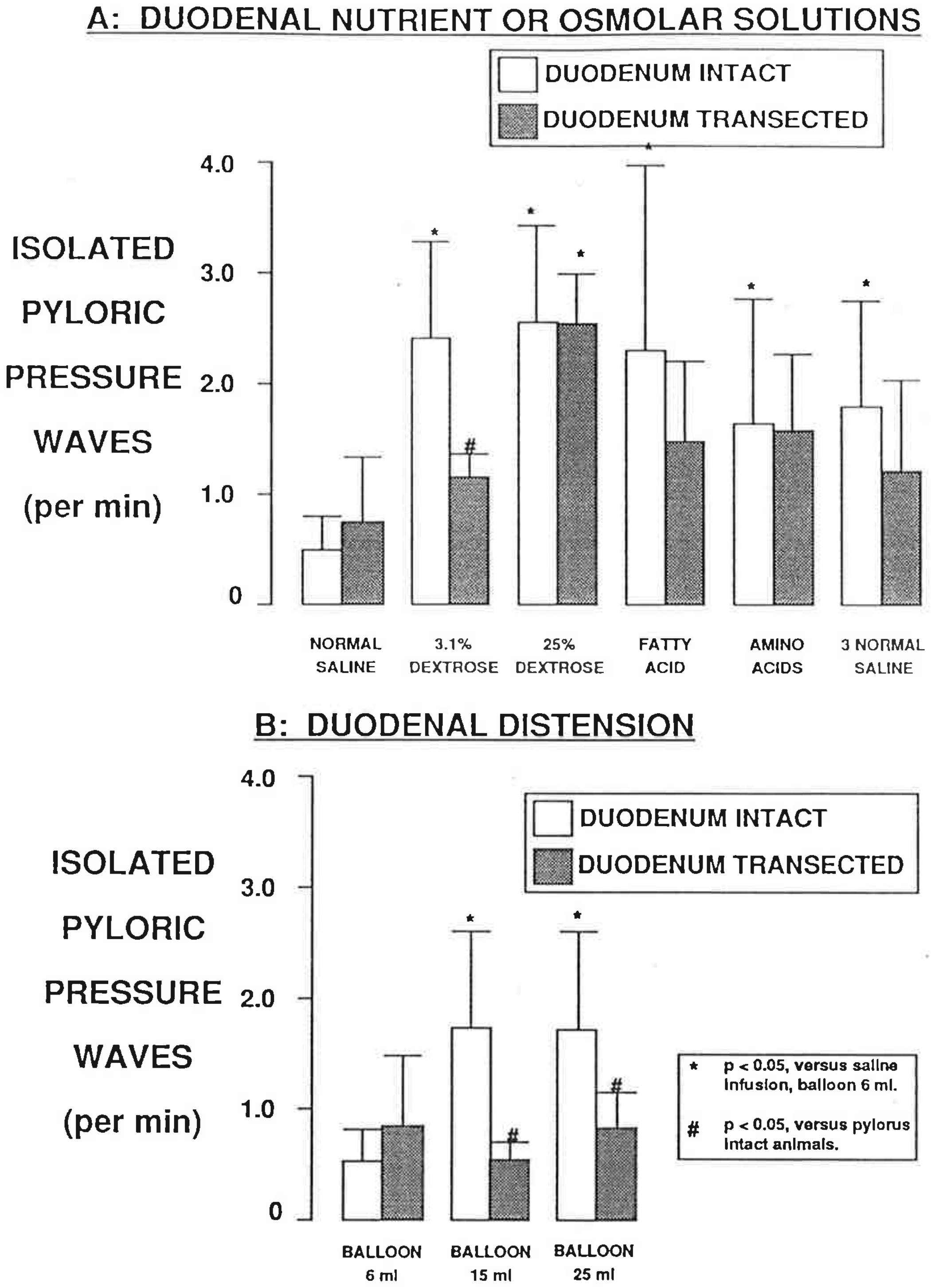


Figure 7.3: Rates of isolated pyloric pressure waves in duodenum intact and transected animals, during

A: Duodenal nutrient and hyperosmolar stimulation.

B: Duodenal distension.

Results from 6 duodenum intact and 6 duodenum transected pigs, one study per pig.

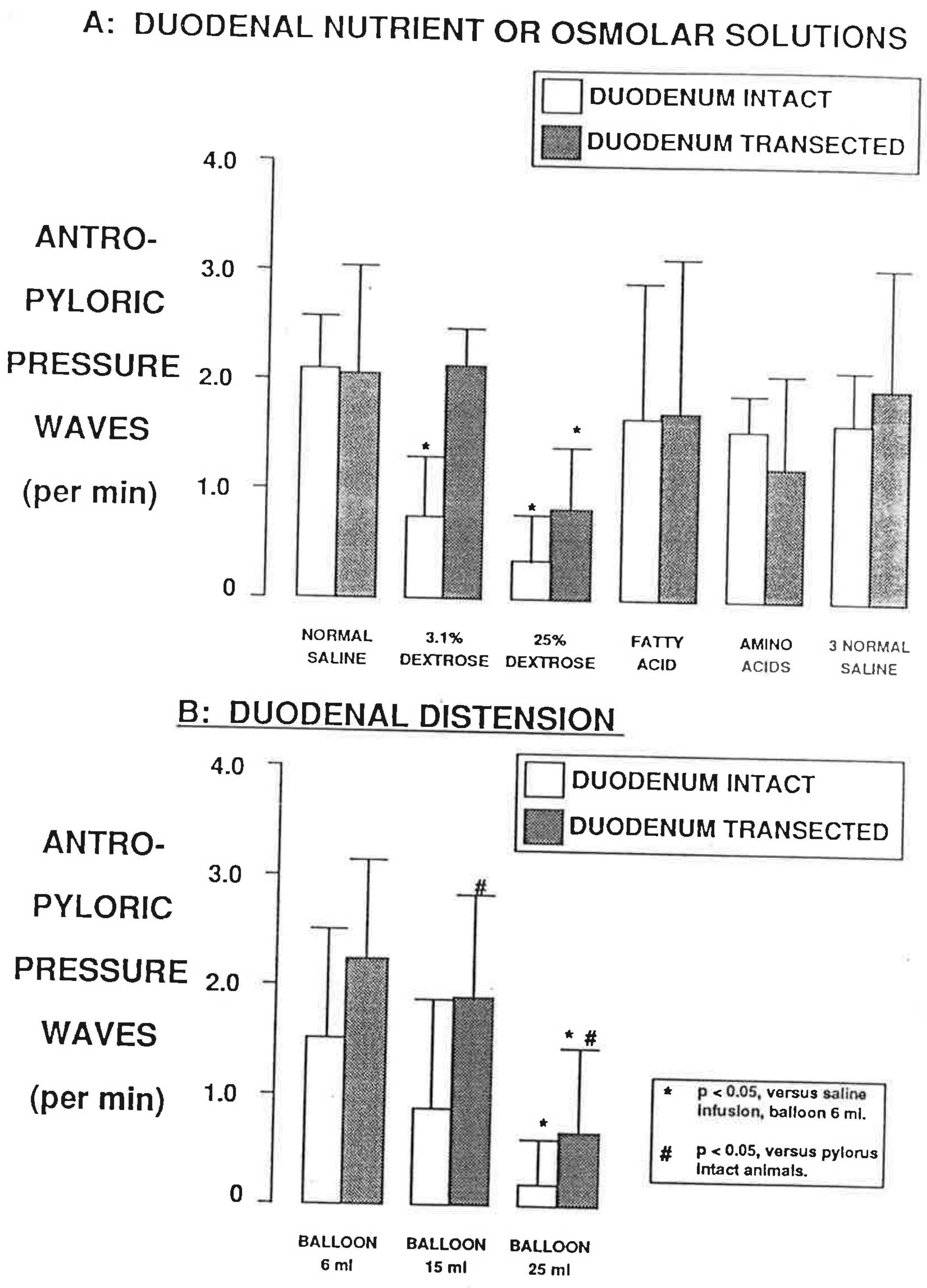


Figure 7.4: Rates of antro-pyloric pressure waves in duodenum intact and transected animals, during

A: Duodenal nutrient and hyperosmolar stimulation.

B: Duodenal distension.

Results from 6 duodenum intact and 6 duodenum transected pigs, one study per pig.

APWs occurred significantly more frequently in duodenum transected animals, compared to duodenum intact animals, at each degree of duodenal distension (p = 0.0388). However duodenal distension still inhibited APWs in duodenum transected animals (p = 0.0153), (Figure 7.4b).

CONCLUSIONS

These studies in awake unsedated pigs have shown that interruption of duodenal intramural nerves, by duodenal transection, leads to impairment of the stimulation of IPPWs by both duodenal nutrient and hyperosmolar solutions and by duodenal distension. Associated with these changes, duodenal transection lead to impairment of the retardation of liquid gastric emptying induced by duodenal nutrient and hyperosmolar solutions, but had no influence on the alterations to gastric emptying induced by duodenal distension. These finding support the hypothesis that ascending duodenal intramural nerves play a significant physiological role in the transmission of feedback signals from nutrient, osmolar or stretch receptors in the upper small bowel to the pylorus.

7.2 EXTRINSIC NEURAL CONTROL: CONTROL OF PYLORIC MOTILITY AND LIQUID GASTRIC EMPTYING BY THE VAGUS NERVES

INTRODUCTION

The aim of this study was to investigate the role of the vagus nerves in the control of pyloric motility and liquid gastric emptying by the use of reversible truncal vagotomy (Gleysteen et al 1983), achieved by vagal cooling, in the pig preparation.

METHODS

Study Protocol

Three animals underwent insertion of vagal cooling devices. All studies were performed without vagal cooling. Liquid gastric emptying and motility studies were performed during intraduodenal infusion of each of normal saline, 20 millilitres per minute (3 animals), 3.1% dextrose-saline, 20 millilitres per minute (2 animals) or during distension of the duodenum by the Foley balloon at 25 millilitres (2 animals). Motility and emptying were analysed as described previously (Sections 3.3 & 3.4).

RESULTS

Gastric Emptying

During normal saline infusion, gastric emptying of the radio-labelled drink followed a linear emptying course over the 30 minutes, in each of the 3 animals with a vagal cooling device in situ. A mean volume of 527 millilitres emptied at thirty minutes, which was less than the 770 millilitres emptied in 6 control animals without vagal devices (Figure 7.5).

During duodenal dextrose infusion, gastric emptying was more rapid in one of the two animals with a vagal cooling device in situ and less rapid in the other animal (Figure 7.5). During duodenal distension, both animals with a vagal cooling device in situ emptied less than during studies without duodenal distension (Figure 7.5).

Motility

In all 3 animals, both before and following ingestion of the drink and irrespective of the stimuli provided (saline, dextrose, distension), the only manometric pattern recorded was that of regularly occurring IPPWs, at approximately 3.3 per minute (Figure 7.6).

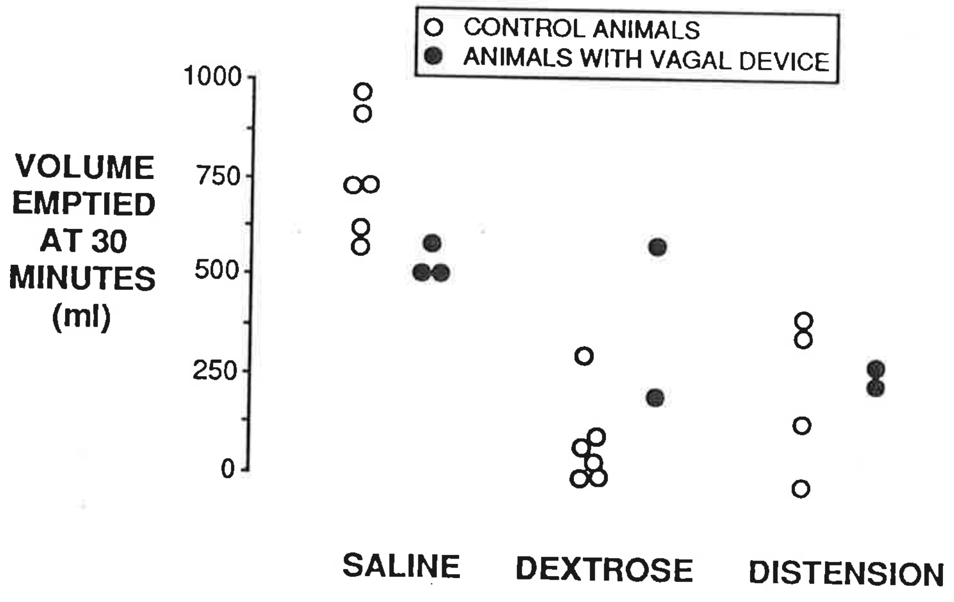


Figure 7.5: Gastric emptying rates in animals with a vagal cooling device, compared to control animals.

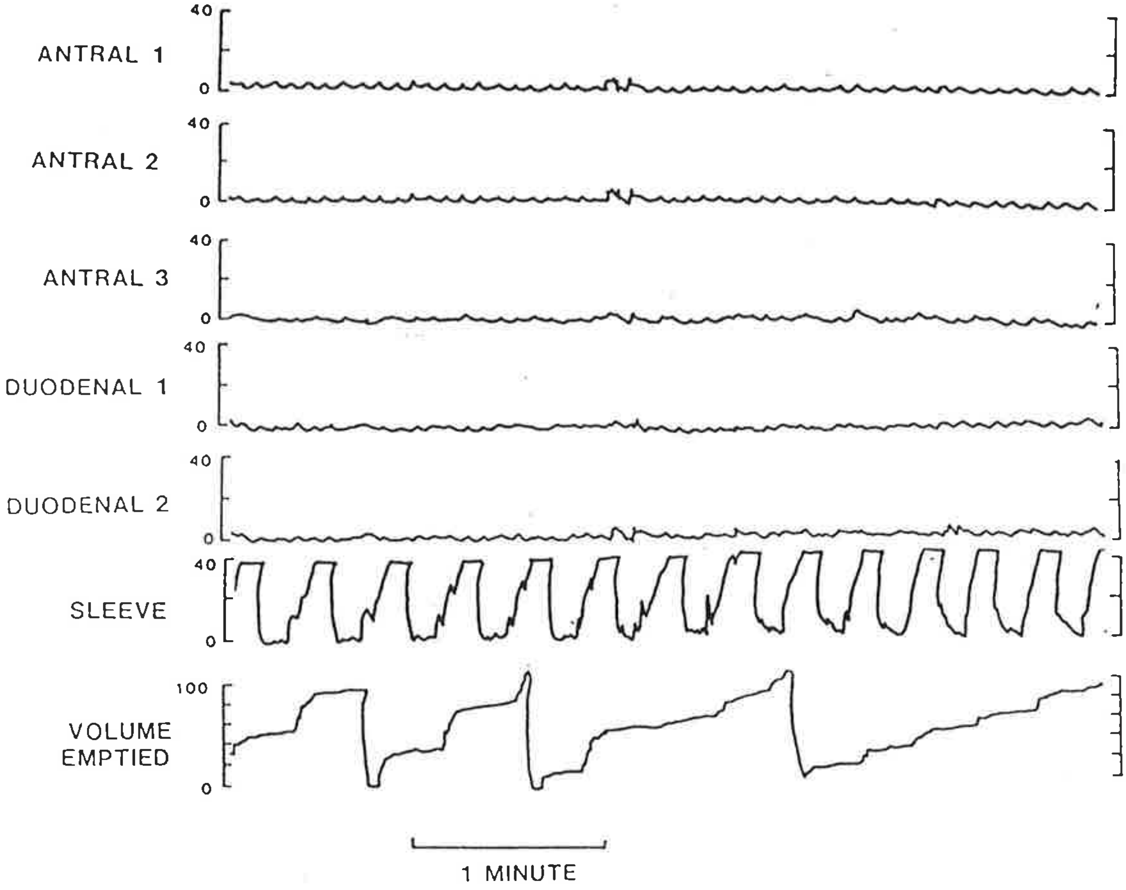


Figure 7.6: Manometric recording of isolated pyloric pressure waves and pulsatile flow, in an animal with a vagal cooling device, during duodenal saline infusion. Antral 1, 2 and 3 refers to pressure recordings from the three separate antral side holes. Duodenal 1 and 2 refers to pressure recordings from the two separate duodenal side holes.

Correlation of Flow and Motility

Irrespective of the stimuli, transpyloric flow occurred predominantly in gushed, intimately timed and just prior to the commencement of each IPPW (Figure 7.6).

CONCLUSIONS

This study has demonstrated chronic alteration to pyloric motility following manipulation of truncal vagal nerves. It is probable that the vagal nerves were significantly damaged in these studies and that a vagotomy was inadvertently achieved. Although insufficient animals were studied, it is of note that the only motor pattern recorded was that of IPPWs, associated with a partial retardation of liquid gastric emptying.

SECTION 8

DISCUSSION

8.1 MEASUREMENT OF PYLORIC MOTOR FUNCTION IN THE UNSEDATED PIG

The technique of pyloric sleeve manometry, with the sleeve positioned across the pylorus by dual point trans-mucosal potential difference (TMPD) recordings, was originally developed and validated in humans (Heddle et al 1988b). As the sleeve records the highest pressure generated at any point along its length (Dent 1976), displacement, with attendant failure to detect pyloric contractions, is avoided, providing the sleeve remains across the pylorus. This technique has been applied directly to the unsedated pig preparation, for prolonged recordings of pyloric motility.

In the application of pyloric sleeve manometry to the pig preparation, two new criteria specific for the pig were established. Firstly, the profile of TMPD across the gastro-duodenal junction of the pig was determined, so that correct localisation of the sleeve across the pylorus could be defined. Secondly, the width of the phasically active zone of the distal pyloric ring was determined, so that an isolated pyloric pressure wave could be defined.

The technical demands associated with the measurement of antro-pyloro-duodenal motility in unsedated large animals are considerable. While other techniques that use extraluminal sensing devices have been employed for recording from the pylorus of awake animals, intraluminal manometry was used in the belief that it would provide the most precise measurements of pyloric motor function. The establishment of this capacity enabled better definition of the role of the pylorus in gastric emptying, given the ability to experimentally manipulate the stimulatory, mediatory and motor mechanisms of gastric emptying.

8.2 PATTERNS OF PYLORIC MOTILITY IN THE PIG

The pyloric region of the pig has been demonstrated to undergo at least three patterns of motility. These patterns are phasic pressure waves localised or isolated to the pylorus, classified as isolated pyloric pressure waves (IPPWs), non-localised phasic pressure waves, classified as antro-pyloric pressure waves (APWs) and periods of motor quiescence. In all studies, no consistent elevation of basal pyloric pressure, or pyloric tone, was recorded.

That periods of motor quiescence were recorded supports the concept that IPPWs are specifically stimulated to occur. IPPWs do not arise merely by inhibition of antral contractions with continuation of pyloric contractions. At no stage were antral pressure waves recorded in the absence of pyloric pressure waves. This is in keeping with the concept proposed by Wood (1984), that the motor patterns of IPPWs and APWs are pre-programmed within the intrinsic neural network of the enteric nervous system of the distal stomach.

The demonstration of a narrow zone of localised phasic motor activity, in response to chemical or mechanical stimulation of receptors within the small intestine, is consistent with the findings from other studies in animals (Bertiger et al 1987, Biancini et al 1981, Reynolds et al 1984, 1985) and humans (White et al 1981, 1983, Fisher & Cohen 1973, Pandolfo et al 1979, Heddle et al 1988a, 1988b, 1988c, Houghton et al 1988a, 1988b). These similarities suggest that the pig is a suitable preparation to study pyloric motility. However the pig pylorus is not an exact mimic of the human pylorus. In humans IPPWs occur in a segment usually less than 9 millimetres in width (Heddle et al 1988b), whilst the multiple side hole manometric analysis reported in this thesis demonstrated that IPPWs occurred over a greater luminal length, of between 12 and 42 millimetres. Torgersen (1942) recognised anatomically the greater length of the pyloric segment in the pig than in man.

Although pyloric tone was not recorded in the pig studies, pyloric tone has been recorded with intraluminal manometric techniques in other animal preparations (Bertiger et al 1987, Brink et al 1965, Isenberg and Czendes 1972) and in humans (Valenzuela et al 1976, Fisher et al 1973, Phaosawasdi and Fisher 1982, Heddle et al 1988a, 1988b, 1988c). The absence of tone in the pig preparation may reflect species variation. Low amplitude pyloric tone may have occurred, but could not be resolved because of the practical difficulties of resolving small pressures caused by animal movement, straining and grunting. Despite this difference, there is a very close similarity in the mechanical patterns of IPPWs in man and the pig.

8.3 STIMULATION OF PYLORIC MOTILITY

The stimulation of pyloric motility can be analysed in three basic components: cephalic, gastric and intestinal.

Intestinal stimulation of IPPWs and inhibition of APWs was recorded with a range of stimuli to the intestine. These stimuli include nutrient solutions of dextrose, fatty acids and amino acids, hyperosmolar saline or dextrose solutions and mechanical distension of the duodenum. The role of gastric acid in control of pyloric motility was not investigated. The latencies and thresholds of response of pyloric motility to these stimuli are consistent with the hypothesis that stimulation of intestinal receptors, such as by foodstuffs emptying from the stomach, acts to control the motor function of the distal stomach. This control of motility is modulated significantly by both cephalic and gastric stimulatory mechanisms.

The demonstration of a narrow zone of phasic motor activity, recorded as IPPWs, in response to stimulation of receptors within the small intestine, confirms the suitability of the pig as a model to study pyloric motility. Stimulation of IPPWs has been demonstrated in humans in response to intraduodenal infusion of various nutrient solutions (Fisher & Cohen 1973, Heddle et al 1988a, 1988c, White et al 1983). Similarly duodenal distension has been shown by others to exert an inhibitory influence on gastric motility (McClure et al 1920, Thomas et al 1934). Electro-physiological investigations have revealed the existence of mechano-receptors at the duodenum, with vagal innervation that responds to distension by increased neural activity (Clarke and Davison 1968, Cottrell and Iggo 1984, Davison 1972, Harding and Leek 1972, Iggo 1957, Leek 1969, Paintal 1973).

Cephalic stimulation of gastric motility is initiated by such factors as the sight, smell and taste of food. Such stimulation was recorded in the pig preparation. The rate of pressure waves following ingestion was over twice the fasting rate. This demonstrates that motility of the pylorus was not omnipresent, but was stimulated in part by ingestion. Regular unrelenting pressure waves commenced within seconds of presentation of the meal to the animal, often before ingestion had begun and always before any significant volume of the drink had entered the stomach (Figure 4.7). This rapidity of response suggests a neural mediation of this stimulus, and warrants further study. Sham feeding was attempted in a few preliminary studies, but was abandoned as the animals became uncontrollable when food was withheld. It is likely that the vagal efferent activity that mediates gastric accommodation (Meyer 1987) also mediates this cephalic stimulation of pyloric motility.

Studies with the water barostat demonstrated a gastric stimulation of motility of both the antrum and pylorus by distension of the stomach. However the data suggest that the mechanisms of gastric stimulation of IPPWs and APWs differ. It is probable that a synergism exists between the gastric stimulation of IPPWs by distension and the intestinal stimulation of IPPWs by duodenal nutrients. The results also support the novel concept of a threshold for stimulation by gastric distension. Below a barostat setting of 15 centimetres, duodenal infusion of dextrose was barely able to stimulate IPPWs. With the barostat set at or above 15 centimetres, duodenal dextrose infusion produced near maximal stimulation of IPPWs, irrespective of the degree of gastric distension (Figure 4.8). This suggests an all-or-none type stimulation of IPPWs by gastric distension, in the presence of intestinal nutrient stimulation.

In contrast to the stimulation of IPPWs, the rate of APWs increased in a near linear response to the pressure within the stomach, during duodenal saline infusion. It may be concluded that antral motility is stimulated directly by distension of the stomach. This reflex has been reported previously (Andrews et al 1980a) and has been described as an "antral reflex" (Meyer 1987). Unfortunately it was not possible to determine from these studies whether stimulation of antral motility arose primarily from distension of the proximal stomach, or from distension of the antrum itself. Duodenal infusion of dextrose had previously been shown to inhibit APWs (Section 4.2). During intraduodenal infusion of dextrose, the rate of APWs increased with an increase in intragastric pressure (Figure 4.9b). Here the inhibition of APWs by duodenal dextrose infusion was overridden by stimulation of APWs achieved through gastric distension. These findings are further evidence of the separate nature of IPPWs and APWs.

8.4 LIQUID GASTRIC EMPTYING

The studies have confirmed a very potent retardation of gastric emptying of liquids, by the nutrient or hyperosmolar stimulation of receptors within the proximal small intestine. The variables of osmolarity, calorie load and nature of infusate were not held constant in such a way that allowed comparison of the effects of osmolarity or calorie in their own right. If one considers that each isosmolar solution (3.1% dextrose-saline, calorie load 2.48 kcal/min, fatty acid, calorie load 0.62 kcal/min and amino acids solution, calorie load 3.72 kcal/min) produce an equivalent retardation of gastric emptying (Table 1), one may conclude that retardation of gastric emptying, calorie for calorie, was greatest for fatty acid, intermediate for dextrose and least for amino acids solution. This suggests the existence of receptors specific for individual nutrients, rather than specific for the nutrient density of solutions. Other studies have confirmed this hypothesis, that receptors specific for fatty acids (Annegars and Ivy 1947) and the amino acid L-tryptophan (Byrne et al 1977) do exist. However a retardation of emptying by isosmolar dextrose, which thus is independent of osmolarity, has not been previously demonstrated. This finding does not support the conclusion by Minami and McCallum, that "carbohydrates .... retard gastric emptying via the osmoreceptors" (1984). Presumably the small bowel contains receptors specific for carbohydrates such as dextrose.

A potent retardation of liquid emptying by distension of the duodenum, in proportion to the degree of duodenal distension, was also demonstrated. Duodenal distension has been reported previously to inhibit gastric emptying (Thomas et al 1934).

8.5 THE PYLORUS AND LIQUID GASTRIC EMPTYING

The studies of liquid gastric emptying presented in this thesis have provided new information about the mechanical factors that control gastric emptying of liquids. This insight has been possible because the techniques used have allowed recordings of detailed patterns of antro-pyloric motility in association with close correlation of timing of emptying of liquids into the duodenum. The major findings were: (1) That stimulation of IPPWs and inhibition of APWs were closely associated with cessation of transpyloric flow of liquids. (2) That more than half of liquid emptying occurred as episodes of pulsatile flow, which were intimately associated in time with APWs. (3) That alterations of motility were closely associated in time with alterations of liquid gastric emptying.

Isolated Pyloric Pressure Waves and Retardation of Liquid Gastric Emptying

The liquid emptying studies in animals with the pylorus intact have demonstrated a close association between IPPWs and cessation of gastric emptying of liquids in two ways. First, a positive correlation was demonstrated between the rates of IPPWs and retardation of gastric emptying over the 30 minute duration of each study. Second, near cessation of transpyloric flow was recorded during individual sequences of IPPWs within each study. These associations support the hypothesis that IPPWs and retardation of gastric emptying are causally linked, that is, that IPPWs obstruct liquid gastric emptying. How can IPPWs obstruct transpyloric flow, when no pyloric pressure gradient exists between each phasic pressure wave of a sequence of IPPWs? Possibly the interval between each isolated pyloric pressure wave, when pyloric pressure equals antral pressure, is too brief to allow the pylorus to open and flow to be established. Further studies utilising concurrent manometry with fluoroscopic imaging may be necessary to resolve this issue. Low-amplitude pyloric tone may have occurred, but could not be resolved because of the practical difficulties of resolving small pressures caused by animal movement, straining and grunting.

The hypothesis that IPPWs are obstructive to liquid gastric emptying is supported by findings from other studies. Stimulation of IPPWs by the intraduodenal infusion of various nutrient solutions has been demonstrated in humans (Fisher & Cohen 1973, Heddle et al 1988a, 1988c, White et al 1983). Such localised pyloric contractions have been shown to occur more frequently during slowing of gastric emptying (Houghton et al 1988a), due to stimulation of intestinal receptors by chyme emptying from the stomach (Thomas 1957, Meyer 1987). IPPWs have been demonstrated radiologically to be associated with obstruction of transpyloric flow (Tougas et al 1987). These studies support the findings original to this thesis, that the latencies, thresholds and magnitudes of retardation of gastric emptying, measured directly, are closely if not causally associated with IPPWs.

Ehrlein and co-workers have similarly studied motor activity of the distal stomach, using extraluminal induction coils combined with radio-isotopic imaging of gastric emptying. Findings from Ehrlein's studies are largely in agreement with this study. Ehrlein reported that after meals "The external pyloric diameter increased and decreased in the rhythm of the antral waves; that is, the pylorus opened and closed rhythmically." (Ehrlein 1988). This motor pattern corresponds with antro-pyloric pressure waves. Ehrlein also reported continued motor activity of the pylorus in the absence of antral activity. Intraduodenal oleic acid "delayed gastric emptying and diminished to a variable extent antral and duodenal motility as well as the pyloric opening" (Keinke et al 1984). These changes are consistent with the motor pattern of isolated pyloric pressure waves we report. Induction coils, as used by Ehrlein and co-workers, signal the pyloric diameter and are not an effective method of recognising a sequence of isolated pyloric pressure waves, as during the marked phasic pressure changes of IPPW, the pyloric lumen rarely opens (Gershon-Cohen et al 1937, Tougas et al 1987, White et al 1983). The conclusion by Ehrlein that "relaxation of the pyloric sphincter is more an isotonic than an isometric phenomenon" (Keinke et al 1984) is not necessarily correct. Although pyloric tone was not recorded in the pig studies, pyloric tone has been recorded with intraluminal manometric techniques in other animal preparations (Bertiger et al 1987, Brink et al 1965, Isenberg & Csendes 1972) and in man (Fisher & Cohen 1973, Phaosawasdi & Fisher 1982, Valenzuela, Defilippi & Csendes 1976). The absence of tone in the pig preparation may reflect species difference.

The studies with the water barostat add further weight to the concept that the pylorus, by way of IPPWs, can produce retardation of gastric emptying. Even in the face of a positive gastro-duodenal pressure gradient, IPPWs were closely associated with retardation of transpyloric flow. The design of previous studies has not made it possible to exclude that retardation of gastric emptying associated with IPPWs was due to relaxation and increased capacitance of the proximal stomach. The barostat, by maintaining constant intragastric pressure, simulated constant activity of the proximal stomach. Relaxation of the proximal stomach, such as occurs during duodenal nutrient infusion (Azpiroz and Malagelada 1985b), was eliminated or reduced by increased filling of the stomach. By alteration of the height of the barostat, varying degrees of tonicity of the proximal stomach could be simulated. With the water barostat, relaxation of the proximal stomach probably did not play a role in the retardation of gastric emptying demonstrated in these studies.

Miller et al (1981) studied gastric emptying during barostatic control of gastroduodenal pressure gradients, and also demonstrated a slowing of gastric emptying during nutrient stimulation of intestinal receptors, which was independent of proximal gastric pressure. They proposed that the antropyloric segment provides only minimal resistance to gastric emptying, and that "the dominant regulator of gastric emptying of liquids is a resistance or series of resistances beyond the stomach".

This conclusion was largely based upon two observations. First, at high intragastric barostat pressures (over 15 centimetres water), the retardation of transpyloric flow by intraduodenal infusion of nutrients was not demonstrated. It is probable that the high intragastric pressures tested exceeded the physiological range, and overcame the ability of the pylorus to resist flow. Second, retardation of transpyloric flow induced by intraduodenal infusion of nutrients was unaltered following removal of the pyloric sphincter mechanism, by either pyloroplasty with vagotomy, or by stenting open of the pylorus. However in all their studies, duodenal resistances were left intact. It is probable that removal of pyloric motor function was adequately compensated for by the remaining mechanisms, especially those of the duodenum. The study by Miller et al did not exclude a major role for the pylorus so much as confirm a role of other factors. In the studies presented in this thesis, drainage of the duodenum beyond the duodenal cap, by the duodenal cannula, minimised duodenal resistances (Parr et al 1987, Shirazi et al 1988). Exclusion of duodenal factors allowed more conclusive demonstration of the obstructive nature of IPPWs.

Paraskevopoulos et al (1988) applied a water barostat with an external reservoir to investigate the relationship between intragastric pressure and gastric emptying of liquids. As demonstrated in this thesis, emptying was not maintained with the barostat pressure at 7 centimetres water. When intragastric pressure was maintained at 20 centimetres water, isosmolar 0.54% glucose-saline solution emptied at 50 millilitres per minute. These findings compare favourably with those of the barostat study, in which duodenal infusion of isosmolar 3.1% dextrose solution at 20 millilitres per minute (2.3 times the calorie load per unit time) was associated with gastric emptying at a mean of 10 millilitres per minute with gastric pressure at 15 centimetres water and 28 millilitres per minute with gastric pressure at 25 centimetres water. They also concluded that factors other than the intragastric pressure induced by fundic contraction regulate the rate at which liquids empty when they are high in nutrients or osmolarity.

The studies of gastric emptying in animals with the pylorus excised provide further evidence for a major role of the pylorus in the control of gastric emptying. Pylorus excision resulted in a complete loss of control of liquid emptying normally produced by entry of nutrient or hyperosmolar solutions into the duodenum. The manometric studies confirmed that pylorus excision was complete, since there was an absence of IPPWs during duodenal infusions of nutrient or hyperosmolar solutions, and during duodenal distension. It seems reasonable to conclude that the rapid emptying after surgical removal of the zone that produced IPPWs resulted from removal of a significant barrier to gastric emptying.

Liquid emptying rates were not significantly different between pylorus intact and excised animals, during infusion of normal saline into the duodenum. The effects of pylorus excision were only evident during stimulation by duodenal nutrient or hyperosmolar infusions. This illustrates that studies with inadequate nutrient, hyperosmolar or other stimulation may fail to probe adequately the effects of an intervention, such as pylorus excision, on gastric emptying. Crider and Thomas reported more rapid liquid emptying during stenting open of the pylorus, but only with a fatty meal, not with saline, acid, dextrose or alcohol meals (Crider and Thomas 1937). Stemper and Cooke reported no change to liquid emptying rates of an acid, fatty or dextrose meal, with the pylorus stented (Stemper and Cooke 1976). It is probable that the nutrient, osmolar or acidic meals tested in these studies provided inadequate stimulation to slow gastric emptying.

In all of my studies, the duodenal cannula probably enhanced the effects of excision of the pylorus. A proximal duodenal cannula minimises resistances beyond the duodenal cap (Parr et al 1987, Shirazi et al 1988). Meyer has proposed that gastric emptying is controlled by a series of motor mechanisms, including the pylorus, antrum, proximal stomach and duodenum (Meyer 1987). It is probable that in pylorus intact animals, loss of resistances beyond the duodenal cap was compensated for by increased activity of the pylorus, antrum and fundus of the stomach. However in pylorus excised animals, loss of both pyloric and duodenal resistances resulted in loss of control of emptying. Removal of both pyloric and duodenal mechanisms has been shown by others to produce greater alterations to gastric emptying than by removal of the pylorus alone. Hinder and Bremner (1978) demonstrated that a pyloroplasty of 5 centimetres or 7 centimetres produced accelerated gastric outflow, but that a pyloroplasty of 3 centimetres did not. Bortolotti et al (1981) reported increased gastric emptying following pyloric myotomy that extended to the third part of the duodenum.

Pylorus excision was undertaken in order to remove completely any effects of the pylorus. Could it have been possible that the pylorus excision included a significant portion of the antrum? Antropylorectomy has been reported to produce more rapid gastric emptying than pylorectomy alone (Hinder and San-Garde 1983). However the amount of antrum excised, if any, was minimised by manometric measurement of the length of the pylorus in each animal. That antral pressure waves were recorded in the pylorus excised animals confirms that the antral mechanism remained active.

Pylorus excision ensured removal of the pyloric mucosal plug. Although pyloroplasty and pyloric myotomy effectively prevent pyloric muscle closure, the pyloric mucosal plug may still influence gastric emptying. The mucosal plug may be an effective barrier to transpyloric flow, even in the absence of muscle contraction (Schulze-Delrieu et al 1984).

The studies of animals with the pylorus excised support the hypothesis that removal or neutralization of the pylorus is a major factor in the development of the rapid uncontrolled gastric emptying that may follow gastric surgery (Goligher et al 1972, 1978, Humphrey et al 1972). These pylorus excision animals appear to be a representative model for the gastric incontinence associated with the dumping syndrome. The symptoms of dumping have been attributed to rapid emptying of gastric contents, high in osmolarity or nutrients, such as occurred in these animals. This is thought to lead to an outpouring of fluid into the lumen of the bowel, a fall in plasma volume (Le

Quesne et al 1960) and the feeling of faintness characteristic of early dumping. Distension of the upper small bowel has been proposed as another cause of dumping (Machella 1950, Stahlgren and Cronek 1972).

Distension of the duodenum was able to elicit significant retardation of gastric emptying, even following pylorus excision. This was an unexpected finding, and contrasted to the rapid uncontrolled emptying during duodenal nutrient or hyperosmolar stimulation studies. Presumably retardation of gastric emptying by distension of the duodenum is due in part at least to motor mechanisms other than those of the pylorus. Such mechanisms include increased relaxation of the proximal stomach or decreased contractility of the antral pump. This demonstrates the remarkable ability of the multiple components controlling gastric emptying to compensate for loss of other components.

The water barostat studies of animals with the pylorus excised enabled investigation liquid gastric emptying whilst minimising the influence of the proximal stomach, the pylorus and the duodenum. Even with these three motor mechanisms minimised, duodenal dextrose infusion was able to reduce gastric emptying rates, albeit partly. Presumably in these studies retardation of emptying occurred through alterations of other motor mechanisms, such as inhibition of the antral pump and increased contraction of the mid-gastric band (Moore et al 1979).

Antro-Pyloric Pressure Waves and Propulsion of Liquid Gastric Emptying

Work presented in this thesis has demonstrated that at least half of liquid emptying of a 1000 millilitre drink occurred as pulsatile episodes, which were closely associated in time with APWs. This observation emphasizes the importance of antral pumping as a normal mechanism of gastric emptying. The strictness of criteria used to define episodes of pulsatile flow probably underestimated the true amount of flow that was pulsatile. Detailed analysis of the data on the frequency and volume of episodes of pulsatile flow indicate a possible mechanism for fine tuning of the antral pump. The frequency of APWs paralleled the rate of gastric emptying, whether emptying was linear or exponential (Figure 5.6). Also, a direct relationship existed between the volume of each episode of pulsatile flow and the extent of the antro-pyloric segment over which the pressure wave was recorded. It may be summised that the volume emptied as pulses was modulated by both contraction rate and stroke volume of the antro-pyloric segment. However this may represent an effect rather than a cause. It may be that during more rapid gastric emptying, larger volumes of fluid entered the distal stomach, which stretched the antro-pyloric segment to a greater extent and so provoked a more extensive contraction of the antro-pyloric segment, through the "antral reflex" (Andrews et al 1980a).

Intermittency of forward transpyloric flow has been recognised previously, with real time ultrasonography (King et al 1984), fluoroscopic observations of barium emptying (Carlson et al 1966) and radioisotopic imaging of semi-solids (Jacobs et al 1982). However none of these techniques allowed measurement of individual pulse volumes and the proportion of gastric emptying that occurred in flow pulses. The methods used in the present study have allowed this to be done and have shown that pulsatile emptying is quantitatively important.

Liquid Gastric Emptying during Motor Quiescence

During the liquid gastric emptying studies, non-pulsatile gastric emptying, albeit slow, was observed in the absence of any antral or pyloric motor activity. It may be concluded that other motor mechanisms, such as proximal gastric contraction or duodenal relaxation account for this gastric emptying. Rees, Go & Malagelada (1979) also noted slow gastric emptying in the absence of antral contractions, measured in humans by radio-isotopic imaging. However the methods used by Rees et al (1979) did not allow accurate recording of pyloric motility. It is possible that isolated pyloric contractions occurred but were not recorded due to inadequate pyloric manometric techniques.

Relationship of Motility Patterns to Gastric Emptying Rates

During periods of motor quiescence, emptying occurred at a rate intermediate between that of pulsatile flow associated with APWs and near cessation to flow during typical sequences of IPPWs (Section 5.2). When IPPWs recommenced, emptying slowed. This supports the hypothesis that IPPWs *per se* produce retardation of gastric emptying and that antral pumping is an important mechanism in the promotion of liquid gastric emptying. These studies support the hypothesis that retardation of liquid emptying is achieved through an orderly series of processes, involving removal of antral pumping, resulting in motor quiescence, followed by stimulation of pyloric resistances through IPPWs.

The stimuli that produced maximal rates of either IPPWs or APWs can be related to those situations when maximal retardation or maximal enhancement of emptying respectively is required. In the studies presented in this thesis, maximal rates of APWs were recorded during maximal distension of the stomach, such as occurs immediately following ingestion, when gastric emptying is required. In contrast, maximal rates of IPPWs were recorded in association with nutrient, osmolar or distension stimuli to the duodenum, in association with any degree of distension of the stomach, such as occurs with rapid emptying of a stomach that contains foodstuffs. It may be concluded that gastric emptying is controlled through modulation of two separate motor activities: propulsive (and retropulsive) antral pumping, by way of APWs, and pyloric resistance to flow, by way of IPPWs.

8.6 THE PYLORUS AND SOLID GASTRIC EMPTYING

In the process of gastric emptying of digestible solids, sieving and grinding have been assigned to the antropyloric segment functioning as a unit (Meyer 1987). Findings from the solid emptying studies presented in this thesis support the hypothesis that the antrum functions primarily for the sieving and grinding of solids whereas the pylorus functions primarily in the control of transpyloric flow of the solid meal, once ground. A similar range of particle sizes emptied in both pylorus intact and pylorus excised animals. With the control of transpyloric flow independent of the process of grinding, the solid meal may be retained within the stomach as a fine suspension, awaiting the pylorus to "open the gate" (Cannon 1911). With removal of the pylorus, more rapid solid emptying resulted. Unfortunately it was not possible in the studies presented in this thesis to determine the time course of the grinding of the solid meal into fine particles.

In these studies, the lag period before commencement of solid emptying was not significantly different between pylorus intact and pylorus excised animals. However the rate of emptying, after the lag period, was more rapid in pylorus excised animals. It is possible that the lag phase of solid emptying is due primarily to sieving and grinding of solids, as well as redistribution of the solid meal from the proximal to distal stomach regions (Collins et al 1988) and that the linear rate of emptying after the lag phase is due largely to pyloric resistance, controlled by nutrient or osmolar content of the material emptying from the stomach. Other studies support this hypothesis. When Gulsrad et al (1980) compared the gastric emptying of radio-labelled solid and liquid starch meals of identical composition, he found the two meals emptied at nearly the same rate. Malagelada et al compared emptying of a homogenised and unhomogenised solid-liquid meals of the same composition (Malagelada et al 1979). The major difference between the two meals was the absence of a prolonged initial lag phase with the homogenised meal, before emptying commenced. The rates of emptying were comparable.

It is possible that the rate of emptying of digestible solids is controlled by the rate of grinding of the solid meal to a homogenised meal. The more rapid solid emptying associated with pylorus excision observed in the studies may be a result of a more active antral grinding mechanism. If antral motility does control solid emptying, we would expect the lag period to be shorter in pylorus excised animals. Homogenised meals have been shown to empty after a shorter lag period than unhomogenised solid meals of the same composition (Malagelada et al 1979). Results from the studies argue against a control of emptying by antral grinding, as the lag period was not significantly shorter and antral pressure waves were not significantly more frequent in pylorus excised animals.

8.7 MEDIATION OF CONTROL OF PYLORIC MOTILITY

Meyer (1987) postulated three interacting mechanisms that mediate the response of the pylorus to stimulation. These mechanisms are intrinsic neural control of the enteric nervous system (Wood 1984), extrinsic neural control involving the autonomic nervous system (Roman and Gonella 1987) and endocrine mechanisms (Valenzuela 1976). Work presented in this thesis has studied the role of ascending duodenal intramural nerves in the control of motility. The role of nerves descending through the antrum to the pylorus has not been studied. The role of the vagus nerves has been addressed, but incompletely. Neither the place of hormones nor of myogenic mechanisms in the control of pyloric motility have been addressed.

Control of Pyloric Motor Function by Ascending Duodenal Intramural Nerves

The studies of duodenal transection examined the role of duodenal nerves in the control of pyloric motility and gastric emptying. The significant findings from the studies were that interruption of ascending duodenal intramural nerves, by duodenal transection, lead to impairment of the stimulation of pyloric motility by both duodenal nutrient and hyperosmolar solutions by duodenal distension. This impaired stimulation of IPPWs was matched with impaired retardation of liquid gastric emptying, but only during duodenal infusion of nutrient and hyperosmolar solutions, not during duodenal distension. These finding support the hypothesis that ascending duodenal intramural nerves play a significant physiological role in the transmission of feedback signals from nutrient, osmolar or stretch receptors at the upper small bowel to the pylorus.

Duodenal intramural nerves have been demonstrated as one pathway in the mediation of a variety of stimuli. If the control of pyloric motility were mediated exclusively through duodenal intramural nerves, there would be no stimulation of IPPWs, following duodenal transection. A significant stimulation of IPPWs was however recorded following duodenal transection, but only during supra-maximal stimulation by 25%

dextrose. Thus feedback from nutrient or osmolar stimuli at the upper small bowel to the pylorus can occur through pathways other than those of duodenal intramural nerves, but this feedback occurs at levels of stimulation which may be unphysiological. This feedback may be via extrinsic nerves of the autonomic nervous system, or endocrine mechanisms.

Are the differences of emptying between duodenum intact and transected animals, during duodenal infusions of nutrient or hyperosmolar solutions, due solely to the differences of pyloric motility? The changes of emptying may be due to interruption of pathways to other motor mechanisms. Pathways from the upper small bowel receptors to the duodenum were not interrupted, so that duodenal mechanisms were not involved in the alterations demonstrated. Further, the duodenal cannula acted to minimise the influence of resistances beyond the duodenal cap. Failure of suppression of the antrum with increased antral pumping may have produced the more rapid emptying observed in duodenum transected animals. However an increase of APWs was not observed during these studies, except during intraduodenal infusion of 3.1% dextrose (Figure 7.4). Impaired fundic relaxation with increased fundic tone may have accelerated emptying. However other studies have provided evidence that the vagus nerve is the primary, if not only, mediator of nutrient stimuli from the duodenum to the proximal stomach (Azpiroz and Malagelada 1986, Kelly 1981). If this is correct, motility of the proximal stomach was unaltered by duodenal transection. Reduced resistance of the pylorus, as shown by a reduced rate of IPPWs, was most likely the primary if not only mechanism that produced the alterations of emptying demonstrated during nutrient or osmolar stimulation of duodenal receptors.

In contrast to the effects observed during nutrient or hyperosmolar stimulation, duodenal transection had no influence gastric emptying during duodenal distension, even though pyloric motility was significantly altered. Here retardation of emptying by duodenal distension was achieved through motor mechanisms other than those of the pylorus. During distension studies and particularly during maximal distension of the duodenum, pigs were noted at times to salivate and become restless. This suggests some central nervous recognition of the stimulus, perhaps mediated through extrinsic nerves. A phenomenon called "mechanically induced entero-gastric inhibitory reflex" with both afferent and efferent pathways in the vagus has been reported (Miolan and Roman 1984, Youmans 1949). It seems likely that feedback from duodenal distension is mediated, in part, through the vagus nerve and to the proximal stomach. Duodenal distension has been shown to induce proximal gastric relaxation (Azpiroz and Malagelada 1984).

Could nerve regrowth across the transected duodenum have influenced the results of this study? If nerve regrowth had occurred it would have mitigated against the effects observed. The stimulation of IPPWs in duodenal transection animals by 25% dextrose may have been mediated through regrown nerves paths. However previous studies have demonstrated duodenal transection as an effective method of complete interruption of intramural nerves, both in the acute situation (Allescher et al 1988, Daniel and Wiebe 1966, Mir et al 1978) and for periods of up to three months, in the dog (Bedi and Code 1972, Bortolotti et al

1981, Bueno et al 1979) and the rat (Weser and Hernandez 1971).

The Control of Pyloric Motor Function by Extrinsic Vagal Innervation

Although studies of vagal mediation of pyloric motility were performed on three pigs only, the results are perhaps worthy of comment. In the event the studies did not reach a stage where vagal nerve cooling was undertaken. However at operation it was noted that the vagal fibres were under tension, once positioned within the cooling device. Presumably this tension exerted sufficient nerve damage to induce blockade of nerve transmission. Subsequent studies with the Kangaroo Island pig preparation, following formal trunkal vagotomy, have demonstrated similar results (Riddell et al 1990). Slavchenko et al (1984) also observed isolated pyloric contractions following vagal blockade in conscious dogs.

The demonstration of IPPWs following probable interruption of vagal pathways suggests that vagal activity, either afferent or efferent, exerts an inhibitory influence on the occurrence of IPPWs. Whilst no conclusions can be made, this study has raised several questions and provides an interesting avenue for further research.

SECTION 9

SUMMARY AND CONCLUSIONS

MEASUREMENT OF PYLORIC MOTOR FUNCTION IN THE UNSEDATED PIG

Work presented in this thesis has demonstrated that existing techniques of pyloric manometry, with the sleeve positioned across the pylorus by dual point trans-mucosal potential difference, can be applied to awake unsedated Kangaroo Island pigs. As in humans, the pyloric region of the pig has been demonstrated to undergo both isolated pyloric pressure waves (IPPW) and antro-pyloric pressure waves (APW). The similarities of pyloric motor function between humans and pigs suggest that the pig is a suitable preparation to study pyloric motility.

STIMULATION OF PYLORIC MOTILITY

The studies presented in this thesis give new information about the intestinal control of pyloric motility. The major findings are that isolated pyloric pressure waves were stimulated and antro-pyloric pressure waves were inhibited by a range of stimuli to the intestine. These stimuli include nutrient solutions of dextrose, fatty acids and amino acids, hyperosmolar saline or dextrose solutions and mechanical distension of the duodenum. In the cases of both intraduodenal dextrose infusion and duodenal distension, a dose-response relationship was investigated and demonstrated. The latencies, thresholds and magnitudes of response suggest a major control of pyloric motor function, through stimulation of upper small bowel receptors by foodstuffs that empty from the stomach.

A cephalic stimulation of pyloric motility was demonstrated in the studies. Regular unrelenting pressure waves commenced within seconds of presentation of the meal to the animal, often before drinking had begun and always before any significant volume of the drink had entered the stomach.

Distension of the stomach by the water barostat has been shown to influence pyloric motility. The data suggest that the mechanisms of gastric stimulation of IPPW and APW differ. The nutrient stimulation of isolated pyloric pressure waves was most marked when intragastric pressure exceeded a threshold. The results suggests that a synergism exists between the gastric stimulation of IPPW by distension and the intestinal stimulation of IPPW by duodenal nutrients. The results also support the novel concept of a threshold for stimulation by gastric distension, in the presence of intestinal nutrient stimulation.

In contrast to the stimulation of IPPW, the rate of APW increased in a near linear response to the pressure within the stomach. It may be concluded that antral motility is stimulated directly by distension of the stomach.

THE PYLORUS AND LIQUID GASTRIC EMPTYING

The liquid emptying studies presented in this thesis give new information about the mechanical factors that control gastric emptying of liquids. These insights have been possible because that techniques used have allowed recordings of detailed patterns of antro-pyloric motility in association with close correlation of timing of emptying of liquids into the duodenum.

The major findings are: (1) That isolated pyloric pressure waves are closely associated with cessation of transpyloric flow of liquids, even in the face of a range of relatively high gastroduodenal pressure gradients. (2) That more than half of liquid emptying occurred as episodes of pulsatile flow, which were intimately associated in time with antro-pyloric pressure waves. (3) That alteration of motility are closely associated in time with alterations of liquid gastric emptying. These findings support the concepts that the pylorus has a major role in the control of liquid gastric emptying, both as a component of an antro-pyloric peristaltic pump and as a resister to transpyloric flow.

THE EFFECT OF PYLORIC EXCISION ON LIQUID GASTRIC EMPTYING

This study provides new information about the consequences of loss or disablement of the pylorus. The major findings are that pylorus excision results in loss of the retardation of liquid emptying that is normally produced by entry of nutrient or hyperosmolar solutions into the duodenum, but does not result in any alteration of liquid emptying rates produced by duodenal distension.

It seems reasonable to conclude that the rapid emptying after surgical removal of the zone that produced IPPW resulted from removal of a significant barrier to gastric emptying. This finding supports the hypothesis that removal or neutralization of the pylorus is a major factor in the development of the rapid uncontrolled gastric emptying that may follow gastric surgery.

THE PYLORUS AND GASTRIC EMPTYING OF A DIGESTIBLE SOLID

Findings from the solid emptying studies presented in this thesis have demonstrated that gastric emptying of a digestible solid in the pig occurs at a near constant linear rate, following an initial lag phase. The ingested solid meal emptied as fine particles, 69% of which were less than 1 millimetre in size. This emptying was associated with a near constant rate of antro-pyloric pressure waves. Following excision of the pylorus the range of particle size in the gastric chyme emptied was comparable to that in animals with the pylorus intact, but the solid meal emptied more rapidly. These findings support the hypothesis that the antrum functions primarily for the sieving and grinding of solids whereas the pylorus functions primarily for the control of transpyloric flow of the solid meal, once ground.

MEDIATION OF CONTROL OF PYLORIC MOTILITY AND GASTRIC EMPTYING

Interruption of duodenal intramural nerves, by duodenal transection, lead to impairment of the stimulation of isolated pyloric pyloric pressure waves by both duodenal nutrient and hyperosmolar solutions and by duodenal distension. Associated with these changes, duodenal transection lead to impairment of the retardation of liquid gastric emptying induced by duodenal nutrient and hyperosmolar solutions, but had no influence on the alterations to gastric emptying induced by duodenal distension. These finding support the hypothesis that ascending duodenal intramural nerves play a significant physiological role in the transmission of feedback signals from nutrient, osmolar or stretch receptors in the upper small bowel to the pylorus.

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