UPPER OESOPHAGEAL SPHINCTER FUNCTION

IN INFANTS AND YOUNG CHILDREN

Thesis submitted for the degree of Master of Science

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SUMMARY

Although monitoring of the upper oesophageal sphincter (UOS) with sleeve sensors is a well established technique in adults, there are no paediatric studies using this technique. There are a range of problems affecting UOS function in children, including oesophago-pharyngeal reflux (OPR), a common clinical entity in infants, where UOS monitoring could provide valuable infomation.

This thesis has established a procedure for monitoring of UOS pressure in unsedated children using a sleeve sensor, and the technique was applied to UOS pressure during OPR in children.

UOS pressure was found to be highly labile, increasing markedly with increasing level of arousal of the child. This correlates well with findings in both adults and opossums and refutes the theory that OPR is caused by lowered UOS tone, as there is no one pressure for this sphincter.

The UOS was also found to be reactive to certain stimuli. Distention of the oesophagus by gastro-oesophageal reflux (GOR) increased basal UOS pressure by a small amount (9mmHg). Whilst this was felt to be negligible when the child was awake, it may be enough of an increase to prevent OPR during sleep. Transient relaxations of the UOS occurred with some episodes of distention of the oesophagus due to GOR. These seem the same as the relaxations found in adults. Straining also provoked an increase in UOS pressure, thus protecting against OPR during a period of stress on the sphincter. The response of the UOS to these stimuli was not found to be different in a group of children with symptoms of OPR, when compared to a group without OPR.

In brief, I have established a technique to monitor UOS pressure continuously in unsedated children and advanced knowlege about the responses of the UOS to various stimuli, thus furthering our understanding of the cause of OPR in children.

Declaration of authorship

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any University, and to the best of my knowledge and belief it does not contain any material previously published or writted by another person except where due reference is made in the text.

I consent to this thesis being made available for photocopying and loan.

Janet K. Willing

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List of abbreviations

A-P	antero-posterior
GOR	gastro-oesophageal reflux
LOS	lower oesophageal sphincter
OPR	oesophago-pharyngeal reflux
RPT	rapid pull-through
SPT	station pull-through
UOS	upper oesophageal sphincter

All values are mean $\pm$ standard deviation unless otherwise stated

CHAPTER 1

LITERATURE REVIEW

1. Upper Oesophageal Sphincter (UOS) Anatomy
2. Measurement of UOS Function
   - 2.1 Methods of Assessment
   - 2.2 Manometric Measurement
     - 2.2.1 Methods of Pressure Detection
     - 2.2.2 UOS Manometry
     - 2.2.3 Methods of Measurement
       - Sampling Techniques
         - Station pull-through
         - Rapid pull-through
       - Monitoring Techniques
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3. Physiology and Pathophysiology of the UOS
   - 3.1 Physiology
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     - 3.1.3 Other relaxations
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     - 3.2.1 Evidence for Disordered UOS Function in Oesophago-pharyngeal Reflux
       - Basa l UOS hypotonicity
       - Inadequate responses of the UOS to challenges
       - Transient relaxations of the UOS

The upper oesophageal sphincter (UOS) is involved in the well being of the organism, separating the storage and digestive sections of the alimentary tract from the external environment. Dysfunction of this sphincter is implicated, rightly or wrongly, in a range of medical conditions present in both children and adults. There is a growing body of research regarding normal and disordered UOS function in adults. There are, however, few paediatric studies, despite the fact that gastro-oesophageal reflux (GOR) and oesophago-pharyngeal reflux (OPR) are very common childhood problems. This paucity of studies is due to the special ethical and practical constraints of studying children.

1. UPPER OESOPHAGEAL SPHINCTER ANATOMY

The UOS is a complicated structure, with intrinsic and extrinsic muscles involved in its function (Cook 1991). Anatomically, the intrinsic musculature has been found to correspond to the cricopharyngeus and the caudal portion of the inferior pharyngeal constrictor. The inferior pharyngeal constrictor muscle fibres insert into the median raphe. The cricopharyngeus is attached to each lateral edge of the posterior portion of the cricoid cartilage, making a semicircle of muscle rather than the usual sphincteric circle of muscle. Because of this, the UOS is seen on endoscopy to have a slit-like aperture running laterally.

The high pressure zone has been found in adults to be 2-4cm long, with a 0.5-1cm zone of maximal pressure toward the proximal end of the sphincter (Goyal 1984). Its position has been confirmed radiologically by findings which showed that the UOS is positioned at the level of the disc space of the 5-6th cervical vertebrae, also

approximating the position of the cricopharyngeus (Goyal 1984, Sokol *et al.* 1966). Station pull-through (SPT) studies have shown the high pressure zone to have a sharply peaked profile (Figure 1.1) (Kahrilas *et al.* 1987a).

The nerve supply to the intrinsic musculature is from the vagus (Cook 1991). The brain stem nuclei and reticular formation control swallowing. The tonic contraction of the intrinsic upper oesophageal sphincter muscles has been shown in the opossum to depend on continuous neural input which ceases on initiation of a swallow to allow sphincter relaxation (Asoh *et al.*). These messages are influenced by afferent signals from the oropharyngeal area which govern the force and velocity of the contractions.

Cessation of the nerve input allows relaxation of the UOS but active opening of the UOS, which is important for bolus transport, relies on contraction of the extrinsic muscles (Cook 1991). These are the suprahyoid muscles, which are attached to the hyoid bone and thereby indirectly attached to the cricoid cartilage. On contraction the muscles elevate the cricoid cartilage forward and upward. This pulls the UOS open, allowing efficient bolus transport.

The UOS has been shown to be mobile especially during swallowing (Isberg *et al.* 1985), but it also moves with respiration and patient movement (personal communication J. Dent). As the UOS is external to the thoracic cavity there is no passive transmission to the UOS of intrathoracic pressure generated by events such as straining.

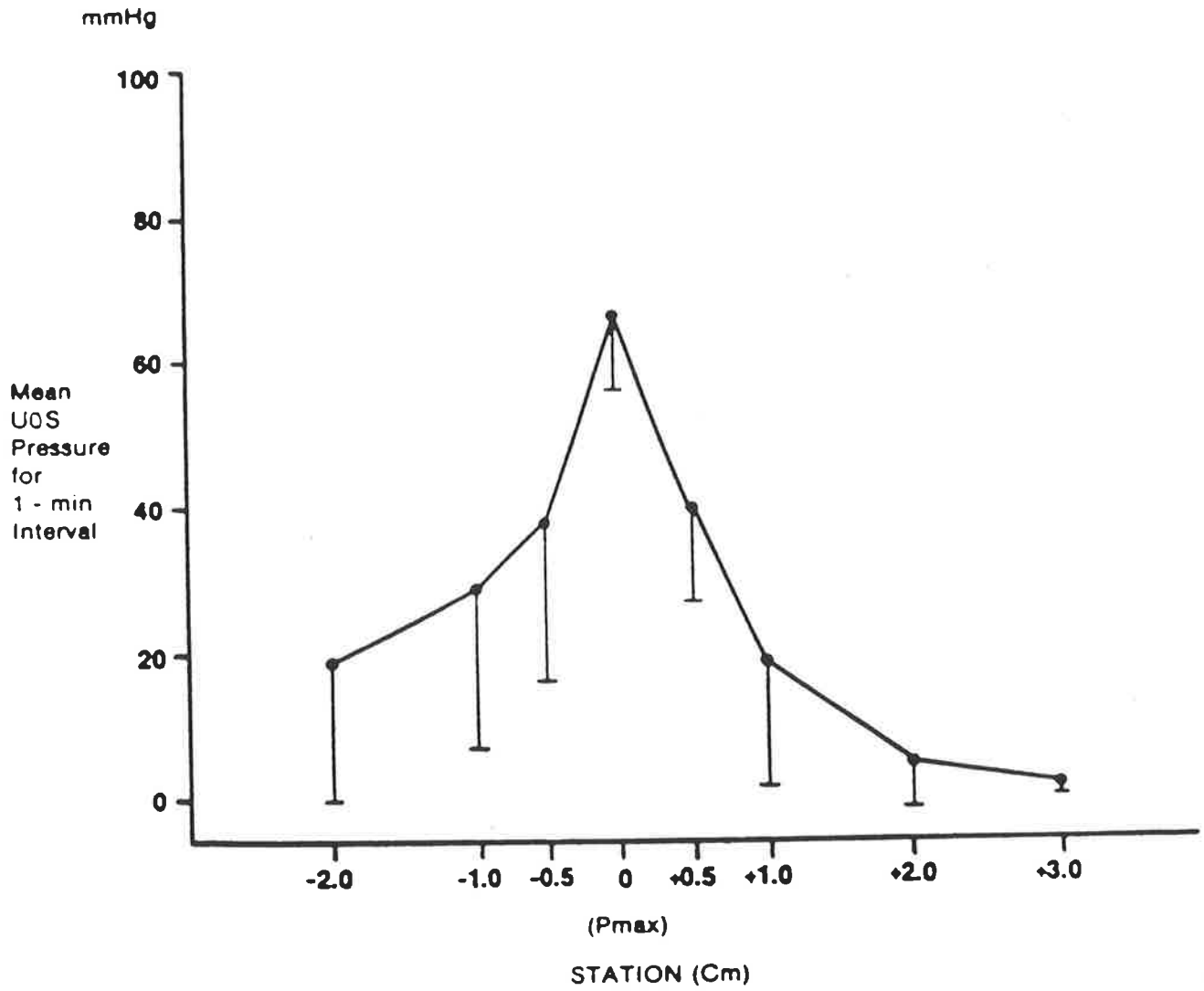

Figure 1.1 UOS pressure profile obtained by station pull-through technique. Each point represents the mean pressure during a 1 minute interval (±SD).
(Adapted from Kahrilas *et al.* 1987a)

2. MEASUREMENT OF UOS FUNCTION

2.1 METHODS OF ASSESSMENT

Electromyography has been used in animal models to determine the level of activity of muscles such as the cricopharyngeus (Asoh *et al.* 1978). The technique gives a precise indication of the timing and intensity of contraction of the muscles studied. It is not applicable to studies in humans at this time as cutaneous electrodes cannot differentiate between the many different muscles in this area, most of which are not involved in UOS function. Surgical implantation of recording electrodes is not appropriate to human studies.

Radiological procedures demonstrate the facility with which contents are transported from the pharynx into the oesophagus by visualisation of the flow of the barium, allowing assessment of the coordination of the pharynx, UOS and oesophagus. For instance, barium may be seen to pool in the pharynx or backflow into the mouth due to an inability to contract the pharynx or relax the cricopharyngeus. Recording of swallowing images on video allows for replaying and slowing of the images, providing more accurate assessment of coordination. A barium swallow also gives information on anatomy and so can allow recognition of structural problems.

Manometric measurement of the pharyngo-oesophageal area allows direct measurement of muscle activity, giving direct feedback to the investigator rather than relying on flow as an indicator of relaxation. It has been shown that relaxation and flow are different and distinct events (Kahrilas *et al.* 1988). Whilst manometry of non-sphincteric regions such as the oesophageal body are well

established, measurement of sphincters was problematical until the development of the sleeve sensor (section 2.2.3 Sleeve sensors). There is an increasing body of knowledge being generated with respect to adult function in this area, both with normal volunteers and those with pathology (Anvari *et al.* 1987, Cook *et al.* 1987, Kahrilas *et al.* 1986, 1987b, 1988). Measurement of UOS function in children however has only just begun to benefit from this methodology.

2.2 MANOMETRIC MEASUREMENT

The UOS is a short, mobile and complex structure. Measurement approaches need to be chosen carefully for the study of UOS physiology. This section deals with the approaches available for manometric measurement of the UOS.

2.2.1 Methods of Pressure Detection

Initial manometric measurements were performed with balloons transmitting pressures to external transducers, but balloons have many disadvantages (Dodds *et al.* 1976b). The techniques which use external transducers have been refined to the low compliance water perfusion systems of the present. The perfused systems as described by Arndorfer *et al.* (1977) have response rates well above that required for sphincter and oesophageal body pressure measurement and can reliably indicate the occurrence of pharyngeal contraction, but not its maximum pressure (Dodds 1976a). This is because fluid filled catheters have inherent compliance and hydraulic dampening which affect the recording of the very fast pressure changes found in the pharynx. Intraluminal transducers are able to measure these rapid changes with accuracy when the perfused systems cannot, and various

different types have been developed (Dodds *et al.* 1975a, Hay *et al.* 1979, Rex *et al.* 1988, Welch *et al.* 1979). In theory they are an improvement over perfused systems as they eliminate the need for any perfusion equipment, and the attendant variation in baseline with positional changes of the subject due to hydrostatic effects, thus allowing the subject to be studied while mobile. Hay *et al.* (1979) found the intraluminal system they were using to be very sensitive to temperature change, and technically unsatisfactory in other ways. Investigations using other intraluminal systems have been technically adequate. Dodds *et al.* (1975a), comparing the Honeywell probe to a perfusion system during pull-through studies, found no difference in results in the UOS. The majority of manometric measurements performed at present use low compliance perfusion systems. The quality of pharyngeal pressure recording achieved with these perfusion systems is high enough to allow accurate correlation of events in the UOS with swallowing.

2.2.2 UOS Manometry

There are problems specifically associated with manometry of the UOS. Due to the anatomical structure of the UOS (described in section 1) there is marked radial asymmetry in its pressure profile. This was first measured by Winans (1972), who found the antero-posterior (A-P) aspect to have pressures more than twice those of the lateral aspect. The UOS pressure profile is also asymmetrical in the axial plane (Figure 1.2) (Goyal 1984). Asoh *et al.* (1978) first found evidence of axial asymmetry in opossums, where the peak pressure of the posterior aspect was proximal to the peak pressure of the anterior aspect. Welch *et al.* (1979) reported axial differences in human UOS pressure profiles soon afterwards, but noted that the

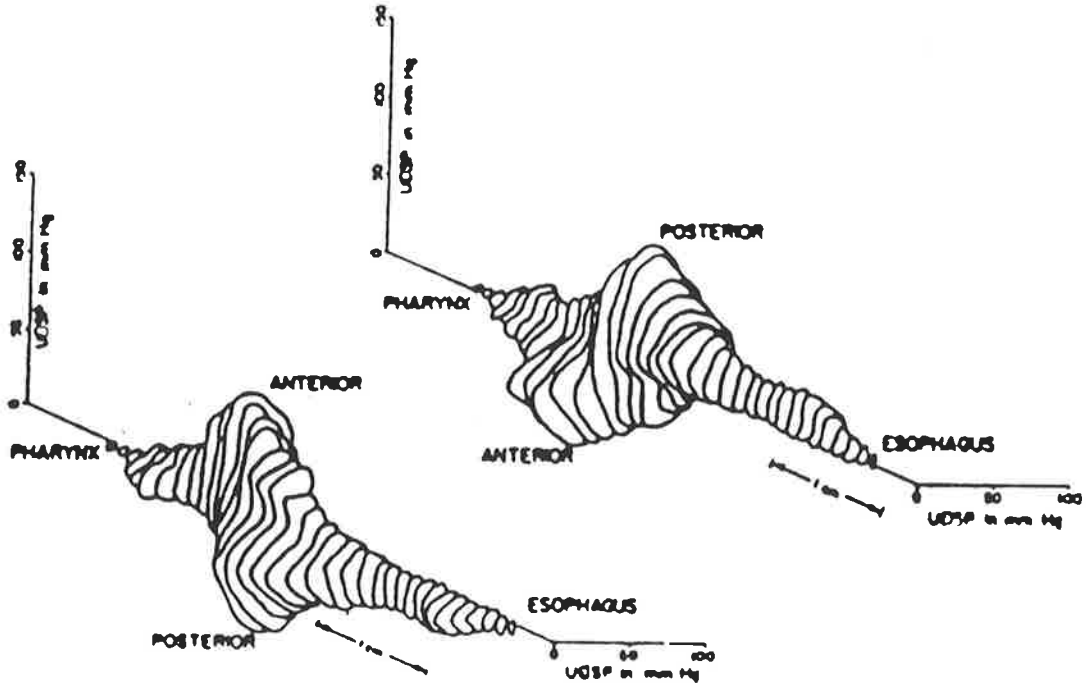

Figure 1.2 Three dimensional pressure profile of the normal UOS. The graphic representation was rotated 180^{0} in the lower panel. (Adapted from Welch *et al.* 1979)

posterior peak pressure was more distal, presumably due to anatomical differences between the species. The direction of the asymmetry in humans was confirmed by Gerhardt *et al.* (1980b), who also found differences in peak pressure values, with the posterior pressure being higher. Kahrilas *et al.* (1987a), while not commenting on axial asymmetry, did note that there was no difference between posterior and anterior pressures. The variation in findings between the studies may be due to the different manometric techniques, as Kahrilas measured much lower absolute pressures (see below).

With such a range in UOS pressures it is necessary to determine which pressure is most indicative of sphincter function. Winans (1972), Welch *et al.* (1979) and Asoh *et al.* (1978) have all commented that the A-P pressure is the most representative. Welch *et al.* (1979) have confirmed that the anatomical arrangement is the source of asymmetry in studies on patients who have undergone laryngectomy. This surgery, which included excision of the cricoid cartilage and rejoining the attached muscle group, abolished the radial asymmetry.

There are three strategies which can be used to ensure that the A-P pressures are measured. Sensors can be positioned so that pressure is recorded from every quadrant, thus measurement is guaranteed from the A-P axis. Because each level of recording will then have four point pressures recorded, the number of levels of pressure recording able to be used is limited by both the size of the catheter and the number of channels on the recorder. Catheters can be oriented carefully so as to measure either the anterior or posterior pressure, involving checking the orientation by looking down the mouth or by fluoroscopy. The easiest option is to design the catheter so that it self-orients to measure pressure in the A-P axis. This can be done by designing the section of the catheter

which will measure UOS pressure so as to have an oval cross-section and placing the sensors on the long axis. Welch *et al.* (1979) first recognised that oval catheters would self-orientate and the observation has been confirmed by Kahrilas *et al.* (1987a).

The UOS has been found to be mobile, its position relative to manometric catheters moving substantially. This causes significant artefact when measuring UOS pressure with point sensors (described in 2.2.3) due to the inability of the sensor to remain in the narrow zone of maximal pressure. Displacement of 0.5cm has been shown to yield UOS pressures significantly lower than maximal (Kahrilas *et al.* 1987a). The UOS has been shown to move asynchronously with the catheter during swallowing, and the sphincter does not always return to the same position on the manometric catheter after a swallow (Kahrilas *et al.* 1988). Movement is also caused by normal respiration and relatively minor movements of the head (Kahrilas *et al.* 1987a, personal communication J. Dent). This problem will always be accentuated with paediatric subjects due to their inability to remain still on request. Asoh *et al.* (1978) and Goyal *et al.* (1976), studying the UOS in animal models, have achieved successful sphincter measurement by surgically pinning the sensor at the level required. This is obviously not appropriate in routine human studies. Pull-through studies (described below) are an attempt to minimise the artefacts caused by UOS movement.

2.2.3 Methods of Measurement

Sphincter pressures can be measured either by sampling, using pull-through techniques, or monitoring, by long term positioning of recording points in the sphincter.

a) Sampling Techniques

Sampling techniques use point sensors such as perfused side-hole manometry, and intraluminal pressure transducers. These measure a small area of pressure from the part of the lumen opposing the sensor. Sphincter pressure is sampled by withdrawing a point sensor across the sphincter. The peak pressure obtained gives a measure of basal tone at that point in time, but cannot give any reliable information about rapid reflex responses as the relative inputs of sphincter action and the effects of movement of the sensor across the sphincter cannot be separated. A pull-through technique is the only way to obtain a pressure profile of the sphincter (Figures 1.1, 1.2).

Station Pull-Through (SPT)

This method involves inserting a catheter past the UOS into the oesophageal body, then withdrawing the catheter in a stepwise manner, 0.5-1cm at a time, pausing at each point for up to 60 sec, while recording pressure. The procedure takes from two to 15 minutes and requires the subject to be breathing quietly. A variety of catheter systems has been used. They range from one to eight pressure sensors, spanning up to 10cm, with the sensors having either radial or longitudinal differences in positioning, or both. Gerhardt *et al.* (1978, 1980b) measured both radial and axial differences using a six lumen catheter with 4 radially oriented side-holes and 2 side-holes distally placed. Winans (1972) used a system with all 8 side-holes radially placed at the same level. For their paediatric study Staiano *et al.* (1987) did not control for radial asymmetry at all, using a round catheter with 3 side-holes placed at different levels and orientations. One attempt to overcome the problem of radial asymmetry led to a design employing multiple holes at one level in

one lumen (Waldeck *et al.* 1973). This measured the lowest pressure at that level, which made it impractical for UOS pressure measurement as the higher pressures of the A-P orientation are considered the most important physiologically. With such variations in methodology, comparison of absolute values of UOS pressure becomes meaningless.

There are many different ways to analyse SPT data (Figure 1.3). Using lower oesophageal sphincter (LOS) data Dodds *et al.* (1975b, 1976a, 1980) and Welch *et al.* (1980) compared four methods of SPT analysis and found conflicting results. Dodds *et al.* found every method gave a different pressure, and questioned which one truly reflected sphincter pressure. Welch *et al.* found different coefficients of variation with the different methods, but found good correlation between them and stated that if absolute values were used, all methods were equivalent. This is difficult to reconcile with Dodds' finding of different absolute values. The range of pressures found by Rex *et al.* (1988) using different analyses of the same tracings further highlights the problem. It seems that the same method of analysis must be used to enable comparison of results.

Catheter movement is associated with augmentation of UOS pressure (Asoh *et al.* 1978, Kahrilas *et al.* 1987a). This means that the pressure may change within the one minute of recording as it falls back to normal levels. If the results are averaged from the beginning of the recording minute to the finish, there is likely to be an upward bias in the recordings. Application of a waiting period between measurement points allows the sphincter to recover, and should result in a truer record of UOS pressure. Investigators who measure pressure for less than one minute may find abnormally high results. The use of one minute averages will also tend to obscure any rapid changes such as transient relaxations, which are

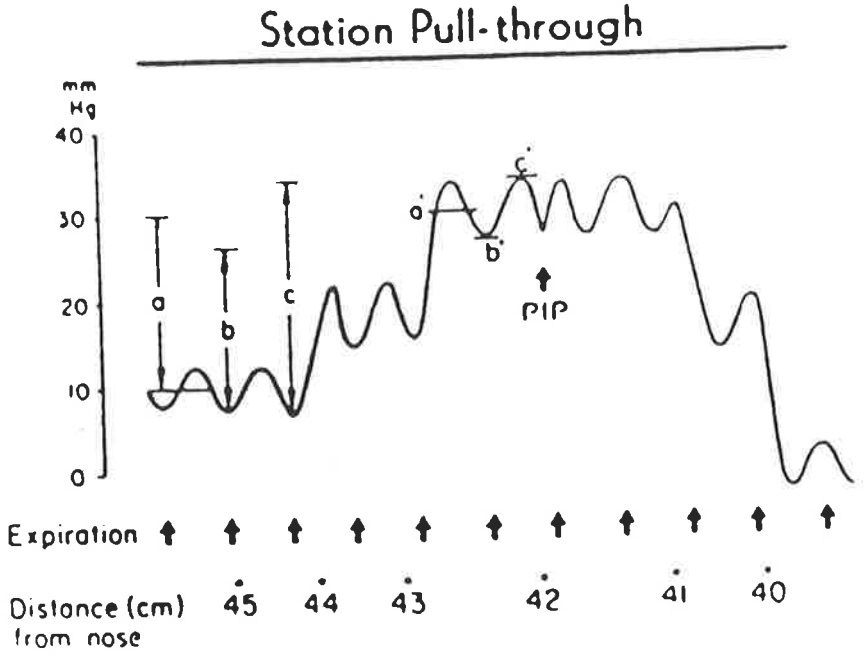

Figure 1.3 Methods of analysis for station pull-through technique in the LOS. a) mean respiration; b) end expiration; c) end inspiration. All values are an average of up to 1 minute of tracing. The other method takes the pressure at the PIP (pressure inversion point).

(Adapted from Dodds *et al.* 1976)

increasingly thought to be important (Kahrilas *et al.* 1986).

Rapid Pull-Through (RPT)

This technique is based on the same principles as the SPT method, with point sensors being withdrawn through the high pressure zone, but is quicker as the catheter is withdrawn continuously. Speeds of withdrawal range from 3-10mm/sec; the most common being 5mm/sec. Most investigators require the subject to hold their breath as the catheter is withdrawn.

Welch *et al.* (1980) reported that less fluid accumulates in the pharynx when using RPT techniques due to the short recording time required. This results in less choking and swallowing during the procedure and hence less disruption of basal UOS pressure measurement. The pressures measured using the RPT may not be meaningful due to physiological disruption by catheter movement and strain artefacts from breath-holding (Anvari *et al.* 1987).

There is only one practical way to analyse tracings from RPT manoeuvres, as there are no respiratory pressure changes (Figure 1.4).

Both pull-through techniques have been evaluated by Waldeck (1972) and others in relation to the LOS. Various investigators have shown more between-sample variability for RPT vs. SPT techniques, and suggest that this may be because there is less irritation to the sphincter with the SPT technique due to pauses in the catheter movement. Dodds *et al.* (1975b) found less variation with analysis of RPT than SPT, however Welch *et al.* (1980) found more variation with RPT and recommended routine use of SPT. Dodds noted that the averaging effect of the SPT analysis may be partly responsible for lowered values using this technique.

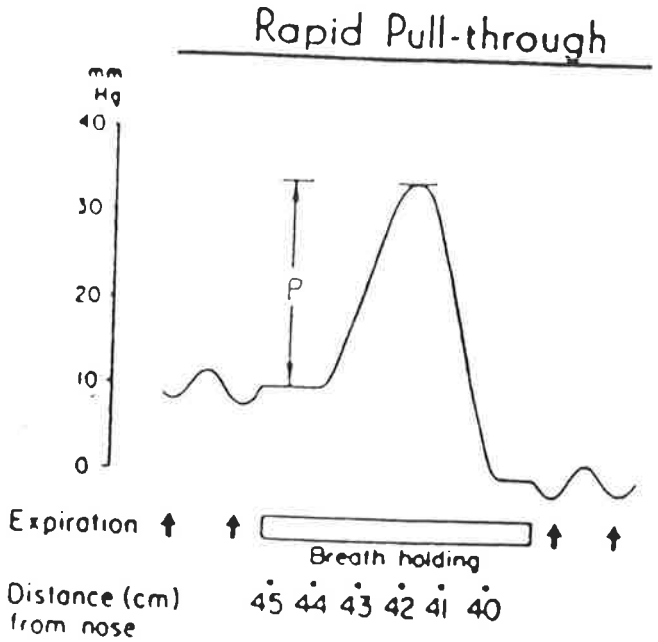

Figure 1.4 Method of analysis for rapid pull-through technique in the LOS.

(Adapted from Dodds *et al.* 1976)

Due to technical problems such as inadequate perfusion equipment, there were no reliable values for UOS pressures prior to the report of Dodds (1976a). Values of 32±10 mm Hg were obtained by this group using SPT, but no indication was given as to whether or not radial orientation was taken into account, despite the problem being mentioned. Gerhardt *et al.* (1978) found pressures in the range of 88±4 to 109±4 mm Hg (M±SEM) depending on orientation in the A-P axis. Rex *et al.* (1988) found a broader range of pressures, from 92.1±42.1 to 162.7±79.3 mm Hg, with different methods of analysis of the same tracings. Sondheimer (1983) recorded very low pressures of 25-27mm Hg in sedated children.

Kahrilas *et al.* (1987a) found higher UOS pressures with a RPT technique compared to a sleeve sensor method (section 2.2.3 Sleeve sensors), and also more variability. They found pressures of 147±14 to 190±19 mm Hg (M±SEM) using an oval catheter. Rex *et al.* (1988) found UOS pressure to be 116.2±57.2 mm Hg. Green *et al.* (1988) also found higher sphincter pressures with RPT techniques compared to SPT methods.

The methodologies of all the sampling techniques mentioned differ to a greater or lesser degree, which may be one cause of the range of UOS pressures found. To enable comparisons between the studies, standardisation of the methods is recommended.

b) Monitoring techniques

Sphincter pressure monitoring requires the sensor to be in continuous contact with the high pressure zone for extended periods of time. The method must be able to overcome the problem of normal mobility of the UOS which has plagued researchers since investigation into this region began. A benefit of monitoring is that it allows

the subject to adapt to the intubation without the catheter being disturbed, thereby reducing artefacts caused by irritation of the sphincter. With the catheter left *in situ*, basal tone can be monitored and reflex responses recorded. Recent evidence suggests that rapid reflex changes will give more information about the function of the sphincter than basal sphincter tone (Kahrilas *et al.* 1986). Reflex changes can only be seen with monitoring.

Point sensors

Early studies monitoring UOS pressure used a single point sensor positioned at the point of highest pressure (Sokol *et al.* 1966). As the measurement techniques improved and more was learnt about sphincter function, the problem of sphincter movement relative to the catheter was recognised. Kahrilas *et al.* (1987a), when comparing the sleeve technique with a side-hole method, found the latter to record a lower pressure, and concluded that the side-hole was displaced from the point of highest pressure. Isberg *et al.* (1987), using point manometry and cineradiography, showed that a side-hole that is recording peak basal sphincter pressure measures very little of the relaxation generated by a swallow, due to asynchrony of movement between the catheter and the sphincter. Thus, single point sensors cannot accurately monitor UOS pressures.

To try to overcome these problems, catheters were built with arrays of side-holes. A 5cm spacing between side-holes has been commonly used (Dodds *et al.* 1975a, 1975b, Gerhardt *et al.* 1978, 1980, Hay *et al.* 1979, Rex *et al.* 1988, Welch *et al.* 1979). Isberg *et al.* (1985) showed that this spacing is too wide to cope with UOS movement and be able to measure pressure continuously from the high pressure zone. They recommended a spacing of 1cm between sideholes to allow

measurement of UOS pressure from one of the 3 side-holes during a swallow. Kahrilas *et al.* (1987a) showed a sharp peak of pressure less than 1cm wide in adults, so side-holes spaced at that width may still not allow measurement of the highest UOS pressure in adults. The pressure band in infants and children may be expected to be even narrower, with accurate measurement requiring closer spacing. The investigators who have published recent data on UOS pressures in children (Sondheimer 1983, Staiano *et al.* 1987) have not mentioned sphincter pressure profiles, despite the fact that they both performed pull-through studies, so the width of the high pressure zone in children is not known.

A disadvantage of both single point sensors and arrays of sideholes is that they perfuse water into the high pressure zone and pharynx which may cause an increased rate of swallowing and irritation of the UOS, with consequent difficulty with recording of basal pressures.

Sleeve Sensors

The sleeve sensor is a hydraulic resistor which functions as a long pressure sensor (Dent 1976), measuring the highest pressure along its length (Figure 1.5). It was developed to be able to remain in contact with mobile sphincters and prevent the under-recording of sphincter pressure that results from displacement of point sensors. It has been used successfully in adults for 16 years (Cook *et al.* 1987, Dent *et al.* 1976, Kahrilas *et al.* 1988). Because it measures the highest pressure, it will always measure sphincter pressure unless swamped briefly by peristalsis. It has a slow response rate to rising pressure after a peristaltic wave has stripped the perfused fluid from the sleeve, due to the time taken to re-establish the

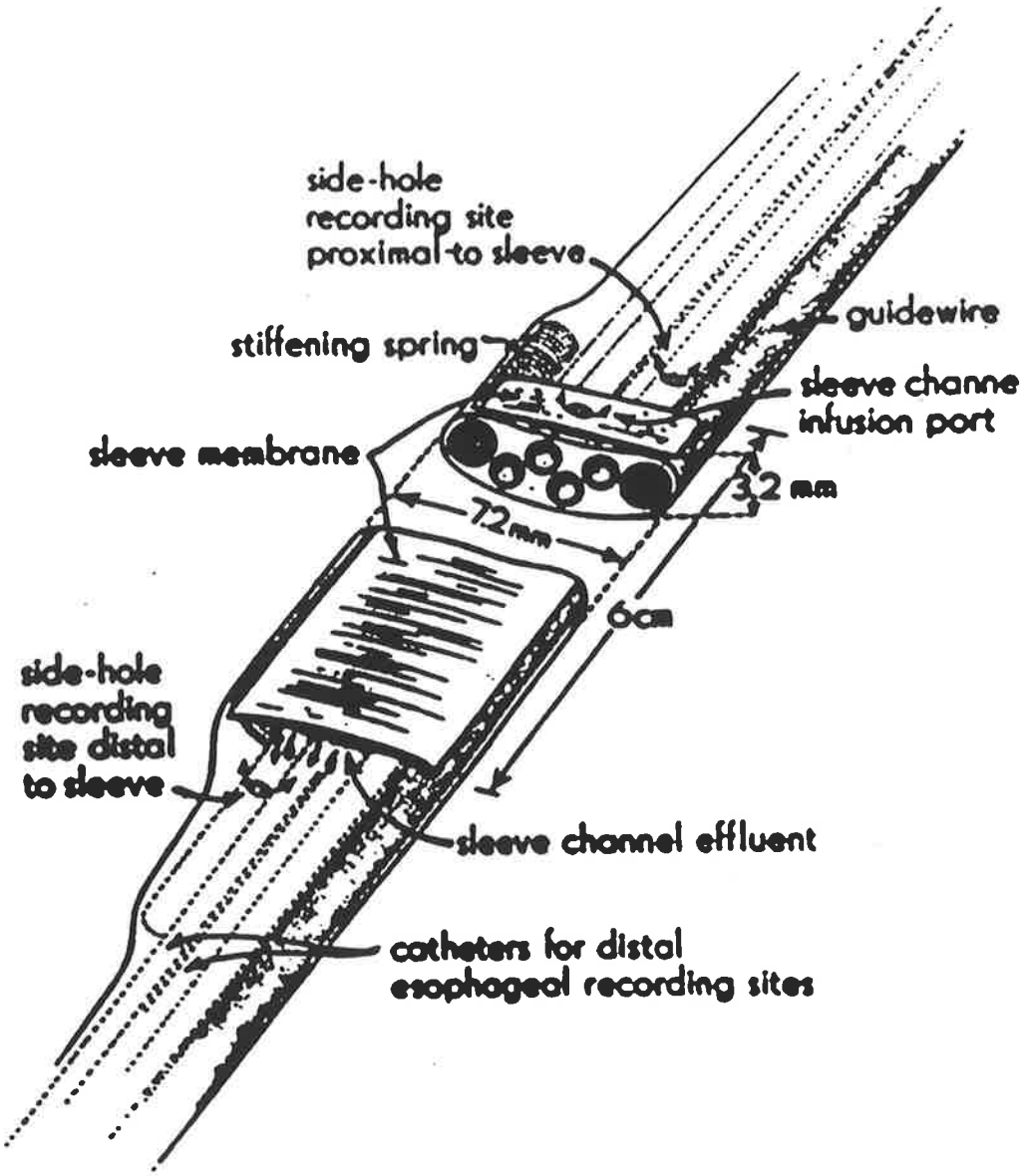

Figure 1.5 Diagram of the sleeve sensor. The pressure-sensitive silicone membrane is sealed to a bed constructed of moulded silicone. Perfusate enters the sleeve channel at its proximal end and exits at the distal end, below the UOS.

(Adapted from Kahrilas *et al.* 1987a)

fluid column and tension the silicone membrane. This can be minimised by positioning the sleeve such that the sphincter is as high on the sleeve as possible. It also underestimates the relaxation time of the UOS consistently by a very small amount (0.1 sec) (Kahrilas *et al.* 1986). Sleeve measurements of UOS pressure by Kahrilas *et al.* (1987a) gave values of 57±8 mm Hg (M±SEM) in adult volunteers and they found no significant difference in pressure with the sleeve facing anteriorly or posteriorly. Self-orientation of the oval sleeve sensor section of the catheter in the A-P axis is adequate control for radial asymmetry (Kahrilas *et al.* 1987).

2.3 ASSESSMENT OF UOS PRESSURE IN CHILDREN

The study of infants and children is associated with additional technical demands when compared to studies in adults. It is logical to assume that radial asymmetry is present in children as in adults and control of the direction of measurement is also as important. Given the three options mentioned (section 2.2.2), the use of an oval catheter is best as it requires no cooperation and minimises the number of recording points needed.

Infants and children are incapable of cooperating with requests such as breath-holding, which are required for some recording techniques. As techniques such as RPT require cooperation, they are impractical for paediatric use. Recent evidence (Cook *et al.* 1987) indicates that stress causes marked augmentation of UOS pressure. As any manipulation of the catheter causes obvious distress in children, the results of pull-through studies of any type will give abnormally high values in unsedated children. Added to this are the artefacts due to straining and patient movement, rendering any measurement in

unsedated children unreadable. Sedation of the subject will reduce the level of stress, and the amount of artefact due to straining and movement. However, data from Kahrilas *et al.* (1987b) showing the effect of sleep on UOS pressure in humans, and Asoh *et al.* (1978) relating various levels of anaesthesia to UOS pressure in opossums, indicate that sedation markedly lowers UOS pressure. Thus sedation adds another confounding factor.

Catheter size must be considered when studying children as it has been shown that larger diameters cause augmentation of pressure (Wallin *et al.* 1980). Side-hole spacing must also be considered, as mentioned (section 2.2.3 Point sensors).

There is a need for a technique for measuring UOS pressure in children which requires no sedation or cooperation, which can cope with the movements which children invariably will make, and can monitor UOS pressure for extended periods of time. The sleeve sensor should be able to deal with all these problems because it is tolerant of sphincter movement relative to the recording assembly, caused by swallowing and patient movement. A major advantage of the sleeve technique is that no movement of the catheter is needed once it is correctly positioned, allowing the child to become accustomed to the procedure without becoming distressed or needing sedation. Thus, long-term monitoring could be achieved without the artefacts inherent in the other techniques, making it possible to compare UOS pressures to other aspects of physiological function.

3. PHYSIOLOGY AND PATHOPHYSIOLOGY OF THE UOS

3.1 PHYSIOLOGY

3.1.1 Tonic Closure

It has been established that the UOS is tonically closed unless relaxed for a brief while. The basal tone of the UOS in opossums (Asoh *et al.* 1978) is generated by continuous firing of the nerves supplying this region. Cessation of firing relaxes the intrinsic musculature and allows opening of the sphincter by the extrinsic muscles (Asoh *et al.* 1978, Kahrilas *et al.* 1987b). It has been confirmed indirectly that the adult human UOS acts in the same way (Kahrilas *et al.* 1987b, 1988), and it is reasonable to assume the same mechanism exists for the UOS in children.

As noted, the UOS has a markedly asymmetric pressure profile and appearance (section 2.2.2). The functional significance of this asymmetry is probably slight. It may allow for easier rapid opening of the UOS, thereby facilitating rapid flow from the pharynx to the oesophagus.

It is proposed that the tonic closure of the UOS provides a barrier to GOR flowing into the pharynx, thus preventing OPR. The normal range of basal pressure of the UOS has been disputed since the area was first identified (Gerhardt *et al.* 1980b, Sondheimer 1983, Staiano *et al.* 1987, Stanciu 1974, Welch *et al.* 1979, Winans 1972). With the advent of the sleeve sensor accurate values of basal pressure have been obtained in adults (Cook *et al.* 1987, Kahrilas *et al.* 1987a, 1987b). It is extremely variable, being very low during sleep (Kahrilas *et al.* 1987b) or while under anaesthesia (Asoh *et al.* 1978) and markedly elevated during periods of mental stress (Cook *et*

al. 1987). There may also be adaptive responses of the UOS to distention or an increase in acidity, but the information is conflicting (Enzmann *et al.* 1977, Gerhardt *et al.* 1978, 1980a, 1980b, Kahrilas *et al.* 1986, Sondheimer 1983, Stanciu *et al.* 1974).

At the start of the work for this thesis there were no reports of technically adequate paediatric UOS pressure measurements. However, a high pressure zone has been found in neonates (Gryboski 1969, Nurko 1991) and older children (Sondheimer 1983, Staiano *et al.* 1987) with pull-through techniques. Due to the technical limitations of these studies (see section 2.2.3), the pressures of the UOS are not accurate, but they indicate that the UOS is present from birth.

3.1.2 Swallow-Induced UOS Relaxation

The action of swallowing has been divided into the oral phase, the pharyngeal phase and the oesophageal phase (Milla 1991, Shearman *et al.* 1989). The oral phase is voluntary, and triggers the involuntary pharyngeal and oesophageal phases. Aspects of swallowing have been quantified in adults (Kahrilas *et al.* 1988, Cook 1991). Relaxation of the UOS occurs with the onset of the pharyngeal phase of swallowing. The opening of the UOS follows 0.06 s later, during laryngeal elevation. The duration of the relaxation of the UOS is about 0.4 seconds with dry (saliva only) swallows, increasing to 0.65 seconds with 20 ml swallows. The duration of opening of the UOS, measured fluoroscopically, increases at the same rate as the relaxation time with increasing volume swallowed. Fluoroscopic closure of the UOS and manometric ending of the relaxation occur in very tight association once the bolus has passed the UOS and entered the oesophagus.

There are no accurate manometric paediatric data on swallow coordination. Staiano *et al.* (1987) found evidence of incomplete relaxation of the UOS in three of their patients which appears not to be artefactual, however the incoordination they documented may be due to problems with their technique.

3.1.3 Other Relaxations

Vomiting is a highly coordinated, mainly somatic activity. It requires a powerful sustained contraction of the abdominal muscles, increased descent of the diaphragm and relaxation of the LOS and oesophagus (Dodge 1991). Presumably there is coordinated relaxation and opening of the UOS and pharynx as well, but there are no manometric data available on UOS relaxation with vomiting.

Belching also requires relaxation of the UOS. It has been measured manometrically as a longer duration relaxation than swallow related relaxations (Kahrilas *et al.* 1986), lasting about 1.2 seconds. In the adult studies no observable ventrocephalic movement of the cricoid cartilage was seen (Kahrilas 1986). This implies that the UOS relaxes but does not open. The possible mechanism is that relaxation of the UOS allows escape of some oesophageal contents by pushing past the residual barrier which remains when active opening does not occur. These transient relaxations of the UOS are more likely to occur with rapid distention, whereas slow or focal distention favours contraction of the UOS (Kahrilas 1986). There are no manometric data available on UOS relaxations of this type in children.

3.2 PATHOPHYSIOLOGY

Dysfunction of the UOS can be outlined on a mechanical basis, with problems with aborad flow and problems with orad flow. Problems with swallow related relaxations may involve the relaxation occurring too soon, too late or being incomplete, thus impeding aborad flow. Oesophago-pharyngeal reflux, one type of orad flow, is a common problem in children, and can cause major clinical problems such as failure to thrive due to calorie loss secondary to repeated vomiting, and respiratory problems due to aspiration of refluxate.

As the research of this thesis centres around the UOS, its response to GOR and mechanisms of OPR, the discussion on pathophysiology will be confined to orad bolus flow, and bolus flow from mouth to stomach will not be discussed.

3.2.1 Evidence for Disordered UOS Function in OPR

There are three concepts of UOS dysfunction which would allow OPR to occur. The sphincter tone may be chronically too low, allowing retrograde flow at any time; the sphincter may not respond appropriately to stimuli such as distention or straining, allowing retrograde flow when stressed; the sphincter may relax inappropriately, allowing retrograde flow if there is material in the oesophagus. It is not known which of these potential mechanisms is operating, but it is possible that any two or even all three may occur.

Basal UOS Hypotonicity

The prevailing concept is that pathologically lowered tonic closure of the UOS allows excessive OPR because of an insufficient

barrier between the oesophagus and the pharynx. There is only one study (Sondheimer 1983) using an adequate perfusion system which has addressed this question in children. Sondheimer (1983) aimed to establish normal basal UOS pressures for infants and compared these values with UOS pressures of infants with GOR, both with and without respiratory symptoms. She found no difference in basal UOS pressure amongst any of the groups of infants.

There are several technical limitations in Sondheimer's work which need to be taken into account. She employed a pull-through technique, with its attendant measurement problems. Briefly, these are: the fact that UOS pressure is sampled for very short periods rather than being monitored (section 2.2.3); patient discomfort created by the use of a pull-through technique, leading to increased UOS pressure with catheter movement (section 2.2.3); the use of sedation to overcome the distress of the subject while performing the pull-through manoeuvre (section 2.3). However, radial asymmetry was recognised and adequately controlled.

Methodological problems also limit the conclusions which can be drawn. To establish UOS pressures for normal children she used infants referred to the hospital with symptoms subsequently diagnosed as caused by something other than GOR. This group was compared to two groups of age-matched infants diagnosed with GOR, one group with respiratory problems and one group without. The group she called normals are not strictly normal as they required investigation of gastrointestinal symptoms, however there are ethical problems involved with attempting to intubate completely normal children. The group with GOR and respiratory problems are assumed to have more OPR than those without respiratory problems. This assumption may not be well justified as there are no other data on the presenting symptoms,

specifically vomiting or spilling, which are indicators of OPR. Although the mean UOS pressure was not different between the patient groups, the range for each group was wide. This could be attributed to the lability of the UOS, and the technical problems with the method used to measure the pressures, and would have served to mask any significant differences which may have been present.

There are more data in adults on basal UOS pressures and the correlation with regurgitation or GOR, however they all used pull-through techniques. Gerhardt *et al.* (1980) found adult patients with symptoms of OPR to have lower UOS pressure than either patients with symptoms of heartburn or normal volunteers. This agrees with the findings of Berte and Winans (1977) and Stanciu *et al.* (1974) who found no relationship between GOR and UOS pressure. It seems the presence of OPR is more closely linked with UOS pressure than the presence of GOR.

There is a need for technically improved studies on basal UOS pressure in adults and children to address the question of basal UOS hypotonicity. These studies need to take into account the radial asymmetry of the UOS (section 2.2.2), the mobility of the sphincter (section 2.2.2), the variability in basal pressure which has been documented (section 2.3) and relate UOS pressure directly to occurrence of OPR. One aim of the research presented in this thesis is to address this question in a paediatric population.

Inadequate Responses of the UOS to Challenges

The UOS is not passive between swallows, but must react to events which challenge its function, including its antireflux function. In a physiological setting this challenge is GOR.

Several studies have looked at how the UOS adapts to changes in

oesophageal pH and oesophageal distention by infusions and intrusions (Enzmann *et al.* 1977, Gerhardt *et al.* 1978, Kahrilas *et al.* 1986, 1987b, Sondheimer 1983). By monitoring UOS pressure with sleeve sensors one can also see how the UOS reacts during spontaneous GOR (Kahrilas *et al.* 1987b).

There are no paediatric studies using sleeve sensors, however Sondheimer (1983), monitoring UOS pressure with a single sidehole, found a larger increase with distention of the oesophagus with acid infusion compared to water infusion. Because of the method used, the results cannot be regarded as accurate due to variable displacement from the high pressure zone which has been shown to occur with sidehole sensors (section 2.2.3 Monitoring techniques).

Kahrilas *et al.* (1987b), using a sleeve sensor in adult volunteers, found no change in UOS pressure with acidification of the oesophagus caused by GOR, but they did not mention whether distention occurred with any or all episodes. In another study (Kahrilas *et al.* 1986) they found an increase in UOS pressure with slow distention of the oesophagus which persisted until a peristaltic wave cleared the distention. Other adult studies, using various pull-through techniques, have generally found an increase in UOS pressure with distention (Enzmann *et al.* 1977, Gerhardt *et al.* 1978, Kahrilas *et al.* 1986), but conflicting results with acidification of the oesophagus (Stanciu *et al.* 1974, Gerhardt *et al.* 1978). These reports cannot be regarded as accurate due to the methodological problems with pull-through techniques which have been outlined in a previous section (2.2.3).

The relevance of some of the procedures, such as infusion of gas or liquids into the oesophagus, to a real physiological response is questionable. The work of Kahrilas *et al.* (1987) monitoring UOS

pressure during GOR is the only truly physiological study performed so far. The other studies may be criticised for the fact that they may have used non-physiological volumes, extent of distention or levels of acidity.

Straining is another stimulus which has been found to lead to augmentation of UOS pressure in adults (Anvari *et al.* 1987). Whereas GOR causes a relatively small oesophageal body pressure change (Kahrilas *et al.* 1986), straining causes large changes in oesophageal body pressure, and has been shown to cause substantial increases in UOS pressure. This has been proposed to be a protective mechanism against OPR. The UOS is removed from the intrathoracic pressure environment in which the spikes of intra-oesophageal pressure which challenge the antireflux function of the UOS are generated. Because of this, the associated elevations of intrapleural pressure are not transmitted to the UOS in the way that increases of intra-abdominal pressure are transmitted to the LOS. Rather, the UOS must tighten through timely augmentation of UOS pressure. This mechanism has a parallel in the external anal sphincter, which contracts when its competence is threatened by abdominal straining, even though the sphincter is external to the abdominal pressure environment (Ihre 1974).

If this response is not present there may, in theory, be an opportunity for refluxate to overwhelm the UOS, thus allowing OPR to occur. There have been no studies which have directly addressed the mechanism of the UOS pressure rise with straining, however it appears that it is a patterned response of the intrinsic nerve supply.

Establishment of inadequate responses of the UOS to stimuli awaits the definition of normal responses of the UOS to stimuli. It may be that children with pathological OPR do not respond

appropriately to the stimuli of straining or distention of the oesophagus by gastric contents. The research presented in this thesis addresses both of these scenarios.

Transient Relaxations of the UOS

There are no paediatric studies which look at the possibility of inappropriate relaxations of the UOS as a cause of OPR. There is evidence in adults of relaxations which are not swallow related, and which occur in response to rapid distention of the oesophagus (Kahrilas *et al.* 1986) with insufflated gas or gas GOR. These relaxations are the basis for the audible component of belching through oesophago-pharyngeal passage of gas (Welch *et al.* 1979) and occur independently of swallowing, having a somewhat longer time course than swallow-induced UOS relaxations. It is thought that the relaxations are a safety valve to prevent injury of the oesophagus due to excessive force by distention. This is a useful reflex as long as it is appropriate. It is possible that, in subjects with OPR, the relaxation is more easily triggered or inappropriately triggered, allowing OPR to occur more frequently. This may be caused by a fault in the control mechanism.

The research presented in this thesis is also investigating the presence and distribution of these relaxations in a group of paediatric patients.

CHAPTER 2

PATIENTS AND METHODS

1. Introduction
2. Patients
   - 2.1 Control children
   - 2.2 Study children
3. Materials
   - 3.1 Adaptation Of Sleeve Sensor For Paediatric Use.
   - 3.2 Manometric Recording Equipment
   - 3.3 Equipment for Control Group.
   - 3.4 Equipment For Study Group
4. Method
   - 4.1 Protocol
   - 4.2 Protocol For Control Group.
   - 4.3 Protocol For Study Group.

1. INTRODUCTION

Manometry requires nasogastric intubation, a relatively invasive procedure which is not ethically acceptable to perform on completely well children. The data collected for this study were gathered from two groups of children, both of whom required nasogastric intubation for other reasons. The study group required manometric assessment of LOS and oesophageal body function for clinical indications and the measurements of UOS function were incorporated into the test procedure. The control group required nasogastric feeding for problems due to other than gastrointestinal disease. Parental reluctance to volunteer their children was one reason for the small number of children in this group.

2. PATIENTS

2.1 CONTROL CHILDREN

Two patients were enrolled from the hospital inpatient population. They had normal pharyngo-oesophageal function, but required nasogastric feeding for other medical problems. Table 2.1 outlines their medical histories. Informed parental consent was obtained before the procedure.

Table 2.1

Characteristics of the control group

	CW	RB
Age	7 months	3 months
Sex	F	M
Medical condition	Bacterial endocarditis	Complex cardiac problems
Manner of feeding	Fed by tube for 1st 2 hours	Bolus

2.2 STUDY CHILDREN

Fifty five consecutively referred children aged 2-81 months (median 13 months) were enrolled in the study, following referral to the Gastroenterology Unit of the Adelaide Children's Hospital for evaluation of symptoms thought to be caused by GOR or a swallowing disorder. The major priority in these children was evaluation of LOS and oesophageal body function as an aid to clinical management. All children were fully assessed clinically by a consultant paediatric gastroenterologist. The study protocol was approved by the Research Ethics Committee of the Adelaide Children's Hospital. Informed parental consent was obtained prior to the study. Table 2.2 gives the classification of major presenting symptoms and incidence of neurological dysfunction in the fifty three children in whom technically satisfactory UOS recordings were obtained. Neurological dysfunction was defined by the presence of symptoms and signs of cerebral palsy or developmental delay confirmed by the Denver Developmental Screening Test (Frankenburg *et al.* 1967).

Table 2.2

Major presenting symptom(s) in study patients

Symptom	Without Neurological Deficit n=42	With Neurological Deficit n=11
Vomiting	27	7
Irritability	23	4
Recurrent Respiratory Disease	3	3
Failure To Thrive	2	2
Abdominal Pain	4	1
Apnoea	5	0
Food refusal	7	1
Swallowing Difficulties	1	1

Note: Some patients presented with more than one major symptom.

3. MATERIALS

3.1 ADAPTATION OF SLEEVE SENSOR FOR PAEDIATRIC USE.

The sleeve sensors used in the paediatric catheters were significantly narrower than those used in adult studies. The silicone membrane was 0.03mm thick compared to the 0.06mm thick membrane used for the adult sleeves. The thinner membrane ensured that the narrower sleeve width did not result in impairment of the fidelity of the paediatric size sleeve compared to one of adult dimensions. The rise rate of the sleeve recording UOS pressure in the control group ranged from 16 mmHg/second at the distal end of the sleeve to 45 mmHg/second at the proximal end of the sleeve. The rise rate of the UOS sleeves used for the study group ranged from 6 mmHg/second to 65 mmHg/second. The wider range for the study catheters is due to the increased length of the sleeve sensors.

3.2 MANOMETRIC RECORDING EQUIPMENT

A low compliance pneumo-hydraulic pump (Arndorfer *et al.* 1977) was used to perfuse the recording channels at rates of 0.15 - 0.6 ml/min, depending on the characteristics of the catheter being used. The total fluid load delivered to the children was within acceptable limits.

Pressures and distal oesophageal pH were recorded on a 12 channel polygraph (Grass Instrument Co., Quincy, Mass, USA, Model 7D). A chart paper speed of 150mm/minute was used to permit subsequent analysis of time relationships among pressure events at different recording points. Prior to each study, signals from the pressure transducers (Deseret Medical Inc., Sandy, Utah, USA, Model 38-848-1) were set to identical baselines and gains. These settings

were checked at the conclusion of each study and were always stable.

The sleeves recording UOS pressure had an oval cross-section to allow positioning in either the anterior or posterior orientation (Kahrilas *et al.* 1987a). As mentioned (Chapter 1 section 2.2.2) radial asymmetry of the UOS is an important variable which has been shown to be adequately controlled with catheters having an oval cross-section.

3.3 EQUIPMENT FOR CONTROL GROUP

The catheter used for the control group is illustrated in Figure 2.1. The four-lumen assembly had an outer diameter of 3mm. The oval cross section of the UOS sleeve segment of the assembly was 2.5mm by 3.5mm. The sleeve sensor monitored UOS pressure. Side holes monitored pharyngeal pressure, proximal oesophageal body pressure and gastric pressure. Oesophageal pH was not recorded. The recording channels were perfused at 0.15 ml/min. A syringe pump (Sage Instruments, Orion Research Inc., Cambridge Mass., Model 351) was used for introducing the feeds through the gastric channel as required, with gastric manometric recordings being carried out at the same time.

3.4 EQUIPMENT FOR STUDY GROUP

Two manometric assemblies were built with different inter-sleeve distances, to cope with the range of inter-sphincteric distances found in this age group. The nine-lumen assemblies had an outer diameter of 3mm. The arrangement of the two sleeves and seven side holes in each assembly is illustrated in Figure 2.1. The oval cross section of the UOS sleeve segment was 2.5mm by 3.5mm. The sleeves were perfused at 0.6ml/minute and the side holes at

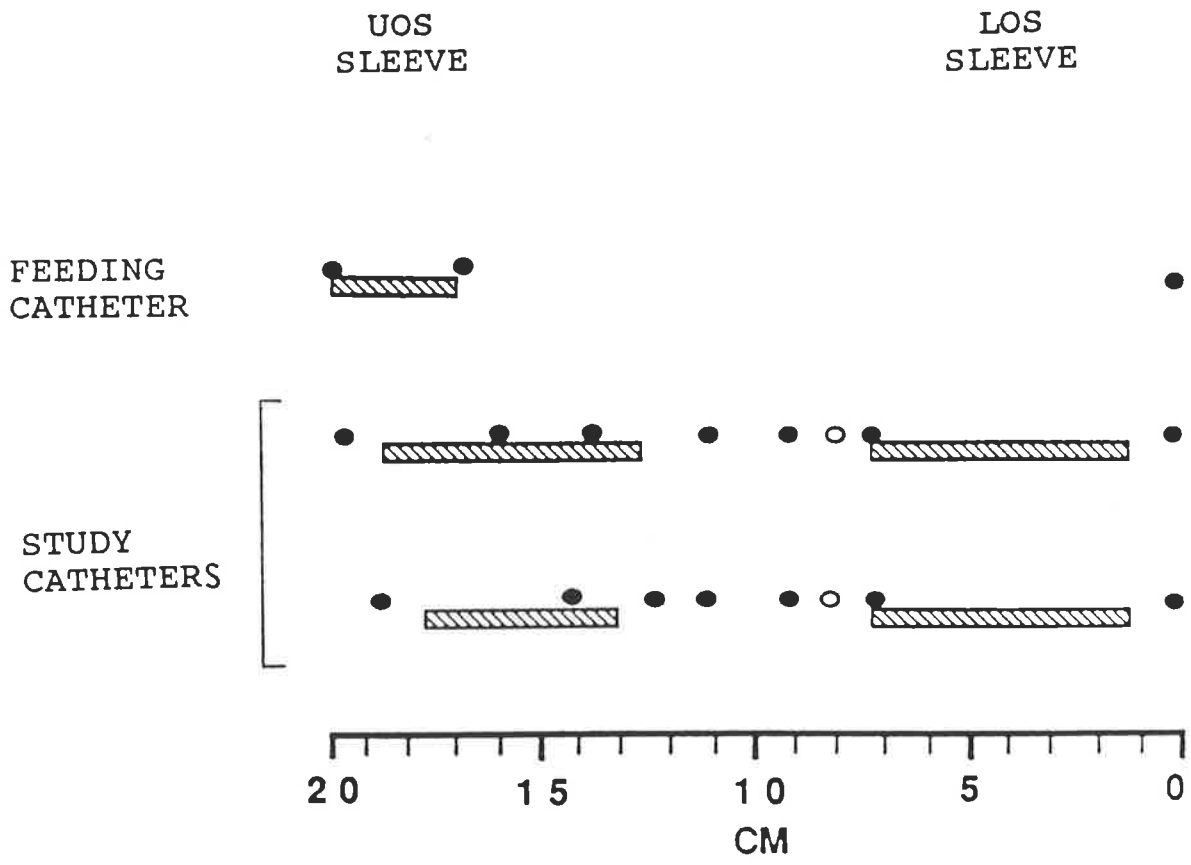

Figure 2.1 Diagramatic representation of the manometric assemblies, showing the position of sleeve sensors, pH electrode, and side holes. Bars = sleeve sensors. Closed circles = side hole sensors. Open circle = pH electrode.

0.3ml/minute, except the pharyngeal side hole channel which was perfused at 0.15ml/minute.

Distal oesophageal pH was monitored concurrently with manometry. The miniature intraluminal glass pH probe (Micro-electrodes Inc., New Hampshire, USA, model MI-506) was passed with the manometric assembly, being taped to it 1cm above the distal sleeve with a 2mm wide band of adhesive tape. An external skin reference electrode (Micro-electrodes Inc., New Hampshire, USA, model MI-402) was fixed firmly to a limb, and made electrical contact with the skin through a conductive gel which was kept in place with an occlusive dressing. The pH electrode was calibrated before and after each test with pH 4 and 7 buffers.

4. METHOD

4.1 PROTOCOL

All children were fasted for three hours to avoid aspiration of gastric contents if vomiting occurred during intubation. The catheter was passed transnasally without sedation or local anaesthesia. Once the catheter was positioned correctly (Chapter 3 section 2.2) it was not moved unless absolutely necessary. Monitoring was carried out for four hours with the children recumbent and unsedated.

4.2 PROTOCOL FOR CONTROL GROUP.

After positioning of the manometric assembly the children were allowed to settle and then fed with formula according to their established tube feeding regime. One was fed continuously throughout the monitoring period and one by bolus at the start of the monitoring

period. Previous experience with dual sleeve catheters was used for initial positioning of the catheter. Feedback from the manometric tracing allowed correction if the position of the UOS on the sleeve sensor was not optimal.

4.3 PROTOCOL FOR STUDY GROUP.

After positioning of the pH electrode and manometric assembly the children were allowed to settle and then fed appropriately for age with formula or non-acid food such as sandwiches and milk. Formula was introduced into the stomach via the manometric assembly if they did not take their usual volume of feed orally. Monitoring of spontaneous patterns of motility and oesophageal pH was started at the end of the meal.

The data of Strobel *et al.* (1979) were used to predict the teeth to LOS distance as an aid to correct positioning of the manometric assembly and to choose the catheter with the most appropriate inter-sleeve distance. The assembly was initially positioned so that the distal sleeve was astride the LOS. The assembly position was then adjusted to give effective monitoring of UOS pressure with the proximal sleeve, provided that this did not result in loss of correct positioning of the LOS sleeve. Figure 2.2 shows a sample of tracing recorded from a study child.

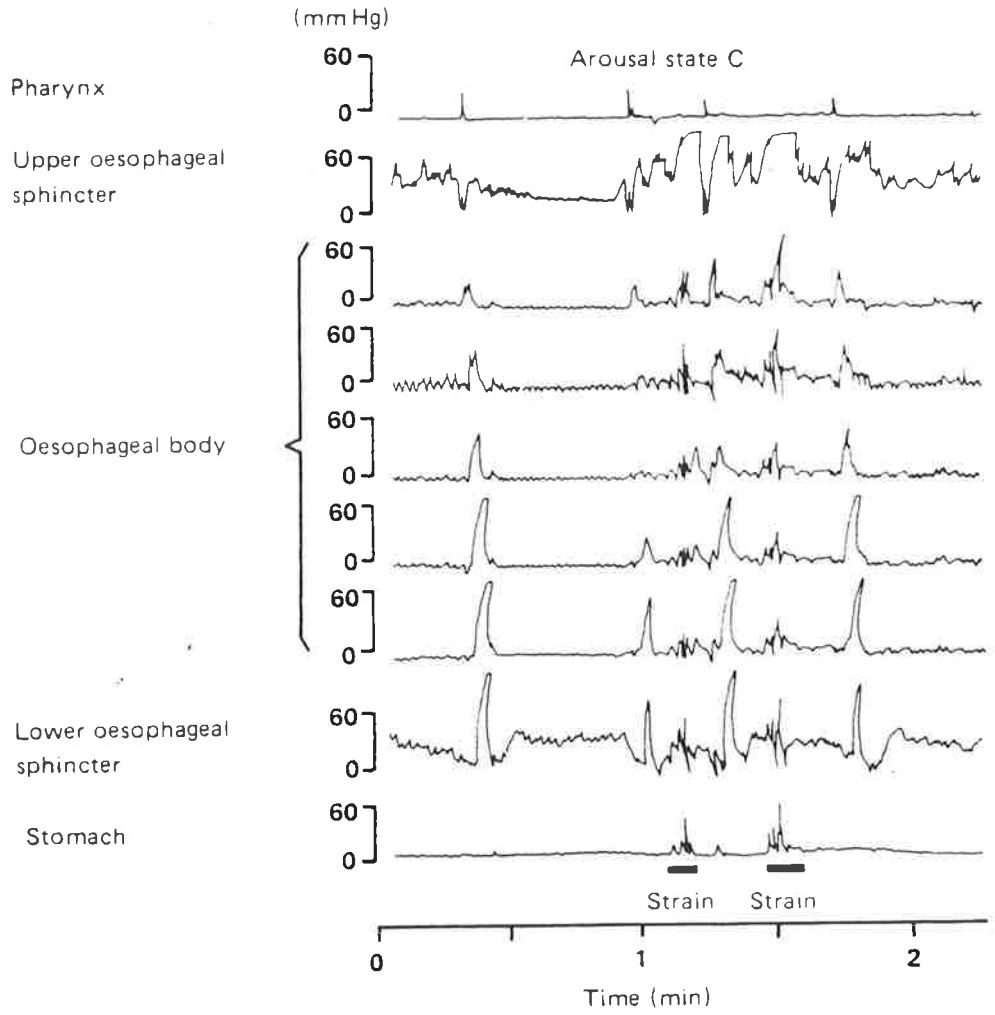

Figure 2.2 A representative tracing from a 9 month old study infant showing the correlation of pharyngeal, oesophageal and gastric events. Swallowing is indicated by the pressure spikes in the pharyngeal channel. Upper oesophageal sphincter pressure was recorded successfully despite swallowing, straining and body movement (arousal level C). The UOS tracing shows considerable variability of pressure with marked augmentation during straining. The catheter used for the control children measured only the top three channels shown here, and the gastric channel.

CHAPTER 3

EVALUATION OF THE SLEEVE METHOD

1. Introduction
2. Method
   - 2.1 Patients
     - 2.1.1 Control Group
     - 2.1.2 Study Group
   - 2.2 Positioning of the Catheter in the UOS
   - 2.3 Assessment of Level of Arousal
3. Results
   - 3.1 Positioning of the Catheter in the UOS
     - 3.1.1 Control Group
     - 3.1.2 Study Group
   - 3.2 Tolerance and Technical Success of the Procedure
     - 3.2.1 Control Group
     - 3.2.2 Study Group
4. Discussion

1. INTRODUCTION

The sleeve method has been shown to monitor UOS pressure successfully in adults (Kahrilas 1987a). The initial aim of this study was to see whether the method was tolerated by children and whether it would yield results which could be interpreted.

2. METHOD

2.1 PATIENTS

2.1.1 Control Group

The tracings from the two control patients were used.

2.1.2 Study Group

This evaluation was done on the first twenty-six consecutively referred children, aged from three to 42 months (median 17.5 months).

2.2 POSITIONING OF THE CATHETER IN THE UOS

The position of the UOS on the sleeve could be confirmed by observing the patterns recorded by the sideholes placed at each end of the sleeve sensor. The position of the manometric assembly used for concurrent nasogastric feeding was defined as satisfactory when the side holes at either end of the UOS sleeve indicated pharyngeal and oesophageal body pressures. Positioning of the dual sleeve manometric assembly was defined as satisfactory when the side holes at each end of the LOS sleeve showed gastric and oesophageal body pressure patterns whilst the UOS sleeve was positioned as described (Figure 2.2).

2.3 ASSESSMENT OF LEVEL OF AROUSAL

Every 12th minute during the monitoring period, the child's level of arousal was assessed by the same trained observer (JW) who sat with the children throughout each study. The arousal levels were marked on the trace as the study proceeded. The classification of arousal level was relatively coarse and designed to allow reliable recognition by simple direct observation of behaviour as follows;

A- resting with eyes shut;

B- resting with eyes open;

C- moving briefly more than twice a minute but comfortable;

D- restless and uncomfortable;

E- crying.

3. RESULTS

3.1 POSITIONING OF THE CATHETER IN THE UOS

3.1.1 Control Group

The sleeve sensor was correctly positioned for the whole of the four hour monitoring period for both children.

3.1.2 Study Group

The results presented below are for the 24 children in whom concurrent LOS and UOS monitoring proved possible. In only 2% of the 12th minute samples was UOS pressure uninterpretable because of malposition of the UOS sleeve.

3.2 TOLERANCE AND TECHNICAL SUCCESS OF THE PROCEDURE

The regular evaluation of the child's level of arousal and the interpretability of the tracings of UOS pressure allowed objective assessment of the child's tolerance to the recording procedure.

3.2.1 Control Group

Eighty six percent of the 12th minutely intervals were in categories A to C. In 72% the children were in category A, indicating acceptance of the procedure. Two of the total of 36 intervals were not analysable due to excessive swallowing, and UOS pressure for one interval was off scale.

3.2.2 Study Group

Sixty-seven percent of the 12th minutely samples were in categories A to C indicating good tolerance of the procedure (Figure 3.1). In 351 of the total of 480 12th minutely samples (73%), a value could be derived for UOS pressure according to the analysis approach described in Methods above. Of the 12th minutely samples that could not be analysed, crying was the cause in 9% and excessively frequent swallowing in 13%. UOS pressure was uninterpretable in 2% of the 12th minutely samples because of malposition of the UOS sleeve. Other forms of technical failure accounted for 3% of uninterpretable values. Missing values of UOS pressure for the 12th minute (129/480) could be obtained from the subsequent 13th or 14th minutes in 49 instances. This gave a total of 400/480 (83%) of samples for which there was a value for UOS pressure.

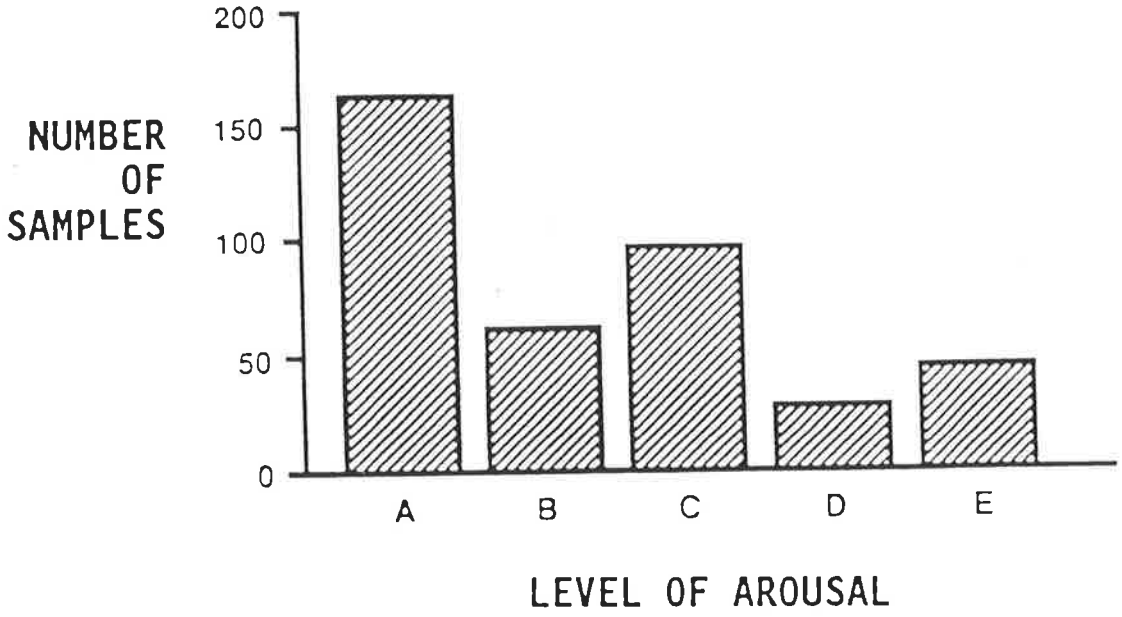

Figure 3.1 Tolerance of the procedure shown by distribution of categories of level of arousal assessed on every 12th minute of recording.

4. DISCUSSION

These findings indicate that it is possible to monitor UOS pressure with manometric assemblies which have overall dimensions that are well tolerated by unsedated children.

There are no data on the radial profile of UOS pressure in children. It is reasonable to assume however, that the sphincter is markedly asymmetric, since it has been a universal finding in animals (Asoh *et al.* 1978), and adults (Welch *et al.* 1979, Winans 1972). This asymmetry is considered to be due to the muscular anatomy of the UOS which is similar in children and adults. If measures of absolute basal UOS pressure are considered to be of physiological relevance, it is important to control for the influence of radial asymmetry on the pressures recorded. The oval cross-sectional shape of the UOS sleeve used in the present studies resembles that of sleeves used in adults which have been shown to orient themselves consistently in the anterior or posterior position (Kahrilas *et al.* 1987a). It is reasonable to assume that the sleeve was orientated in this manner in the children studied and that there was consequently adequate control for radial asymmetry of the UOS pressure profile.

The concurrent monitoring of pharyngeal and upper oesophageal body pressures provided continuous feedback on the adequacy of the sleeve position within the UOS. Correct positioning of the sleeve (Chapter 2 section 2.2) was maintained in 95% of the sample times for the study children, indicating a high success rate for this method. In two of the study children the inter-sleeve distance was not compatible with simultaneous, technically satisfactory recording from both the UOS and LOS. In these children the assembly was positioned to meet the clinical requirement for adequate LOS manometry and they

are not included in any of the results.

Results from the two control children showed that the catheter was correctly positioned for the whole of each test, and the tracings were able to be analysed in 92% (33/36) of the 12th minutely intervals, indicating that this is a technically feasible way to collect data from children with no gastro-oesophageal problems.

The length of time UOS pressure was able to be monitored in both the control and the study groups is a good indication of the adequacy of this technique. The percent of sample times in which the study children (78%) and the control children (86%) were asleep or happy (arousal levels A, B or C) indicates that the children adapted well to the intubation without sedation and that stress should not have had a major influence on results. The sleeve length used proved more than adequate to cope with the range of UOS movement on the recording assembly in response to subject movement, even when the child was restless (Figure 2.2).

Recording of UOS pressure with the sleeve was made more demanding by the need to combine this with another reason for requiring intubation of the children. In the case of the control children, it was necessary to feed them via nasogastric tube, and the study children required simultaneous monitoring of oesophageal body, LOS and gastric pressures for clinical reasons. It was felt that these were the only ethically acceptable approaches to the gathering of manometric data from the UOS in children. The dual sleeve catheter also allowed the study of integration of motor function of the oesophagus, both lower and upper oesophageal sphincters and the pharynx. Episodes of spontaneous GOR and OPR could be captured and analysed, and their effect on UOS pressure determined.

CHAPTER 4

EFFECT OF LEVEL OF AROUSAL ON UOS PRESSURE

1. Introduction

2. Method Changes

   2.1 Designation of Level of Arousal

   2.2 Analysis of Basal UOS Pressure

      2.2.1 All Levels of Arousal

      2.2.2 Symptom Groups, Arousal Levels A and B

   2.3 Statistical Analysis

      2.3.1 All Levels of Arousal

      2.3.2 Symptom Groups, Arousal Levels A and B

3. Results

   3.1 Effect of Level of Arousal on UOS Pressure

   3.2 Symptom Groups, Arousal Levels A and B

4. Discussion

1. INTRODUCTION

In view of the lability of the UOS in adults and its association with sleep (Kahrilas *et al.* 1987b) and stress levels (Cook *et al.* 1987) I sought to ascertain whether there was a similar relationship between UOS pressure and level of arousal in children. None of the previous paediatric studies have taken this into account. Basal UOS pressure was also related to symptomatology to clarify the relationship between basal UOS pressure and the presence of GOR or OPR.

2. METHOD CHANGES

2.1 DESIGNATION OF LEVEL OF AROUSAL.

Described in Chapter 3 section 2.3.

2.2 ANALYSIS OF BASAL UOS PRESSURE

2.2.1 All Levels of Arousal

Tracings from the first 24 technically satisfactory studies were evaluated, as described in Chapter 3. For the purposes of this study basal UOS pressure was defined as UOS pressure in the absence of swallow induced disturbances of UOS pressure. Swallowing was indicated by characteristic pharyngeal pressure waves in the most proximal sidehole and timing for the swallows was taken from the onset of the pressure wave. Basal UOS pressure was referenced to basal end expiratory oesophageal pressure.

Mean basal UOS pressure was determined for the one minute periods in which the level of arousal was noted. If the designated minute of tracing was not interpretable, then the 13th, or the 14th

minute was used to derive a value. The UOS pressure disturbances caused by swallowing were excluded from the UOS pressure tracing by drawing a line from four seconds before to six seconds after the occurrence of pharyngeal peristalsis associated with swallowing. Basal UOS pressure was determined from the minute of tracing as a visual mean of the swallow edited trace. A minute of tracing was deemed valid as a measure of basal UOS pressure if there was at least 15 seconds of unedited tracing in the minute sample. Values of UOS pressure were referenced to basal end expiratory oesophageal body pressure.

Tracings from the two control children were analysed as above with respect to editing of the swallows and relation to level of arousal.

2.2.2 Relationship Between Symptom Categories and UOS Pressure

The aim of this analysis was to examine whether basal UOS pressure differed according to symptom category. To minimise the effects of level of arousal and straining, only arousal levels A and B were analysed, using the rules outlined above (section 2.2.1), for all 53 subjects referred to the Gastroenterology Unit for evaluation of gastro-oesophageal problems.

The patients were divided into four groups based on their most prominent presenting symptom, and also divided based on the presence or absence of neurological deficit. The group of children with symptoms of vomiting (27/29) or failure to thrive (2/29) were the group whose problems were considered to be primarily due to regurgitation.

2.3 STATISTICAL ANALYSIS

2.3.1 All Levels of Arousal

A mean value of the data points for each level of arousal was calculated for each of the 24 patients, and the group as a whole. An analysis of variance for repeated measures was performed. The overall mean for a particular arousal category was substituted for any missing values. There was no difference in significance using this method as compared to an analysis of variance run on the eight patients with values in all categories.

A mean value of the data points for each level of arousal was calculated for each of the controls.

2.3.2 Relationship Between Symptom Categories and UOS Pressure

A pxq factorial experiment with adjustment for unequal cell frequencies was used for comparison of basal UOS pressure among symptom groups, the presence or absence of neurological deficit and the influence of level of arousal. An average of six values was available for estimation of a representative cell observation (Weiner 1962).

3. RESULTS

3.1 EFFECT OF LEVEL OF AROUSAL ON UOS PRESSURE.

Marked changes of UOS pressure were seen in association with changes in the level of arousal of the children. Even when the arousal level was stable, basal UOS pressure showed some variation (Figures 2.2, 4.1). Upper oesophageal sphincter pressure was lowest when the child was resting with eyes closed (level A). When there was an abrupt change in the level of arousal there was an associated

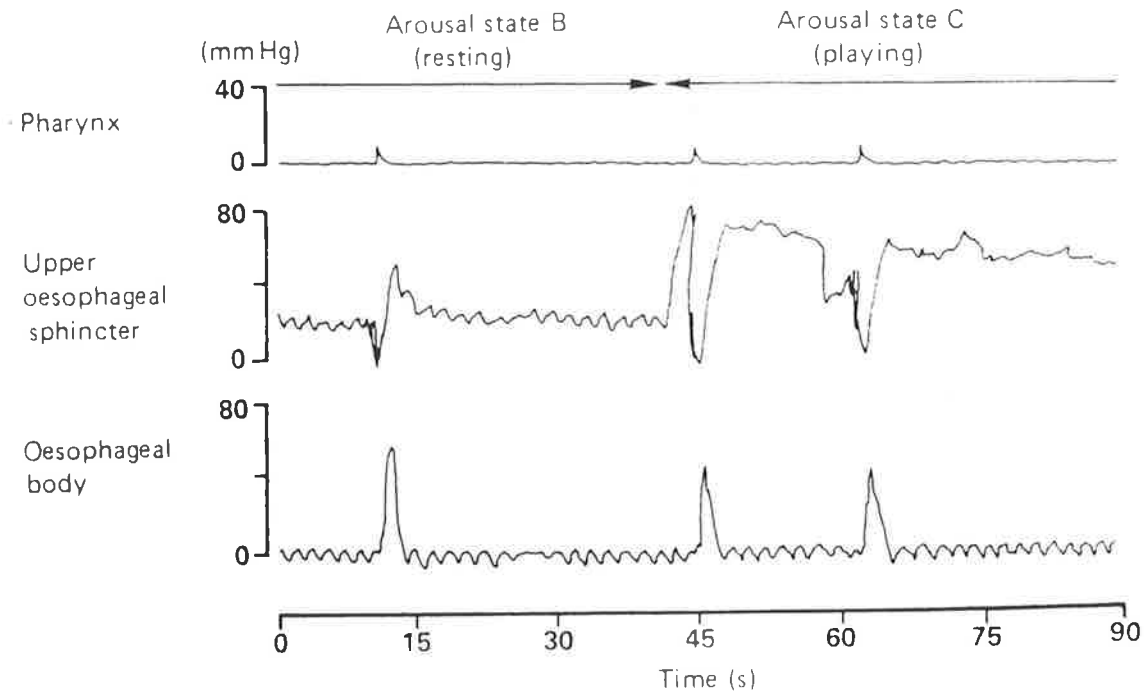

Figure 4.1 Representative tracing showing an abrupt increase in UOS pressure with change from arousal level B to arousal level C.

immediate change of UOS pressure which was often severalfold. Mean values for UOS pressure shown in Figure 4.2 ranged from 18.0±10.3mm Hg for arousal level A to 55.7±13.2mm Hg for level D. Meaningful values could not be derived for level E because of very large pressure swings in pharyngeal, oesophageal and gastric pressures related to repeated straining and crying. During crying however, there was a differential and marked augmentation of UOS pressure which often resulted in an off scale UOS recording (>100mm Hg). There was a highly significant relationship between level of arousal and UOS pressure ($p<0.0001$).

Table 4.1 shows the mean values for each level of arousal from the two children without gastro-oesophageal symptoms. Due to the small number no statistical analysis can be performed.

Table 4.1

Mean values for levels of arousal for the control group

(n = number of samples)

Level of Arousal	CW	RB
A	26.3±7.0 n=11	3.9±7.0 n=14
B	27.8±12.5 n=4	13.0±11.0 n=2
C	n=0	n=0
D	100^{+} n=1	66.5±14.8 n=2
E	100^{+} n=1	n=0

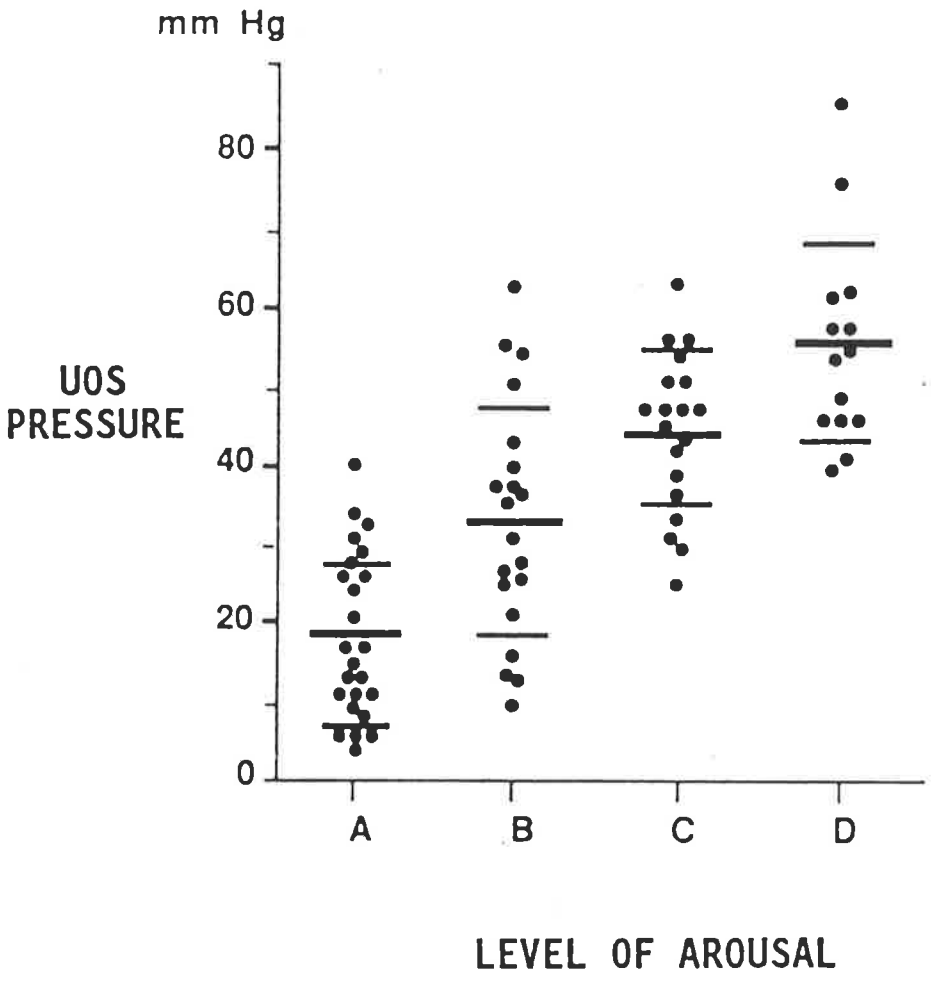

Figure 4.2 Individual subject and group mean(± SD) values of UOS pressure for each level of arousal. There is a highly significant ($p<0.0001$) correlation between level of arousal and UOS pressure.

3.2 RELATIONSHIP BETWEEN SYMPTOM CATEGORIES AND UOS PRESSURE

Tables 4.2 and 4.3 show the mean values for basal UOS pressure according to arousal level, symptom classification and presence or absence of neurological deficit. There was no significant difference in UOS pressure between this group and any of the other three symptom groups when controlled for level of arousal. Presence or absence of neurological deficit was also shown to have no significant effect on basal UOS pressure. In all four symptom categories and the division based on neurological deficit, there was a significant increase in basal UOS pressure from category A to category B ($p<0.001$).

The control group showed the same relationship between level of arousal and UOS pressure as the patient groups.

Table 4.2

Relationship between neurological deficit and basal UOS pressure (mm Hg, mean±SD)

	Arousal State	
	A	B
Without deficit	16.1±9.2 n=40	24.1±18.7 * n=31
With deficit	10.7±9.6 n=11	23.4±17.7 * n=8

Note: values were not available for both arousal groups in every child because of variations in behaviour pattern.

* indicates significant differences between arousal classifications.

Table 4.3

Relationship between symptomatology and basal UOS pressure (mm Hg, mean±SD)

Symptom Group (category)	Arousal State A	Arousal State B
Vomiting/ Failure To Thrive (a)	15.4±11.2 n=20	23.3±21.1 * n=14
Irritability/ Abdominal Pain (b)	16.2±7.8 n=24	23.3±16.7 * n=18
Recurrent Respiratory Disease/Apnoea (c)	20.0±4.3 n=3	26.0±3.3 * n=3
Food Refusal/ Swallowing Difficulties (d)	12.0±5.6 n=4	29.8±19.0 * n=4

Note: For this analysis, patients were grouped without reference to neurological status and according to the most prominent symptom. Values were not available for both arousal states in every child because of variations in behaviour pattern. No significant differences were found between symptom groups, within arousal classifications.

* indicates significant differences between arousal classifications.

4. DISCUSSION

The data indicate that UOS pressure had a highly significant correlation with the level of arousal, with pressures increasing as the level of arousal increased. These results are consistent with recent observations that mental stress augments UOS pressure in adults (Cook *et al.* 1987), and the reports of markedly low basal pressure levels during sleep in adult volunteers (Kahrilas *et al.* 1987b) or with anaesthesia in opossums (Asoh *et al.* 1978). The finding that the level of arousal has a substantial influence on UOS pressure has major implications for research into the UOS in children. Until now, the major emphasis has been to obtain sample values of basal UOS pressure by catheter pull-through and to relate these to suspected UOS dysfunction. To this end both Sondheimer (1983) and Staiano *et al.* (1987) used sedation to counteract the stress of the procedures they used. Even if regurgitation results from defective basal UOS tone, previous measurements will have been so influenced by stress and sedation that any such defect of basal tone may not be recognizable.

These findings have obvious repercussions for any measurement of absolute UOS pressure. Comparison of results must take the level of arousal of the subject(s) into consideration. As only arousal levels A and B were analysed in this study, one of the variables which might cloud the issue of symptom-related differences in basal UOS pressure was avoided.

The finding that there was no difference in basal UOS pressure among the symptom divisions or neurological division suggests that there is no group of children with an abnormally low basal UOS pressure. This does not support the theory that lowered basal UOS

pressure is a mechanism of OPR. Thus, the findings of Sondheimer (1983) and Staiano *et al.* (1987) that basal hypotonia of the UOS is not a cause of pathological oesophago-pharyngeal reflux are supported.

Some studies have examined whether adult regurgitators have UOS hypotonia. Gerhardt *et al.* (1980a), using a station pull-through technique, found that adults with OPR had UOS pressures (54±3 mmHg SEM) that were just over half the pressure of those with no gastro-oesophageal symptoms (101±5 mmHg SEM) or with heartburn (108±9 mmHg SEM). They comment in the discussion that there is some overlap in UOS pressure values between the group with OPR and the two groups without, indicating that the range of values in each group is wider than the figures suggest. The values for the non-regurgitator groups seem high when compared to the values of around 60 mmHg found by using a sleeve sensor (Kahrilas *et al.* 1987a). The method used has a number of technical problems which have been outlined in Chapter 1. Briefly these are the inability of a pull-through technique to monitor UOS pressure (Chapter 1 section, 2.2.3) and the increase in UOS pressure when a pull-through manoeuvre is performed (Chapter 1 section 2.2.3), probably due to increased emotional stress of the subject. These render the findings unreliable.

Wilson *et al.* (1990), however, found no relationship between UOS pressure and acid exposure in two groups of adults, consisting of patients with laryngopharyngeal symptoms and asymptomatic volunteer controls. They also used a pull-through technique, with the attendant problems outlined above. Although the problems associated with the method of measuring UOS pressure mean that the absolute values are not reliable, it would still presumably find any differences between the groups.

The findings of these two studies illustrate the problems of drawing conclusions from the adult literature, given the differing results and problematical methods.

On the basis of the work presented here there is no evidence that OPR is caused by low basal UOS pressure. In addition, presence of GOR made no difference to UOS pressure.

CHAPTER 5

EFFECT OF STRAINING ON UOS PRESSURE

1. Introduction

2. Method Changes

   2.1 Data Analysis

   2.2 Patient Division

   2.3 Statistical Analysis

3. Results

   3.1 Inspiratory Strains

   3.2 Single Cough Strains

   3.3 Multiple Cough Strains

   3.4 Sustained Strains

   3.5 UOS Pressure And Symptom Groups

4. Discussion

1. INTRODUCTION

Previous studies with the sleeve technique have shown that various forms of sustained abdominal or thoracic straining are associated with similarly sustained augmentations of UOS pressure (Anvari *et al.* 1987). I sought to find out whether this mechanism is present in children, and whether children with GOR have a different or defective mechanism of augmentation.

2. METHOD CHANGES

2.1 DATA ANALYSIS

Due to a lack of recording points in the oesophagus the tracings from the control children could not be used for this analysis.

The fifty three patient tracings were scanned for the presence of strains and up to ten of each type of episode was analysed in each patient, in order of occurrence. In most children there were fewer than 10 of each strain type suitable for analysis. Any events which were a combination of any of the four types of strains we identified were not analysed. The complex strains seen during crying were not analysed. To remove the possibility of interference of basal UOS or oesophageal body pressures by swallow induced disturbances strains were only analysed if there was at least one second free of swallow related pressure change following the strain, and at least six seconds free of swallow related disturbances or secondary peristaltic oesophageal body waves prior to the onset of the strain. Swallowing was indicated by characteristic pharyngeal pressure waves in the most proximal sidehole (Figures 2.2, 4.1) The reference point for timing of swallows was taken from the onset of this pressure wave.

Four types of strain were analysed:

i) Inspiratory strains (Figure 5.1), which were identified from the oesophageal body tracing as a negative, inspiratory excursion of at least twice the size of the normal excursions, with a minimum of 10 mm Hg below the end expiratory oesophageal body pressure. To ensure that it was monophasic, any expiratory component had to be less than 5 mmHg above the usual end expiratory point. Any inspiratory excursions less than 0.5 seconds in duration were excluded from the analysis. UOS pressure was measured at the moment of maximum pressure excursion for the strain related value. Point pressures were measured from the UOS at the end inspiratory point for 3 respiratory cycles before and after the strain. The change in gastric pressure was measured.

ii) Single cough strains (Figure 5.1), which were identified from the gastric tracing as a spike-like pressure elevation, greater than 40 mmHg and not longer than 1.5 seconds, with a temporally associated abrupt positive pressure change in the oesophageal body tracing. The UOS pressure was measured at the point corresponding to the peak of the strain and the point pressures at end expiration in the respiratory cycle for 3 cycles before and 3 cycles after the strain. The peak oesophageal body pressure at the time of the strain was measured.

iii) Multiple cough strains (Figure 5.1), which were identified from the gastric tracing as 3 or more of the above strains within three seconds of each other. Peak gastric pressure was measured over the period of the strain. The duration of the strain was measured from the time it exceeded 5 mmHg above the baseline to the time it returned to below the threshold. The peak oesophageal body pressure over the period of the strain was measured. UOS

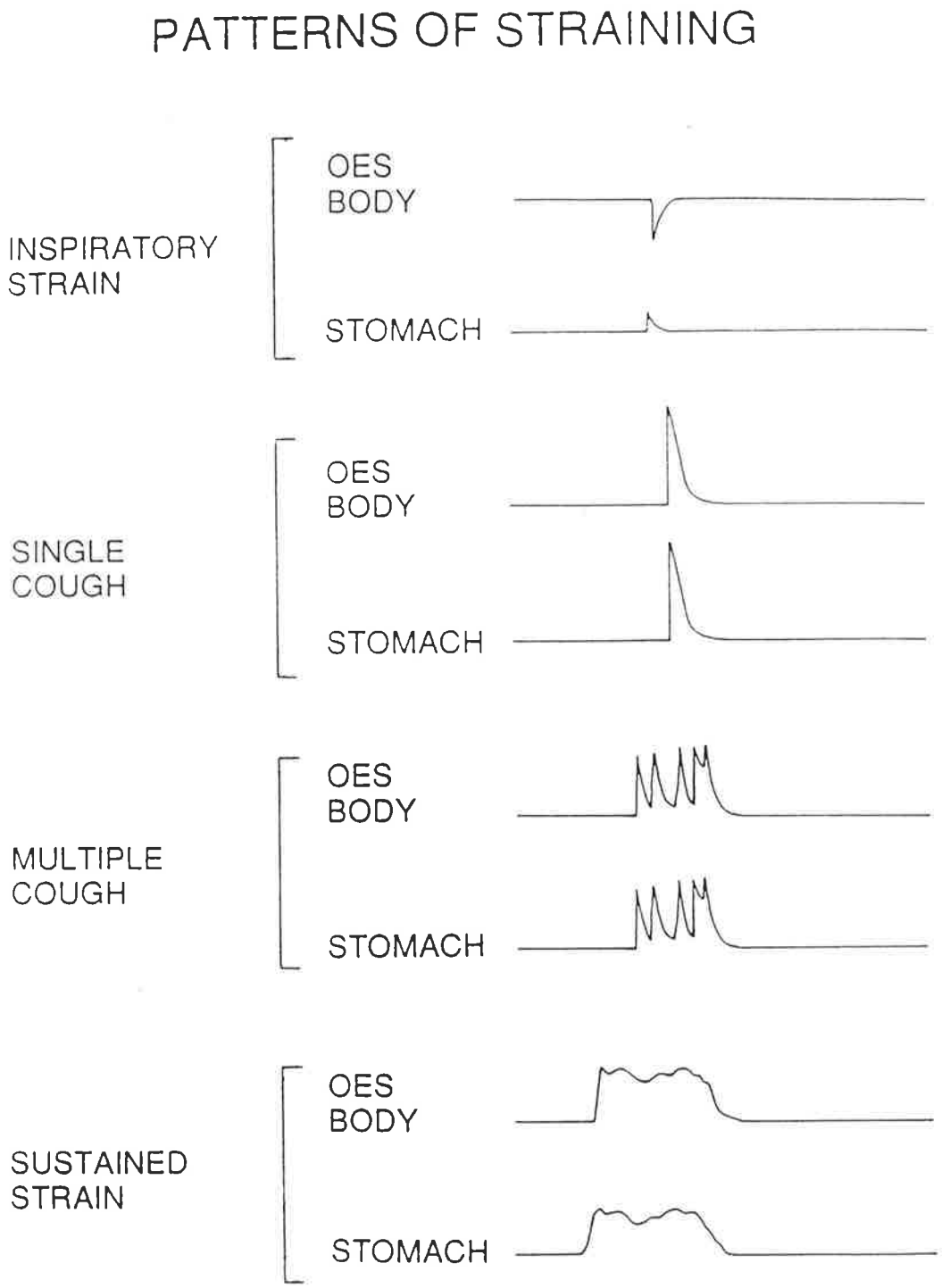

Figure 5.1 Diagramatic representation of the four types of strain analysed.

pressure was measured during the strain in 2 second intervals by visual mean. UOS pressure was also measured for up to 10 seconds before and after the strain by visual mean of 2 second intervals if clear from swallow interference.

iv) Sustained strains (Figure 5.1), which were identified from the gastric tracing as elevations of pressure to more than 5 mmHg for 2 to 20 seconds with a corresponding rise in oesophageal body pressure. Peak gastric pressure was measured over the period of the strain. The duration of the strain was measured from the time it exceeded 5 mmHg to when it fell below the threshold. Peak oesophageal body pressure was measured over the period of the strain. UOS pressure was measured during the strain in 2 second intervals by visual mean. UOS pressure was measured for up to 10 seconds before and after the strain by visual mean of 2 second intervals if clear from swallow interference.

2.2 PATIENT DIVISION

The patients were subdivided into those with clinical evidence of OPR (symptom category a) and those with no evidence of OPR (symptom categories b, c and d). (see page 46)

2.3 STATISTICAL ANALYSIS

Pressures within each strain or subdivision were compared by constructing a correlation matrix. Levels of significance were then observed. Differences between the groups with and without OPR were examined using Student's t-test.

3. RESULTS

There were 172 inspiratory strains able to be analysed in 40 patients, seven single cough strains in six patients, 35 multiple cough strains in 14 patients and 149 sustained strains in 34 patients. There were five patients with no episodes suitable for analysis.

Table 5.1 shows the mean UOS pressure values for the periods before, during and after strains for each strain type.

Table 5.1

Pressures for each strain type

(mm Hg, M±SE)

Strain type	Before	During	After
Inspiratory	26.9±2.7	55.8±3.4	32.3±2.9
Single cough	36.8±6.7	59.3±11.8	58.3±8.3
Multiple cough	42.9±4.1	59.3±4.6	65.5±6.2
Sustained	39.1±2.9	59.8±3.4	54.3±3.8

3.1 INSPIRATORY STRAINS

UOS pressures are shown before, during and after the strain in Figure 5.2a. UOS pressure was significantly higher ($p<0.01$) during the strain than before or after the strain. The changes in gastric, oesophageal and UOS pressure during straining are shown in Figure 5.2b. Thirty seven of the total of 172 events showed no change in gastric pressure. There was no significant correlation between UOS pressure change and either oesophageal body or gastric pressure change.

3.2 SINGLE COUGH STRAINS

UOS pressures are shown before, during and after the strain in Figure 5.3a. UOS pressure was not significantly higher ($p>0.05$) during the strain than before or after the strain, however there was a trend toward higher UOS pressures during the strain. The changes in gastric, oesophageal and UOS pressure during straining are shown in Figure 5.3b. There was no significant correlation between UOS pressure change and oesophageal body pressure change or gastric pressure change.

3.3 MULTIPLE COUGH STRAINS

The duration of the strains ranged from 2-12 seconds. UOS pressures are shown before, during and after the strain in Figure 5.4a. UOS pressure was significantly higher ($p<0.01$) during the strain than before the strain. UOS pressure after the strain was also significantly higher than that before the strain ($p<0.05$). The changes in gastric, oesophageal and UOS pressure during straining are shown in Figure 5.4b. The gastric pressure change was found to correlate significantly with UOS pressure during the strain ($p=0.087$), and with UOS pressure following the strain ($p=0.03$).

3.4 SUSTAINED STRAINS

The mean duration of the strains was 5.6 ± 0.4 seconds, range 2-18 seconds. UOS pressures are shown before, during and after the strain in Figure 5.5a. UOS pressure was significantly higher during the strain than before ($p<0.01$) or after ($p<0.01$) the strain. The changes in gastric, oesophageal and UOS pressure during straining are shown in Figure 5.5b. There was a significant correlation between UOS pressure changes and both gastric pressure changes ($p=0.04$) and oesophageal pressure changes ($p=0.03$).

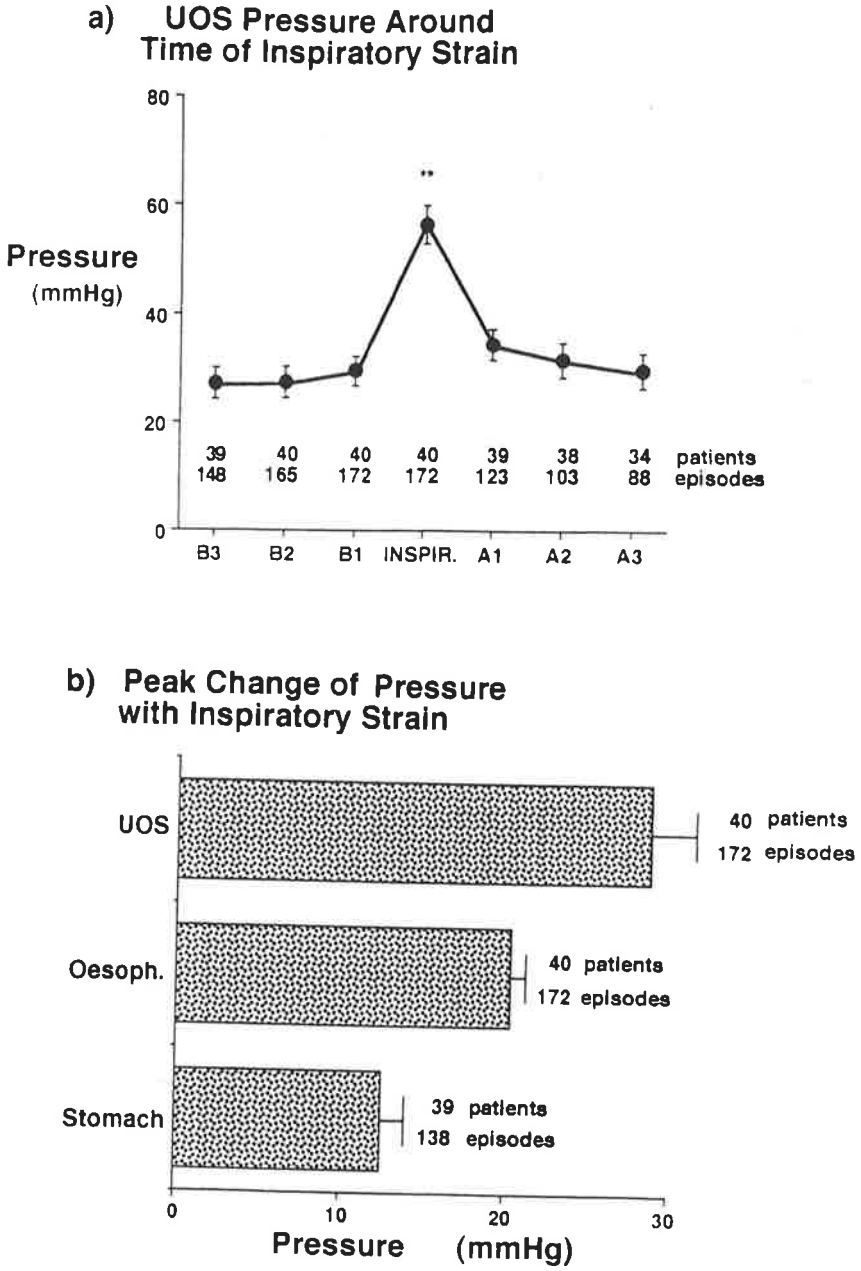

Figure 5.2 Inspiratory Strains.

(a) UOS pressure (mean±SE) before, during and after inspiratory straining. (** $p<0.01$ for comparison with prestrain pressure). (b) Peak changes of pressure during straining in the UOS, oesophageal body and stomach, referenced to basal pressures just before straining.

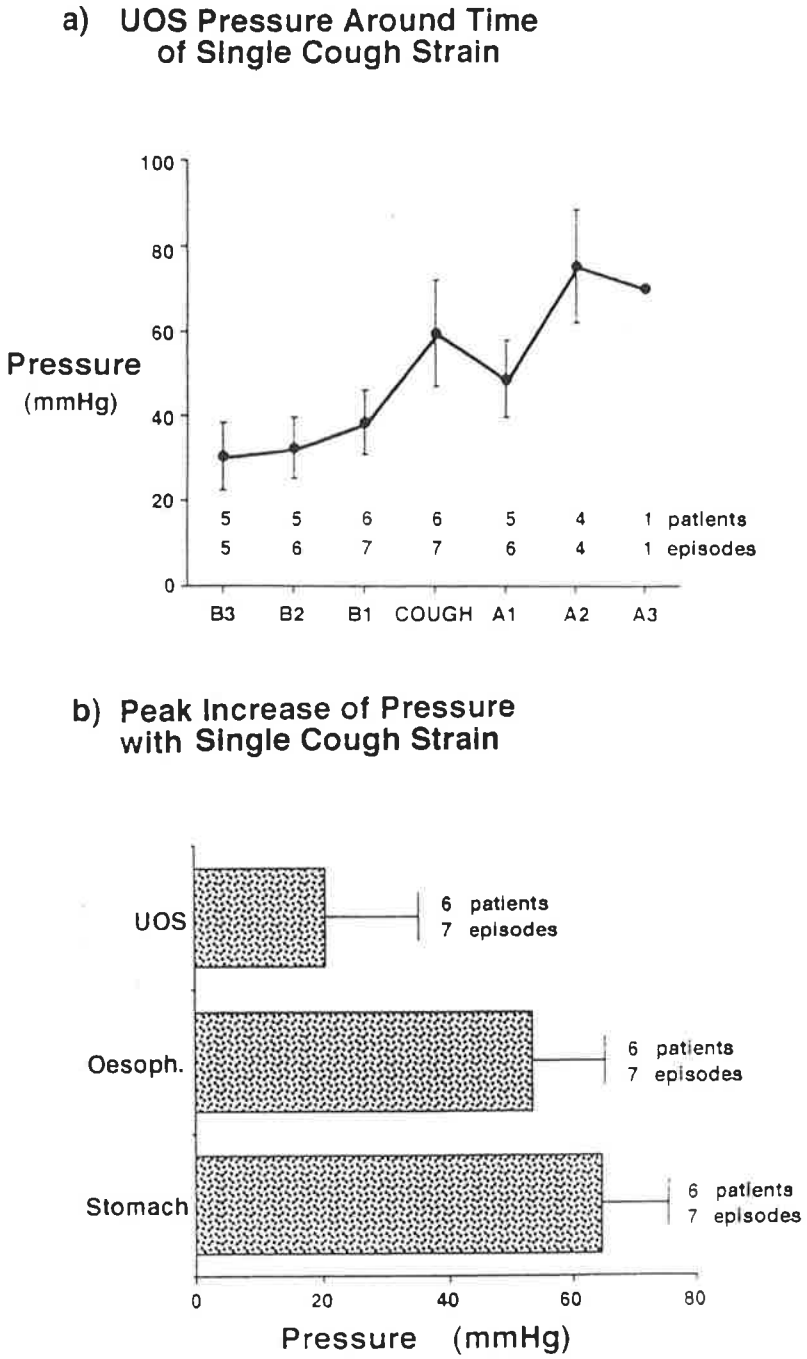

Figure 5.3 Single Cough Strains.

(a) UOS pressure (mean±SE) before, during and after expiratory straining. The UOS pressure during straining was not significantly different from prestrain UOS pressure ($p>0.05$). There were few data points following the strain because swallowing occurred frequently following this.

(b) Peak pressure increase during straining in the UOS, oesophageal body and stomach, referenced to basal pressures just before straining.

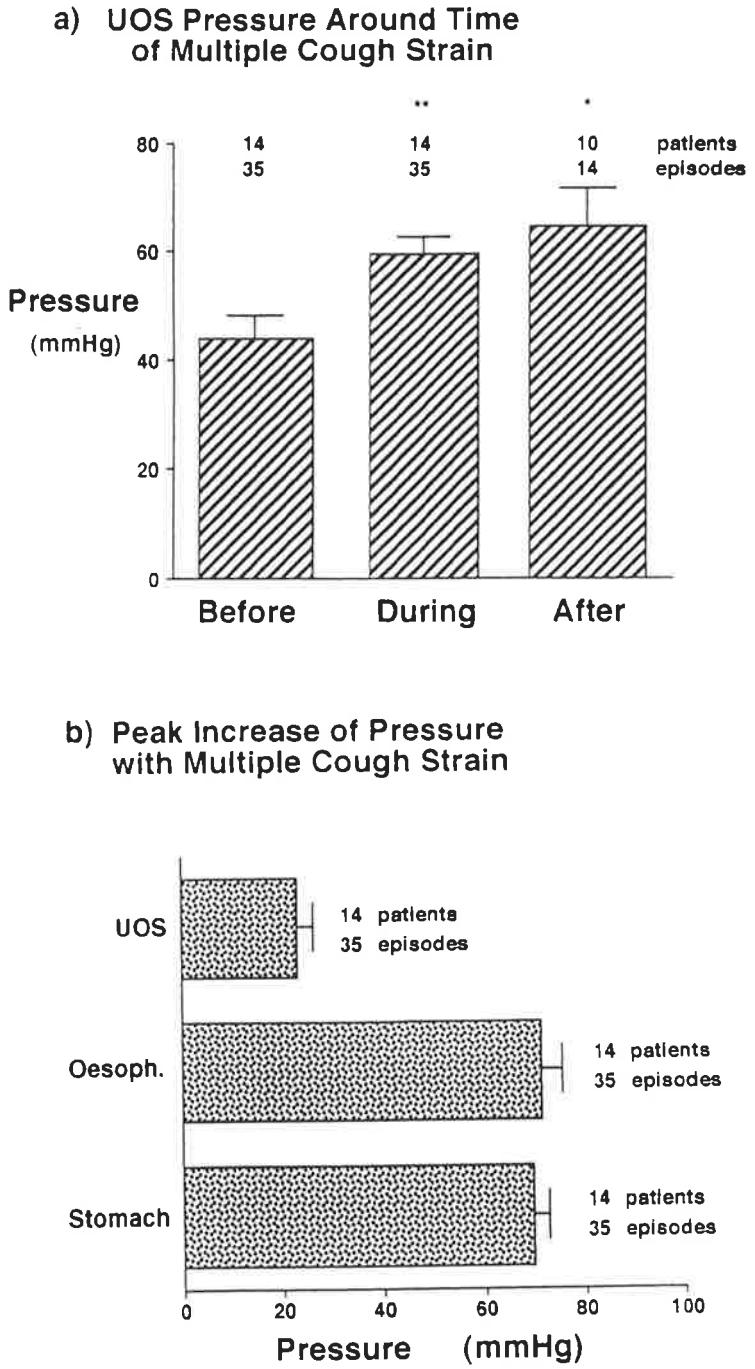

Figure 5.4 Multiple Cough Strains.

(a) UOS pressure (mean±SE) before, during and after multiple cough straining. (* $p<0.05$, ** $p<0.01$ for comparisons with prestrain pressures).

(b) Peak pressure increases during straining in the UOS, oesophageal body and stomach, referenced to basal pressures just before straining.

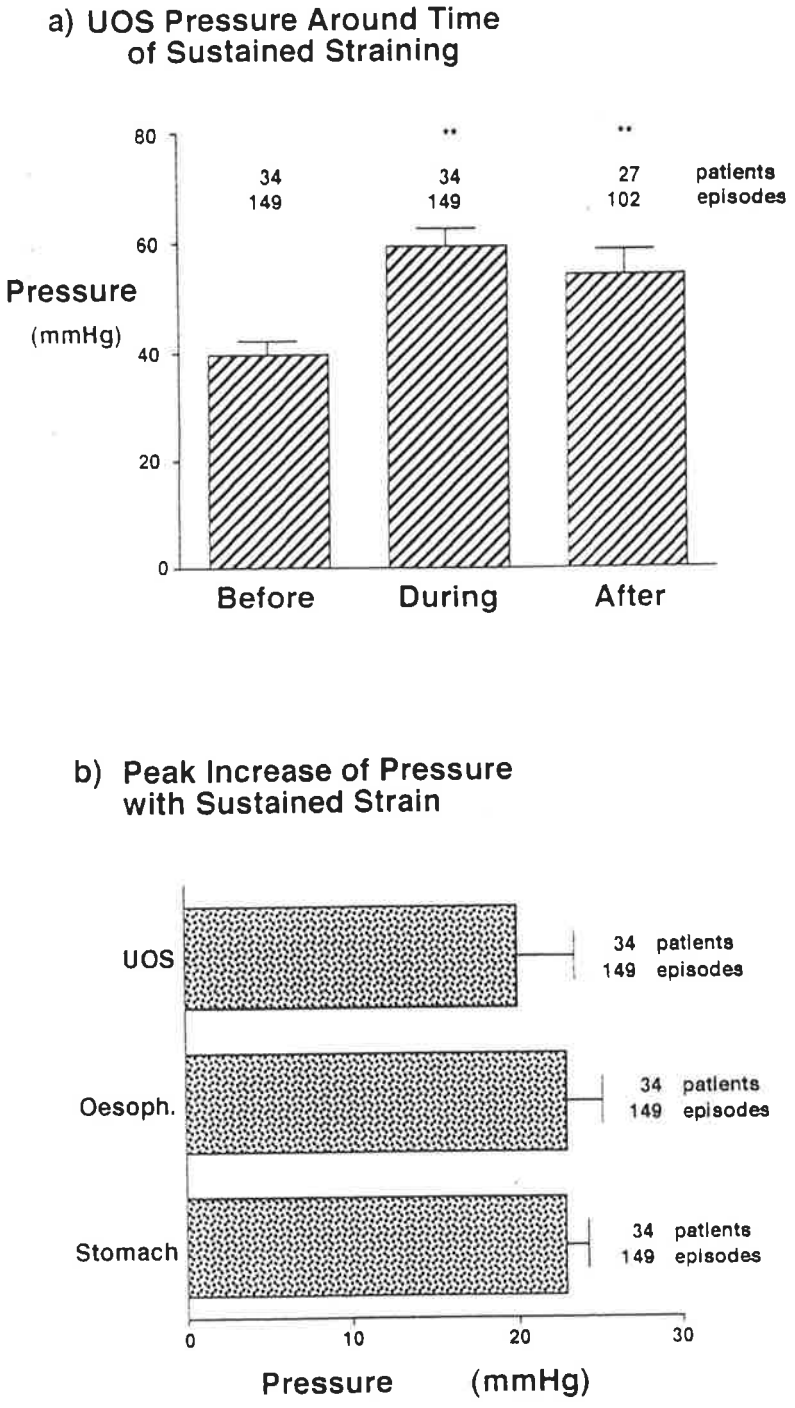

Figure 5.5 Sustained Strains.

(a) UOS pressure (mean±SE) before, during and after sustained straining (** $p<0.01$ for comparisons with prestrain pressure). (b) Peak pressure increases during straining for the UOS, oesophageal body and stomach, referenced to basal pressures just before straining.

3.5 UOS PRESSURE AND SYMPTOM GROUPS

UOS pressure during sustained straining was significantly higher ($p<0.01$) in the group with OPR (68.2±14.7 mmHg, M±SD, n=17) than the group without OPR (50.6±20.2 mmHg, n=17). No difference was found between the groups for the other strains. There were no significant differences in UOS pressure changes between the neurological categories.

4. DISCUSSION

This study has established that physical straining in children is consistently associated with substantial and simultaneous elevation of UOS pressure. The analysis of patient subgroups indicates that these straining responses are preserved in all groups.

The mechanical functioning of gastrointestinal sphincters is substantially influenced by their position relative to body cavities. In this regard, the UOS differs significantly from the LOS as it is situated in the base of the neck, outside the intrathoracic pressure environment. Consequently, abrupt changes of intrathoracic pressure caused by straining are not transmitted directly to the extraluminal aspect of the UOS, but are transmitted to the lumen of the UOS via the oesophageal body. This physical arrangement means that straining induced increases of intrathoracic pressure are not cancelled out in the way that they are with a normally situated lower oesophageal sphincter.

The mechanics of the UOS resemble most closely those of the anal sphincter, the external aspect of which is also removed from the

pressure environment of the peritoneal cavity (Ihre 1974), yet its lumen is exposed to this. Consequently, accurately timed augmentations of the external anal sphincter occur during straining and are important for maintenance of anal continence (Ihre 1974). The rapid responses of the external anal sphincter to straining depend upon its being composed of striated muscle. The UOS also consists of striated muscle and has been shown to be capable of very abrupt augmentations of pressure during periods of increased levels of arousal (Figure 4.1).

If oesophago-pharyngeal reflux does not result from defective basal function of the UOS, then it might result from defective augmentation of UOS pressure during events that stress the antireflux function of this sphincter, such as straining. If a defect existed, it would only be relevant to the pathogenesis of oesophago-pharyngeal reflux associated with straining, rather than the more common "effortless" regurgitation. These data indicate that such tightening occurs in all groups of children studied. In fact, the group of children with clinical indications of OPR showed a higher UOS pressure during sustained straining than those without OPR. This may be due to an increase in level of arousal when the UOS is potentially threatened by OPR.

The straining induced augmentation of UOS pressure occurs synchronously with the strain and appears to be of sufficient magnitude to maintain a pressure barrier between the lumen of the oesophageal body and pharynx (Figure 5.6). Maintenance of this pressure barrier was demonstrated with the recording methods used, despite the fact that the sleeve has a limited capacity to record abrupt elevations of sphincter pressure because of its compliance. This compliance is likely to have partly obscured any dose response

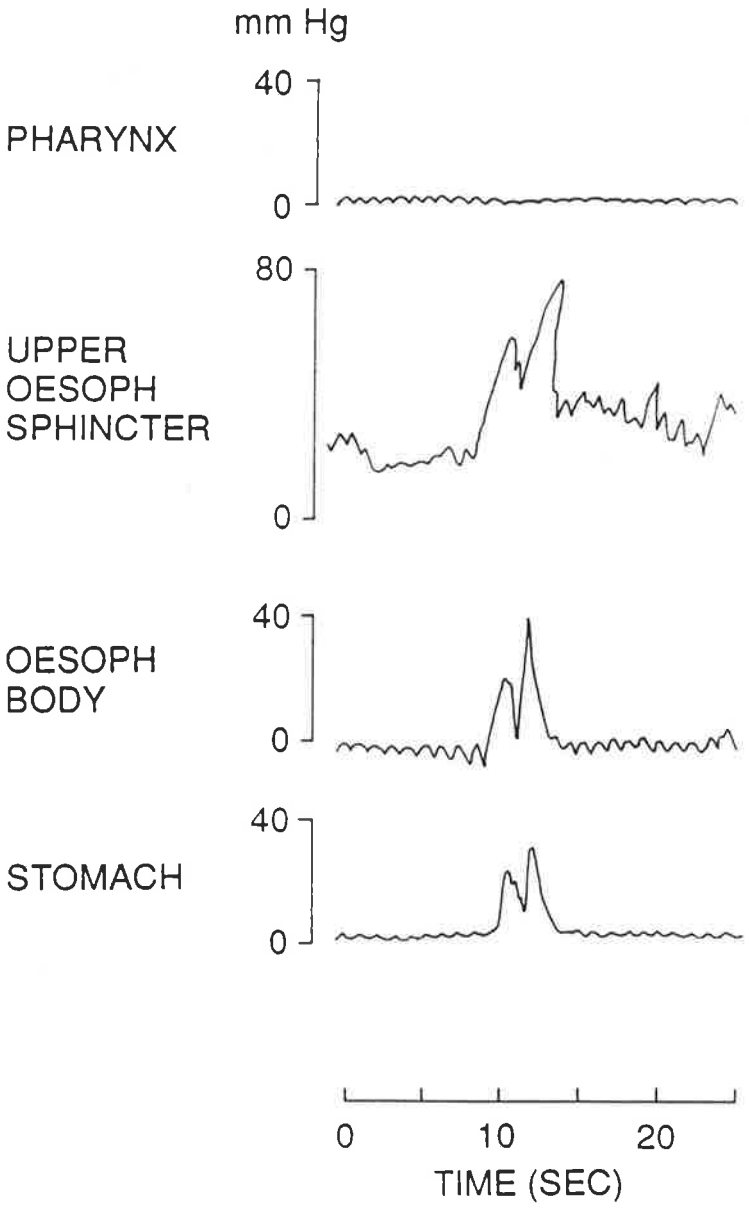

Figure 5.6 Segment of manometric tracing showing the response of the UOS to sustained straining involving the abdominal and thoracic cavities.

relationship of the magnitude of straining and the magnitude of the UOS pressure response. It is notable that this dose response relationship was most firm for sustained straining, probably because the duration of the strain allowed the sleeve to catch up to the true augmented UOS pressure.

Four different patterns of straining were chosen for analysis. Because these were spontaneous strains they had to be standardised to some degree by somewhat arbitrary definitions derived from combinations of intrathoracic and intraperitoneal pressure. This approach was found to be possible in children and had the advantage of analysis of naturally occurring events. Evaluation of the timings and relationships between intrapleural and intraperitoneal pressures indicate that there are several generic patterns of straining. Probably, the most important grouping of strain patterns is where there is a simultaneous elevation of intra-abdominal and intrathoracic pressure, such as occurs during coughing or during body movement associated with partial or complete glottic closure. In the other major pattern of straining, produced by deep inspiration and open glottis, there is a larger than normal inspiratory decrease of intrathoracic pressure, associated with an increase of intra-abdominal pressure. These data show that either pattern of straining is associated with abrupt augmentation of UOS pressure. This is similar to the findings from a study of nine normal adult volunteers (Anvari *et al.* 1991).

It is possible that the augmentation of UOS pressure found in the present analysis could be due solely to arousal and not due to the strain itself. Undoubtedly, many episodes of straining are associated with increased arousal and so this factor must contribute to the effects observed. These data suggest though, that strain per

se is important, since the UOS pressure augmentation in response to inspiratory straining only occurred during the single inspiration. It is most unlikely that arousal could have produced such a discrete response.

Thus, straining causes a simultaneous increase in UOS pressure, which occurred irrespective of presenting symptoms, indicating that failure of augmentation of UOS pressure during straining is not likely to be a cause of OPR.

CHAPTER 6

(PART A)

EFFECT OF GOR ON BASAL UOS FUNCTION

1. Introduction

2. Data Analysis

   2.1 Manometric Indicators Of GOR

   2.2 Statistical Analysis

3. Results

   3.1 Basal UOS Pressure Associated With Common Cavity Episodes

4. Discussion

1. INTRODUCTION

Currently there is little information about the relationships among GOR, UOS pressure and OPR in adults, and practically none in children. The concept that OPR occurs because of abnormally low basal UOS tone has dominated thinking about the pathogenesis of OPR. This concept has been expanded recently to include the idea that transient changes in UOS pressure may be responsible for OPR, either as well as, or instead of lowered basal UOS pressure. In healthy adult volunteers Kahrilas *et al.* (1986) showed that gas reflux from the stomach triggered transient relaxations of the UOS unrelated to swallowing which allowed gas flow across the UOS.

The aim of this section was to record patterns of UOS motility associated with the occurrence of GOR in children and examine both basal (Chapter 6a) and transient (Chapter 6b) changes of UOS pressure. I sought to investigate the hypothesis that episodes of spontaneous GOR cause transient reflex UOS relaxations which may be the mechanism of regurgitation, rather than a deficiency of basal UOS tone.

No data is available from the control group of children because oesophageal pH was not recorded, and there were insufficient oesophageal body pressure recording points in the feeding assembly to collect meaningful information.

2. DATA ANALYSIS

2.1 MANOMETRIC INDICATORS OF GOR

Abrupt, sustained elevations of intra-oesophageal pressure to intragastric pressure, known as common cavity episodes, were used to recognise oesophageal distension by reflux, without reference to any changes in the pH recording (Figure 6.1). Common cavity events were first described by McNally *et al.* (1964) who correlated cineradiographic distention of the oesophagus by gas refluxed from the stomach with manometric evidence of pressure equalisation between the stomach and the oesophagus. Common cavity episodes were only scored when the elevation of intra-oesophageal pressure was recorded in at least two oesophageal body manometric channels. Similar appearing elevations of basal oesophageal pressure due to straining or breath-holding were excluded by recognition of characteristic elevations in the gastric pressure tracing.

UOS pressure around common cavity episodes was analysed if there were no swallows in the 13 seconds before and the 3 seconds after onset of the common cavity episode. UOS pressure was measured in 2 second intervals as a visual mean starting from 10 seconds before the onset of the common cavity episode until 1 second before the first swallow after the common cavity episode, or the onset of the first secondary oesophageal peristaltic wave which occurred during the common cavity episode. Values for mean basal UOS pressure before and after the common cavity episode were obtained for the 6 seconds before and up to 6 seconds after the onset by averaging the individual two second values.

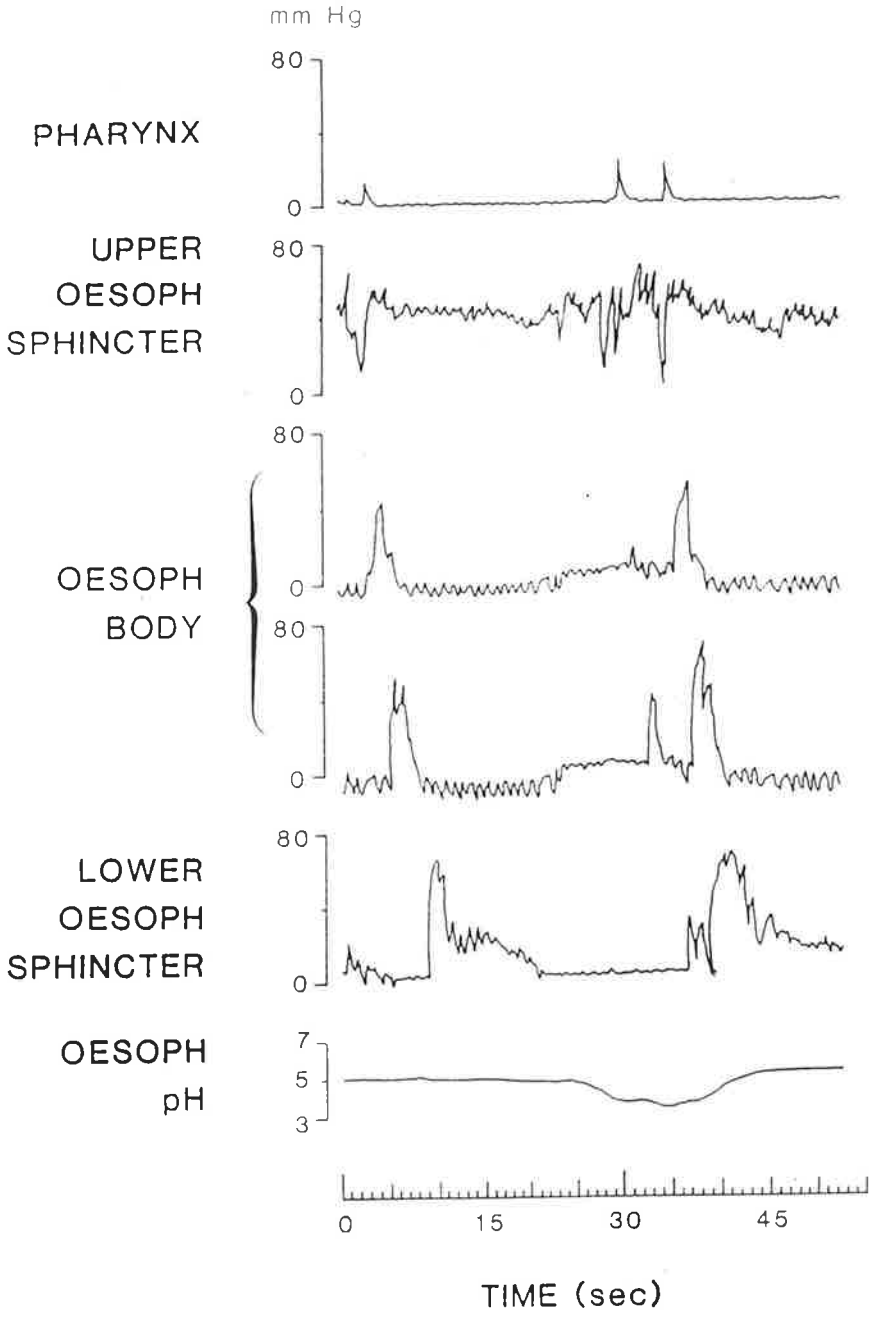

Figure 6.1 Segment of manometric tracing showing pharynx, UOS, oesophageal body and lower oesophageal sphincter pressures. The bottom tracing is intra-oesophageal pH recorded 3cm above the lower oesophageal sphincter. The first pressure spike in the pharyngeal tracing indicates a normal swallow, initiating a normal oesophageal body peristaltic wave simultaneous with lower oesophageal sphincter relaxation. Following this sequence lower oesophageal sphincter pressure is re-established for ~10 seconds before there is a transient lower oesophageal sphincter relaxation which is associated with an oesophageal body common cavity episode and oesophageal acidification.

2.2 STATISTICAL ANALYSIS

Student's t-test was used to compare basal UOS pressure for the six seconds before the common cavity to the six seconds after the onset of the common cavity.

The difference in increase in UOS pressure for those episodes with acid reflux, and those without was compared using ANOVA (one way).

3. RESULTS

3.1 BASAL UOS PRESSURE ASSOCIATED WITH COMMON CAVITY EPISODES

Screening of the tracings revealed 369 common cavity episodes. The median number of common cavity episodes identified per child was 5, with a wide variation from 0 to 29. One hundred and twelve episodes fitted the criteria described in Methods which were designed to ensure that the effects of swallowing or straining did not influence the effect of reflux on UOS pressures. These episodes yielded a total of 551 2-second time intervals prior to the onset of the common cavity episodes, and 476 2-second time intervals after the common cavity onset.

The median duration of the common cavities was 8 seconds (interquartile range 4-10 sec). The median elevation of basal intra-oesophageal pressure was 6 mmHg (interquartile range 5-8 mmHg).

The pattern of basal UOS pressure about the time of the common cavity is shown in Figure 6.2. The increase in UOS pressure of 9 mmHg for the 6 seconds after the common cavity onset, compared to the 6 seconds before the onset, although modest, was highly significant ($p<0.0001$). This effect did not depend on oesophageal acidification, since it occurred to the same extent with both pH positive and pH negative common cavity episodes.

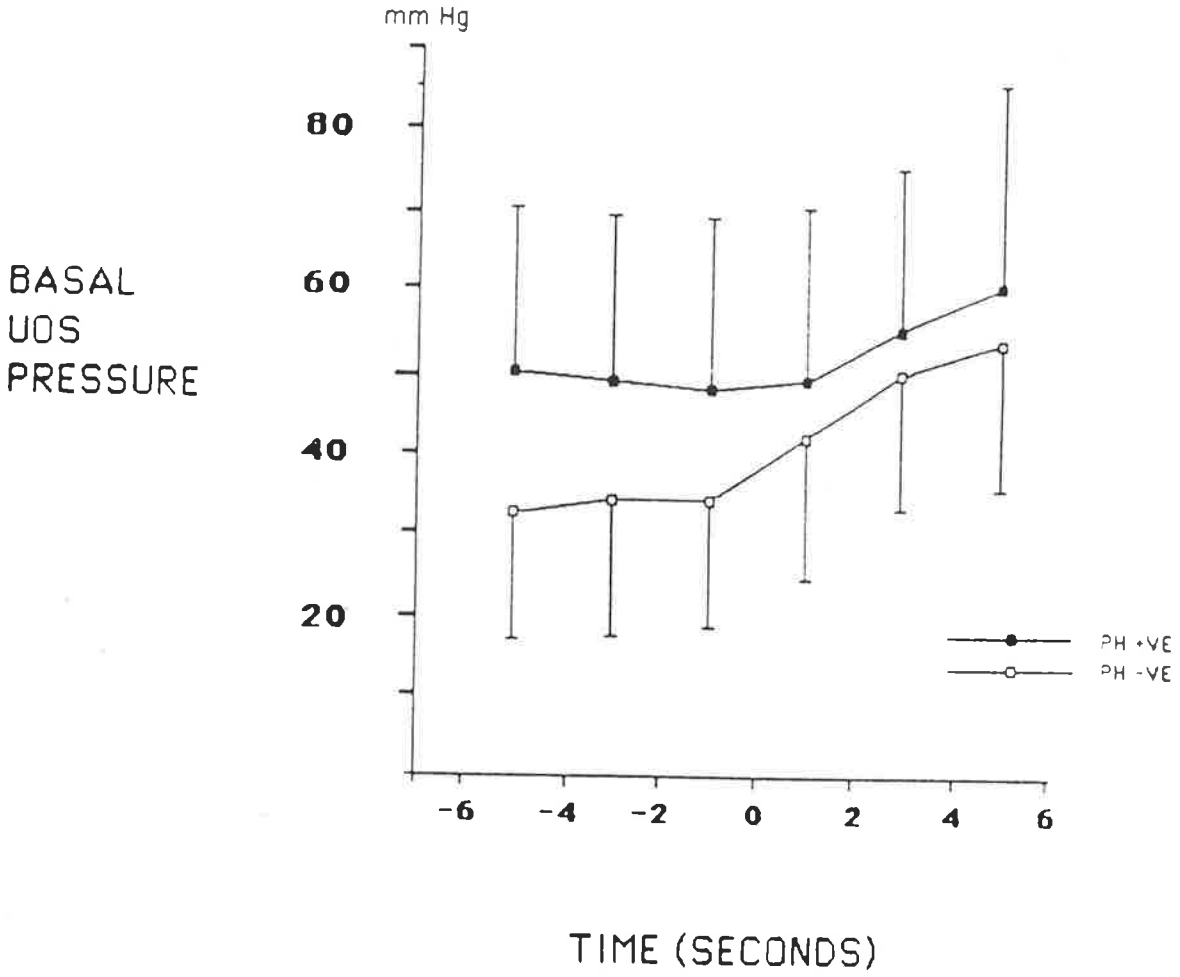

Figure 6.2 UOS pressure measured in two second intervals from six seconds before the onset of the common cavity episode to six seconds after the onset. Episodes associated with pH change are shown with filled squares, those with no pH change are shown with open squares. Means ± standard deviations are shown.

4. DISCUSSION

There has been conflicting evidence as to the effects of distention and acidification of the oesophagus on UOS pressure. This study allowed me to relate physiological distention of the oesophagus, as indicated by the occurrence of common cavity episodes, and acidification of the oesophagus, as indicated by pH drops, to changes in UOS pressure. There was evidence of both basal and transient UOS pressure changes in response to GOR. Changes of basal UOS pressure are discussed in Chapter 6a, transient changes in UOS pressure are discussed in Chapter 6b.

Because of the perceived significance of augmentation of basal UOS pressure as a mechanism that may prevent GOR (Hunt *et al.* 1970), the effects of oesophageal distention and acidification on basal UOS pressure were analysed. Although there is general agreement that distention of the oesophagus causes an increase in basal UOS pressure (Enzmann *et al.* 1977, Gerhardt *et al.* 1978, 1980b, Kahrilas *et al.* 1986, Sondheimer 1983), there is confusion as to the effects of oesophageal acidification on basal UOS pressure (Gerhardt *et al.* 1978, 1980b, Kahrilas *et al.* 1987b, Sondheimer 1983, Stanciu *et al.* 1974, Wilson *et al.* 1990). In the present study, distention of the oesophagus alone caused an overall, significant increase of 9 mmHg, and concurrent acidification had no added effect. Unfortunately there were only three episodes of acid GOR without associated oesophageal distention, too few to be able to comment on the effects of acidification alone.

The lack of effect of acidification by GOR on basal UOS pressure was noted by Kahrilas (1987b) in adult volunteers, although Sondheimer (1983) found an increase in UOS pressure with acid

infusion into the oesophagus in children, and several studies have found the same effect in adults (Gerhardt 1978, 1980b). This may reflect differences between physiological GOR and non-physiological infusion of acid into the oesophagus.

The change in UOS pressure in response to oesophageal distention ranged from -82 to +89 mmHg, thus indicating that there is not a uniform response. This may be due to a required threshold of distention before the UOS will react. The threshold may depend on the size of the increase in volume of the oesophagus, the rate of distention and individual factors.

Although the post reflux augmentation of UOS pressure is statistically highly significant, in absolute terms it is a modest effect and it is doubtful that it is of great significance for the prevention of oesophago-pharyngeal reflux. In the past it has been implied that this increase in UOS pressure following oesophageal distention is important for prevention of the UOS barrier being overcome by the increase in oesophageal pressure, leading to the occurrence of oesophago-pharyngeal reflux (Gerhardt *et al.* 1978, Kahrilas *et al.* 1986, Sondheimer 1983). The size of the increase in oesophageal body pressure in this study (median 6 mmHg) is insignificant when compared to basal UOS pressures of 20 mmHg or more when the person is awake. There is a possibility that OPR may occur when basal UOS pressure is lowered during sleep as UOS pressures can reach less than 10 mmHg. However, if the UOS pressure increases by 9 mmHg with the occurrence of GOR, a sufficient barrier remains to prevent OPR.

It has been proposed that some children may have a hyporeactive UOS which would not respond to stimulation with an increase in pressure, thereby predisposing them to excessive OPR. The lack of

difference in UOS response to GOR among the symptom groups, or those with and those without neurological problems, indicates that none of these groups were associated with a hyporeactive UOS.

CHAPTER 6

(PART B)

TRANSIENT REFLEX UOS RELAXATIONS AND GOR

5. Data Analysis

   5.1 Transient UOS Relaxations

   5.2 Factors Responsible For Triggering Of Transient UOS Relaxations

      5.2.1 Magnitude Of Oesophageal Distention

      5.2.2 Duration Of Oesophageal Distention

      5.2.3 Extent Of Oesophageal Distention

   5.3 Analysis Of pH Recording

   5.4 Statistical Analysis

6. Results

7. Discussion

5. DATA ANALYSIS

5.1 TRANSIENT UOS RELAXATIONS

The tracings were scanned for UOS relaxations that occurred independently of swallowing. This excluded any relaxation which had its onset within 3 seconds before or 1 second after the onset of a swallow. A transient UOS relaxation was defined as a swallow independent drop in UOS pressure that occurred within 1 second to less than 50% of the prevailing UOS pressure. In the case of relaxations that occurred prior to common cavities, the UOS pressure was derived from the 10 seconds prior to the onset of the common cavity episode. For those relaxations associated with common cavity episodes, the UOS pressure was derived from the UOS pressure values after the common cavity onset. The transient UOS relaxation was defined as having ended when the pressure rose to more than 50% of the drop in pressure (Figure 6.3).

The time of occurrence of transient UOS relaxations was determined relative to the onset of the common cavity episode. For this analysis, the nadir of UOS relaxation was the most clear-cut point and so was used. Timings were recorded to the nearest second. In addition, the duration of the nadir of transient UOS relaxations was recorded to the nearest second. Nadir pressure was referenced to the prevailing oesophageal body pressure in that second.

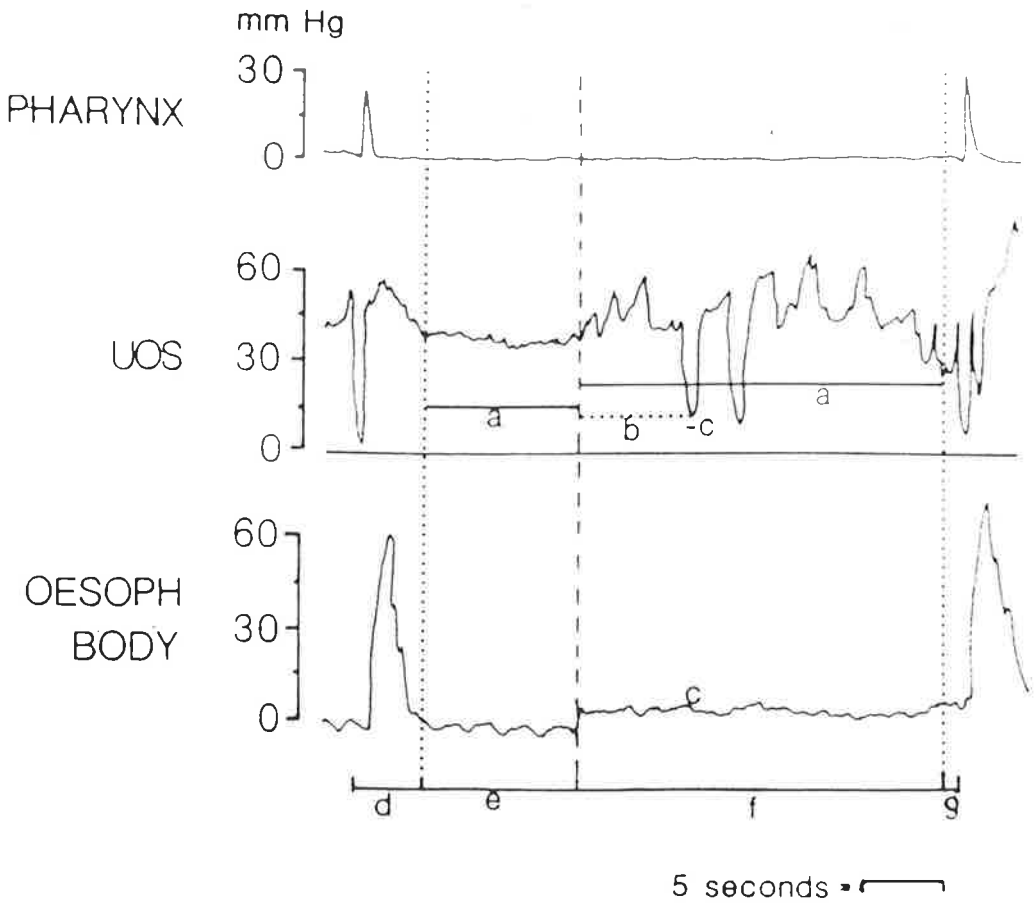

Figure 6.3 Measurement of transient UOS relaxations. The spikes in the 'Pharynx' pressure tracing are generated by swallows. a = 50% of UOS pressure, referenced to basal end expiratory oesophageal body pressure before the common cavity onset. b = timing of transient UOS relaxation. c = prevailing oesophageal body pressure. d = excluded time interval after a swallow. e = 10 second time interval preceding the common cavity onset from which UOS pressures were measured. f = time interval following the common cavity onset from which UOS pressures were measured. This time period ranged from 2-42 seconds. g = excluded time interval preceding a swallow.

5.2 FACTORS RESPONSIBLE FOR TRIGGERING OF TRANSIENT UOS RELAXATIONS

5.2.1 Magnitude Of Oesophageal Distention

The magnitude of the common cavity episode was measured in two ways: i) from an oesophageal body channel as the difference between the visual mean of the periods before and after the onset of the common cavity; ii) when intra-oesophageal body pressure showed a pattern of oscillation identical to that of intragastric pressure during a common cavity episode, this was taken as an indication of a period of communication between the lumina of the oesophageal body and stomach. The percentage of time that the common cavity events had a pressure pattern identical to the stomach was recorded.

5.2.2 Duration Of Oesophageal Distention

The duration of the common cavity episode was measured in seconds from the onset of the distention as measured by oesophageal body distention.

5.2.3 Extent Of Oesophageal Distention

The number of oesophageal body sideholes in which the common cavity episode was recorded indicated the extent of the distention.

5.3 ANALYSIS OF pH RECORDING

Acid reflux was defined as a fall of oesophageal pH to 4 or less for 4 or more seconds. The pH changes associated with each common cavity episode were evaluated by reading the pH 5 seconds before and 5 seconds after the onset of the common cavity episode. The pH nadir during the common cavity episode was also noted.

5.4 STATISTICAL ANALYSIS

Incidence of transient UOS relaxations among symptom groups and between neurological divisions were compared with Chi squared tests. Incidence of transient UOS relaxations was compared to oesophageal acidification, change of oesophageal body pressure and extent of communication using Chi squared tests.

Differences among nadir pressures of transient UOS relaxations occurring before the onset of the common cavity, and the first, second and third and subsequent transient UOS relaxations after the onset of the common cavity were analysed as a single factor experiment with adjustment for unequal sample size (Weiner 1962).

6. RESULTS

One hundred and one transient UOS relaxations, as defined in Methods, occurred in 60 of the 112 common cavity episodes. Figure 6.4 shows the distribution with time; 49% occurred in the first four seconds after the onset of the common cavity episode and 34% were scattered over the 5th-27th seconds after the onset of the common cavity. The remaining 17% occurred over the 10 seconds preceding the onset of common cavity episode, being evenly distributed through this time. The majority of common cavity episodes had a single transient UOS relaxation, but up to 5 were observed during a single episode. There were 65 first transient UOS relaxations, 24 second transient UOS relaxations, and 12 third and subsequent transient UOS relaxations.

No grouping of the patients according to symptoms or the presence or absence of neurological deficit revealed any difference in incidence of transient UOS relaxations.

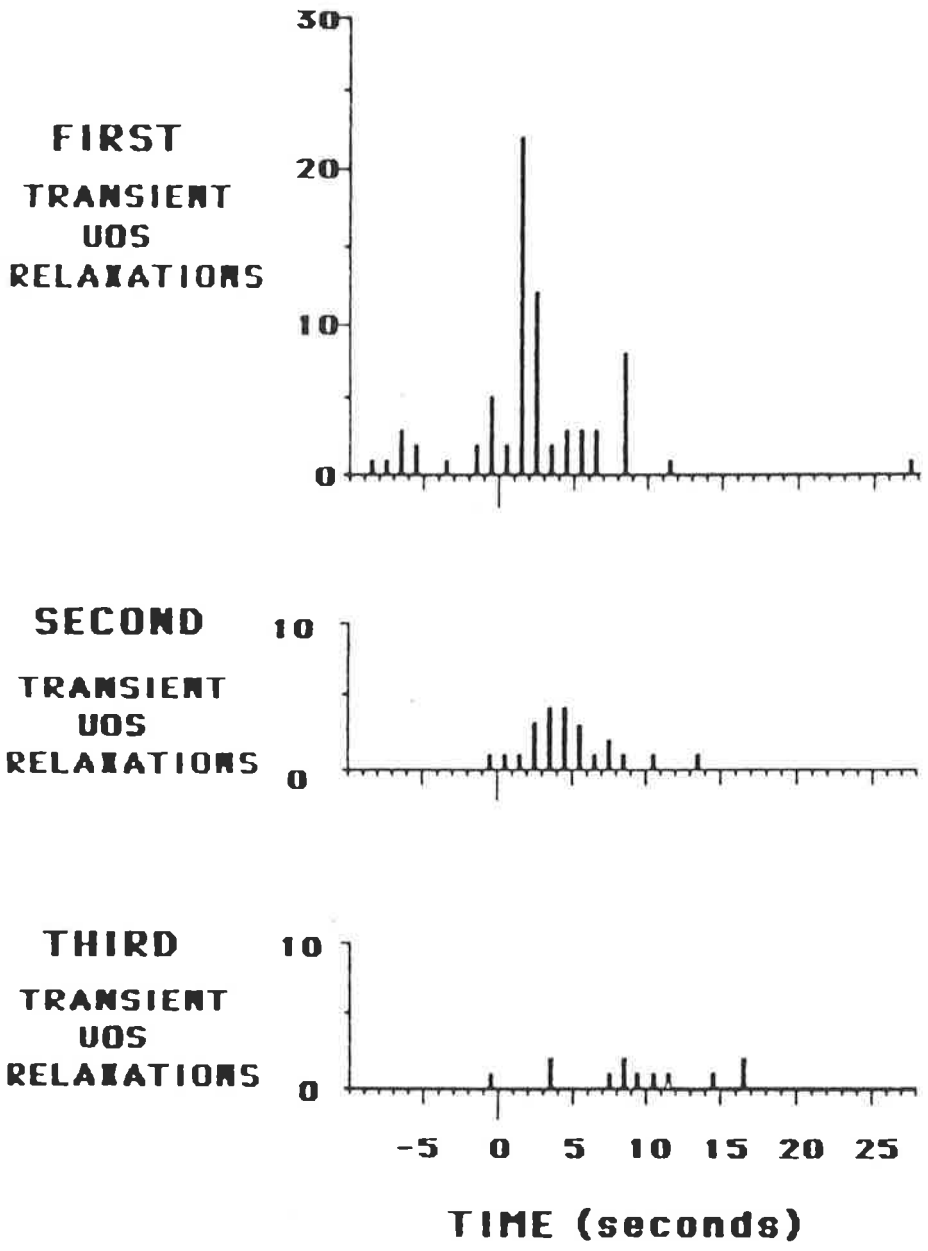

Figure 6.4 Timing of transient UOS relaxations with respect to the onset of the common cavity episodes.

The range of nadir pressures of transient UOS relaxations before and after the common cavity episode is shown in Figure 6.5. The nadir pressures of the first post common cavity onset transient UOS relaxations differ significantly from the first pre common cavity onset nadir pressures ($p<0.05$), and differ significantly from the combined group of first pre common cavity episode relaxations, and second, third and subsequent post common cavity onset relaxations ($p<0.05$).

The duration of the nadir could only be graded into coarse divisions of <1 second, 1-2 seconds, >2 seconds, as the paper speed at which the recordings were made did not allow greater accuracy. Eighty two percent lasted <1 second, 16% were from 1-2 seconds, and 2% were >2 seconds. There were no differences in the duration of the nadirs of transient UOS relaxations according to symptom groups or timing relative to the common cavity onset.

Triggering of transient UOS relaxations by oesophageal distension was measured in two ways. Table 6.1 shows the change in oesophageal body pressure that occurred during common cavity episodes.

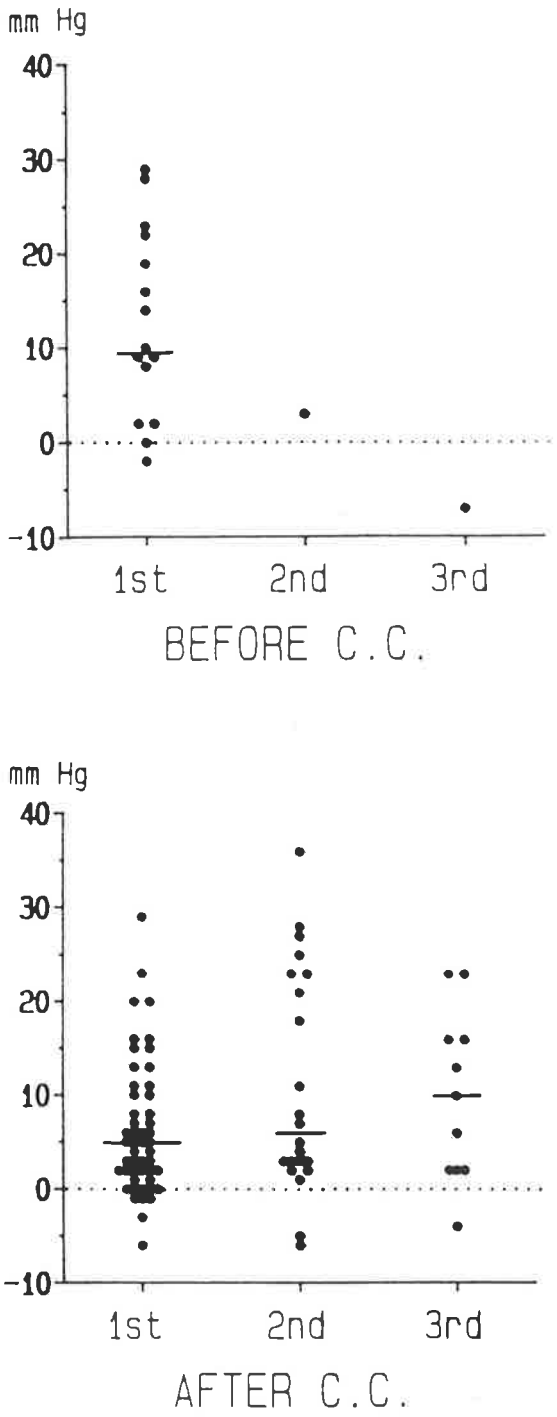

Figure 6.5 Nadir pressure of the transient UOS relaxations. Bars show median values.

Table 6.1

Relationship between increasing oesophageal body pressure and triggering of transient UOS relaxations

Oesophageal Body Pressure (mmHg)	3-5	6-8	9-11	12-21
No. of Episodes With Relaxations	19	33	11	2
No. of Episodes Without Relaxations	18	20	8	1

Note: There was no significant difference between the numbers that triggered transient UOS relaxations and those that did not.

Table 6.2 shows the completeness of communication between the stomach and oesophagus, as indicated by similarity of gastric and oesophageal pressure oscillations.

Table 6.2

Relationship between percentage of time oesophageal body pressure and gastric pressure are identical, and transient UOS relaxations

Length of Time With Communication (%)	0-49	50-99	100
No of Episodes With Relaxations	19	33	11
No of Episodes Without Relaxations	18	20	8

Note: There was no significant difference between the numbers that triggered transient UOS relaxations and those that did not.

In all but one of the common cavity episodes the pressure elevation was seen in all oesophageal body manometric recording ports.

The effect of acidification on triggering of transient UOS relaxations was tested by comparing the numbers of acid negative (48/84) and acid positive (14/22) episodes which triggered transient UOS relaxations. These proportions were not significantly different ($p>0.05$).

7. DISCUSSION

Abrupt relaxations of the UOS are seen in healthy adults after abrupt oesophageal distention with insufflated gas or gas GOR. They are the basis for the audible component of belching through oesophago-pharyngeal passage of gas (Kahrilas *et al.* 1986) and occur independently of swallowing, having a somewhat longer time course than the swallow induced UOS relaxation. It is thought that these relaxations are a safety valve to prevent injury of the oesophagus due to excessive force by distention. The present analysis was designed to determine whether transient UOS relaxations occur during GOR in children, and in fact, demonstrated evidence of such relaxations during episodes of spontaneous GOR.

The analysis approach used also identified dips of UOS pressure that occurred in the control period prior to the onset of oesophageal distention by GOR. These apparent transient UOS relaxations are probably misclassified events, since the criteria used to screen the manometric tracing for transient UOS relaxations were necessarily broad. In support of this, the mean nadir pressure of these pre common cavity UOS relaxations was significantly higher than that of

the first relaxations that occurred during the common cavity episodes. Respiration induced dips of UOS pressure are the most likely cause for these apparent transient UOS relaxations, and it is likely that a similar number of these were scored during the common cavity episodes as well. Despite this presumed noise in the analysis there is good evidence of a response to oesophageal distention, in view of the clustering of transient UOS relaxations predominantly into the first few seconds of oesophageal distention. This is consistent with the triggering of transient UOS relaxations reported by Kahrilas *et al.* (1986) in adults. The pattern of relaxations was similar to those found in adults with respect to timing, nadir pressure and duration.

Acidification of the oesophagus in the presence of distention had no effect on triggering of transient UOS relaxations, as can be seen by the proportions of common cavity episodes with and without acidification which were associated with transient UOS relaxations. This finding confirms a report by Vakil *et al.* (1989) which found that there was no correlation between oesophageal acidification and occurrence of transient UOS relaxations in normal volunteers or in patients with oesophagitis. There were no transient UOS relaxations in the three episodes of acidification of the oesophagus without associated common cavity episodes, however this sample is too small to draw any firm conclusions.

These transient UOS relaxations, whilst triggered by oesophageal distention, do not always occur. There may be a critical level of distention required before triggering can ensue. Kahrilas *et al.* (1986) found that the extent of distention of the oesophagus has a bearing on the reaction of the oesophagus. He also found a large amount of variation amongst individuals with respect to the

size of the stimulus required to elicit a response. An attempt was made to quantify the amplitude of distention of the oesophagus to test this effect in children. Distention was scored in two ways. The first was by measuring the change in basal oesophageal body pressure from before the onset of the common cavity episode with basal oesophageal pressure after the onset. This gave a wide range of pressure changes, but, when correlated to incidence of transient UOS relaxations, showed no influence on triggering of the relaxations. The lack of correlation may be due to the relatively large range of oesophageal volumes in this age range, so that a small pressure change in a young child may distend the oesophagus more fully than a larger pressure change in an older child.

The second method of measuring the extent of distention was by looking at the extent of communication between the stomach and oesophagus. This was based on the assumption that a fully distended oesophagus will be at the same pressure as the stomach, will have complete transmission of the pressure changes up the column of oesophageal contents, and so will show gastric pressure changes in the oesophageal tracings. If there is only partial filling of the oesophagus the LOS will restrict the transmission of pressure changes and there will be oesophageal patterns on the oesophageal manometric channels. The comparison of number of transient UOS relaxations and percent time in communication showed no correlation. All but one common cavity episode extended the full length of the oesophageal body, so no comment can be made on differential distention of the oesophagus.

Neither of these relatively crude measures suggest that there was any correlation of degree or duration of oesophageal distention with triggering of transient UOS relaxations, however this does not

exclude the possibility that there is a correlation between these things. Kahrilas *et al.* (1986) did find such a dose response relationship in adults, but also considerable variation in thresholds for triggering of transient UOS relaxations amongst different adult subjects. There is a possibility that transient UOS relaxations may be unusually easily triggered in some subjects and so predispose them to oesophago-pharyngeal reflux. This theory requires direct examination by correlation of events following spontaneous GOR episodes in which the volume of refluxate is monitored scintigraphically, or by standardised testing of thresholds for transient UOS relaxations in infants by air insufflation.

The comparison of symptom groups and incidence of transient UOS relaxations did not identify any group that was more susceptible to relaxations, and thereby possibly more susceptible to OPR, however this may be due to the problems mentioned above.

These findings suggest that transient relaxations of the UOS in response to distention may be a cause of OPR but no specific pathology of the UOS has been found.

CHAPTER 7

DISCUSSION

The success of this project relied on the appropriateness of the sleeve sensor for monitoring of UOS pressure in unsedated children. It has been shown to be both well tolerated by the children, and technically effective. As well as overcoming the fundamental problems of UOS measurement such as sphincter asymmetry and mobility, and allowing monitoring of UOS pressure rather than sampling pressure, the technique has overcome the major problems facing paediatric researchers in this area, namely patient distress and the necessity to overcome that, usually by sedation.

These studies of the UOS in children show that it functions in much the same way as the adult UOS. Interpretation of basal tone needs caution, taking into account the level of arousal of the subject. This aspect of recording of UOS function is more relevant to children than adults as the level of alertness in children may range from asleep to highly distressed, with rapid changes between levels, compared to most adult subjects who may be more or less nervous but are still cooperative and alert.

The UOS has been shown to react to stimuli within the oesophageal body. Distention of the oesophagus by GOR led to both an increase in UOS pressure, and transient relaxations of a similar type to those seen in adults (Kahrilas *et al.* 1986). Straining also caused an increase in UOS pressure. These effects have been recorded in adults (Anvari *et al.* 1987, 1991, Kahrilas *et al.* 1986). The fact that I recorded them in this age group indicates that the reflexes seem to be in place from two months onward. Whether they are slow to develop in some infants, or are not present in premature infants is an area requiring further investigation.

I have considered the three concepts of UOS dysfunction which would allow OPR to occur.

Briefly, these concepts are:

that sphincter tone may be chronically too low, allowing retrograde flow at any time;

that the sphincter may not respond appropriately to stimuli such as distention or straining, allowing retrograde flow when stressed;

that the sphincter may relax inappropriately, allowing retrograde flow if there is material in the oesophagus.

Whilst there is no evidence to support any of these theories, there is evidence to refute the first two possibilities.

The evidence against the theory of lowered basal UOS tone allowing OPR is the range of pressures the UOS attains and the lack of difference between the patients with symptoms of OPR and those without. The control children also showed similar patterns of response and ranges of pressures as the patients.

The theory that the UOS may respond inappropriately to stimuli such as straining or distention of the oesophagus has not been upheld. Although the small numbers of patients in some groups in the straining experiment made the statistical analysis unreliable in some cases, in the cases where there was a large enough sample there was either no difference between the group with OPR and those without, or the group with OPR had a higher UOS pressure than the non-regurgitators. The information found about distention of the oesophagus indicates that distention does stimulate an increase in basal UOS pressure. Again, the lack of difference in response between the groups of patients refutes the theory that those with OPR have a hyporesponsive sphincter. These data fit with that recorded in adults, especially that collected with sleeve sensors (Kahrilas *et al.* 1986).

The fact that transient relaxations of the UOS were found indicates that inappropriate relaxation of the UOS may occur, however this was not supported by any difference in incidence found when the groups of patients were compared.

The lack of difference between the OPR and non-OPR groups may be because the patient groups weren't sufficiently divided. They were divided on the basis of their main presenting symptom, however a number of children had more than one presenting symptom, creating overlap between the groups. A difference may be found if comparisons were made between either end of the spectrum rather than dividing the group in two. Prospective rather than retrospective enrolment may allow better division of patients. Also, systematic sleeve measurements of UOS function can be made in children with well defined disorders. An intermittent failure of the protective mechanism would be more difficult to identify and characterise. There is also the possibility that the problem may not be the sphincter itself, but other control mechanisms below the sphincter.

One aim of this study was the documentation of UOS pressure during regurgitation events. Although some events occurred during monitoring periods they did not fit into our criteria as they were immediately followed by rapid swallowing, coughing, crying or a combination of events. The resulting artefacts added so many extraneous factors that no statement could be made about UOS pressure changes, either basal or transient.

There are modifications of the present method that would enable more effective recording of episodes of OPR and give better insights into UOS function in children. Measurement of pharyngeal pH would give a direct indication of acid OPR during recording with little extra inconvenience. With very small pH sensors becoming available

minimal discomfort in the pharynx would occur.

Catheters capable of measuring UOS pressure from infants in the first two months of life may record more episodes of OPR, and therefore potentially more that are suitable for analysis. Prolonged recording, or periods of recording from the same child over several days, may help. This would be especially feasible in the group I have called the control group, which have no gastrointestinal problems but a requirement for nasogastric feeding for other medical purposes. Measurements made in this group of children would give valuable information about those children who may be called 'normal' with respect to their gastrointestinal function.

To achieve more successful quantitation of UOS pressure during spontaneous strains, the problem of the lag time of the sleeve needs to be overcome. Measurement of the UOS as the primary objective would allow optimal positioning of the UOS on the proximal end of the sleeve, improving the response rate markedly. Modification of the sleeve with a stiffer membrane will increase the response rate, giving a faster rise rate. There are problems with this, as silicon rubber, the material currently used, is not stiff enough, and other materials such as dialysis membranes, which have the required stiffness, pose problems in the manufacture of the sleeves. Smaller sleeves may be used as they have a better rise rate, but less absolute fidelity. An array of closely spaced sideholes or intraluminal transducers over the length of the UOS sleeve would seem to be beneficial, however the sideholes would exude perfusate into the pharynx, creating problems with swallowing and fluid load, and the intraluminal transducers are as yet too bulky for this application. Both the sideholes and the intraluminal transducers also have the disadvantages of positioning outlined in Chapter 1

(section 2.2.2).

There are also alternative methods of assessing function of the UOS and related areas. Analysis of peristalsis, both primary and secondary, may show that children with OPR have defective bolus transport or defective clearance of refluxate from the oesophagus, thus allowing more opportunity for OPR to occur. These analyses can be carried out on spontaneous recordings, as the present analyses have been, although conditions may not be ideal. If standardised tests can be developed which do not require the co-operation of the subject they would be useful, however the investigator has no control over variables such as length of time between swallows when studying this age group. Secondary peristalsis can be tested using standardised distention of the oesophagus with air or liquid boluses.

Testing of trigger points for transient relaxations of the UOS can be achieved with graded distention of the oesophagus. This would answer the question of whether these relaxations are more easily triggered in those with OPR than those without OPR.

Continuous scintigraphy combined with manometry would give direct feedback on the occurrence of both GOR and OPR, as well as information as to the volume of the refluxate, amount of oesophageal distention caused and the height of the liquid refluxate column in the oesophagus. This has been done with pH and scintigraphy (Mittal *et al.* 1987), and adding manometry should present minimal further problems.

Digitisation and storage of the manometry and pH recordings would benefit all the methods outlined by providing the capacity to expand the time base of the tracing, allowing the temporal relationships to be examined with more sensitivity and accuracy.

This thesis indicates the feasibility of addressing unanswered

questions about function of UOS with the techniques which are now established, despite the substantial practical and ethical constraints on such studies in children. The major priority for further study is recording and precisely timing motor events of the pharynx, UOS and oesophageal body with episodes of OPR. This would lead to the generation of hypotheses concerning the nature of the control dysfunctions that lead to OPR in children, and hopefully, major new insights into the pathogenesis of regurgitation.

APPENDIX

Published work arising from the research presented in this thesis.

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ERRATA

piv, line 6 'writted', read as 'written'

p45, line 10 'category A to category B', read as 'arousal state A to arousal state B'

ADDENDA

p25(a)

SUMMARY OF AIMS

1) To investigate whether basal UOS hypotonicity correlates with the presence of symptoms indicating OPR, or with the occurrence of OPR.

2) To investigate the response of the UOS to a) straining, b) distention and c) acidification of the oesophagus, and to relate these findings to the occurrence of OPR.

3) To investigate whether infants and young children demonstrate transient, non-swallow related relaxations of the UOS, and to relate these relaxations to the occurrence of OPR.

p30, line 7 Following 'dimensions', reference '(Dent 1976)'

p30, line 12 Following 'sleeve sensors.' 'The UOS was positioned as close as possible to the proximal end of the sleeve sensor to ensure as rapid a rise rate as possible.