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Publication date:
2010

Document Version
Publisher's PDF, also known as Version of record

Link to publication from Aalborg University

Citation for published version (APA):
Gravesen, F. H. (2010). *Measurement of the axial force during primary peristalsis in the oesophagus using a novel electrical impedance technology*. Center for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Aalborg University.

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Measurement of the axial force during primary peristalsis in the oesophagus using a novel electrical impedance technology

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This thesis is partly based on three scientific studies, which are referred to in the text by Roman numerals. The studies have been carried out in the period from 2006-2009 at Mech-Sense, Department of Gastroenterology, Aalborg Hospital in collaboration with Centre for Sensory-Motor Interactions (SMI), Aalborg University. This is the electronic version. Papers are not included.

I. **Gravesen FH**, McMahon BP, Drewes AM and Gregersen H. *"Measurement of the axial force during primary peristalsis in the oesophagus using a novel electrical impedance technology"*, Physiological Measurement 2008; 29(3):389-399

II. **Gravesen FH**, Gregersen H, Arendt-Nielsen L and Drewes AM. *"Reproducibility of axial force and manometric recordings in the oesophagus during wet and dry swallows"*, Neurogastroenterology and Motility, 2009, E-pub ahead of print.

III. **Gravesen FH**, Behan N, Drewes AM and Gregersen H. *"The viscosity of food boluses affects the axial force in the oesophagus"*, Submitted to Digestive Diseases and Sciences

ISBN: 978-87-7094-055-9

Acknowledgments

This Ph.D. thesis is based on experimental investigations carried out from 2006 to 2009 during my employment at the Centre for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Aalborg University and Mech-Sense at the Department of Medical Gastroenterology, Aalborg Hospital, Århus University Hospital.

I owe my most sincerely gratitude to my main supervisors Professor MD., Ph.D., DMSc., Asbjørn Mohr Drewes and Professor MD., DMSc., MPM Hans Gregersen, for outstanding inspiration, encouragement, supervision and positive criticism of the research projects and manuscripts. Furthermore I want to express my thankfulness to my other supervisor Professor M.Sc., Ph.D., DMSc Lars Arendt-Nielsen, who have provided excellent research conditions and have contributed to my scientific work in any aspect including advice, inspiration and fruitful discussions.

I want to express my appreciation to Barry McMahon for inspiration, technical discussions, and for never letting me forget the words of Tom Hanks[1]. My gratitude also goes to Peter Kunwald for long discussions about technological issues. I would like to thank Christina Brock for making hard times easier and for always having energy to be present.

For practical assistance during experiments and logistics regarding recruitment of healthy volunteers, I want to thank Mech-Sense research nurses Birgit Koch-Henriksen and Isabelle M. Larsen, for their never lacking support and helpfulness. Also I like to give my grateful thanks to all colleagues at Mech-Sense for creating an inspiring and positive work environment.

I have a special thank to all the volunteers who participated in these comprehensive experiments, without their contribution this research project would not have been possible.

I would also like to thank Professor Jan Tack at the Centre for Gastroenterological Research, KU Leuven, Belgium for the interest in my work and for giving me the opportunity to collect patient data which are included in this thesis as preliminary data. I would also like to thank his very good colleagues Kathleen Blondeau and Rita De Vos for assistance during the patient data collection and giving me wonderful insight into the laboratories in Leuven.

The work has received financial support from “Det Obelske Familiefond”, “SparNord Fonden” and “Karen Elise Jensens Fond”. All contributions have been of great value.

Last but not least, I want to thank my family, especially Iben for her never failing support, and my children Celina and Caitlin for their never failing task of putting a smile on my face.

Flemming Gravesen – December 2009, Aalborg, Denmark

[1] “If it was easy, everybody would be doing it!” - From the movie “A League Of Their Own”.

Summary

The mean deglutition frequency in man is 585 times per day. Each deglutition involves the oesophagus, which facilitates the complex transport mechanism from the mouth to the stomach. The transport mechanism is named peristalsis. The conventional clinical tool to examine motility is manometry. It measures the squeeze of oesophageal contractions at multiple locations. The squeeze is measured as radial pressure often by water perfused manometry systems. Only preliminary studies have been able to measure the actual function of the oesophagus that is to push or transport a bolus in the axial direction into the stomach. The objectives of the studies giving basis for the current thesis were: to construct and test an impedance based probe able to measure axial force and manometry generated during primary peristalsis; to verify the reproducibility in vivo; to study how peristalsis are modulated by viscosity and to examine how axial force and manometry can contribute to a better understanding in the examination of patients (preliminary data).

A probe, able to measure axial force and manometry at multiple sites, were constructed. The axial force transducer was based on impedance technology. The first probe version was sensitive to bending and temperature changes and a second version was further developed. The length of the axial force transducer was, in the second probe, reduced from 10 cm to 1.5cm and the diameter from 6.1 mm to 4.6 mm. Both versions had an inflatable bag mounted distal to the force transducer, which mimicked a food bolus in vivo. The first probe was tested in vitro and on one volunteer. The second probe was tested against previous studies strain gauges technique in an in vitro setup. The difference was minimal and acceptable. The in-vivo protocol included five dry swallows and five wet swallows. This was repeated with 0 ml, 2 ml, 4 ml and 6 ml of fluids in the bag mounted distal to the axial force.

Ten healthy volunteers were examined twice and the reproducibility of axial force and manometry measurements was verified. The axial force amplitude increased 129% and 117% when 0 ml and 6 ml bag volume for dry and wet swallows were compared. For manometry the increase was only 28% (dry) and 25% (wet). This indicates that axial force was more sensitive to modulations than manometry. In general no association between manometry and axial force was found at higher bag volumes (4 ml and 6 ml). This indicates that different information is gained from the two modalities.

Using the developed probe peristaltic modulation with increasing bolus viscosity was studied. Six healthy volunteers swallowed 5- and 10-mL fluid boluses with viscosities in the range of 1mPa·s to 10kPa·s during simultaneous measurement of axial force and pressure in the esophagus. Both axial force and manometry measurements showed prolonged contraction duration with increasing bolus viscosity. Axial force and pressure showed a relatively high correlation at low bolus viscosities. The association became weaker at higher viscosities. The pressure amplitude and axial force amplitude was not modulated by viscosity, but axial force amplitude increased marginally with bolus volume. Hence, pressure recordings failed to show some of the modulation shown with axial force measurements.

A preliminary study including 20 patients with a variety of upper gastrointestinal motility disorders was examined using the developed probe. The preliminary results show that axial force provides additional information and in combination with manometry, a better basis for patient classification and thereby a better treatment is created.

In conclusion a probe able to measure axial force and manometry simultaneously was tested and found acceptable both in vivo and in vitro. The developed probe can contribute considerable with information to better understand oesophageal peristalsis and thereby improve and validate treatment of patients.

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Chapter 1 *The oesophageal body*

Swallowing is an task we on average do 585 time per day[1]. Masticated food and fluids are transported into the oesophagus from the mouth, through the oesophagus and into the stomach. The swallowing process starts voluntarily but continues with involuntary and complex interactions to propel food into the stomach and intestines for further digestion. This chapter provides an overview of the oesophagus anatomy and function.

1.1 Anatomy of the oesophagus

1.1.1 Location and structure of the oesophagus

In an adult the oesophagus is an 18-26 cm long muscular flattened dynamic tube that consists of different muscle types. The oesophagus connects the pharynx to the stomach. At either end the oesophageal body is bordered by sphincters, both preventing backflow of food. The oesophagus descends anteriorly to the vertebral column through the superior and posterior mediastinum (Figure 1.1). After traversing the diaphragm at the diaphragmatic hiatus (T10 vertebral level) the oesophagus extends to the orifice of the cardia of the stomach at (T11 vertebral level).[2]

The musculature of the oesophagus below the cricopharyngeus constitutes three layers: the outer longitudinal muscle layer, the inner circular layer of the main muscle coat (the muscularis propria) and the muscle layer of the mucosa, the muscularis mucosae. The longitudinal muscle layer is as thick as or thicker than the underlying circular muscle. This is in contrast to the small bowel where the longitudinal muscle layer is thinner than the circular muscle layer[3]. The muscle type changes along the length of the oesophagus. The proximal third consists of striated muscle, the distal third of smooth muscles while the middle third is a mixture of the two.[4]

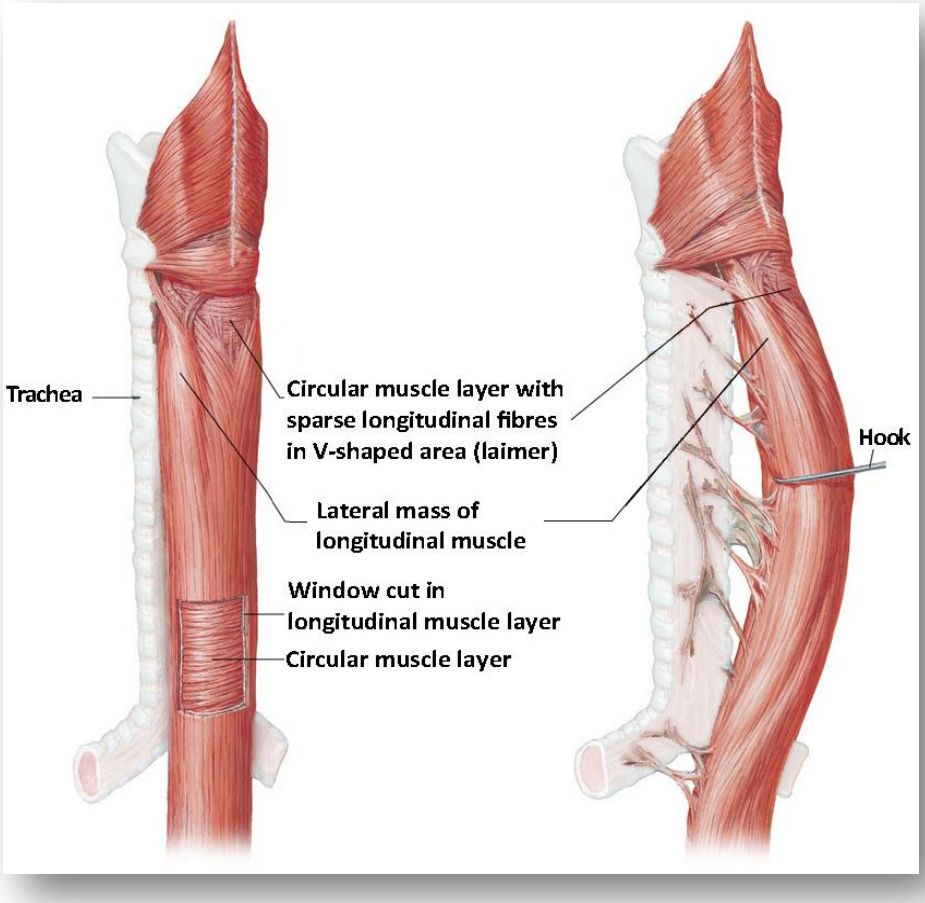


Figure 1.1: The oesophageal muscles with trachea. A small part of the longitudinal muscles are taken away (left) to show the circular muscle layer below. Image is adopted and modified from Netter medical illustration (netterimages.com; Image ID 604 and 4733).

1.2 Function of the oesophageal body

The function of the oesophageal body is to assist transportation of a bolus from the mouth to the stomach. The mechanical process, known as peristalsis, involves wavelike muscle contractions that move or push food or liquids through the digestive tract. At rest both the upper and lower sphincters are tonically contracted and therefore are closed with a high resting pressure (10-35 mmHg[5]). They open transiently to allow passage of the swallowed food into the stomach. At rest the oesophageal body is collapsed but can expand 2-3 cm to accommodate passage of food.[6]

1.3 Innervation of the oesophageal body

The oesophagus, like the rest of the viscera, receives dual sensory innervations from vagal and spinal nerves[7;8] (Figure 1.2). Oesophageal activity does not normally reach higher brain centres, except information related to pain or discomfort. When the oesophagus is damaged, for example by acid reflux, symptoms reported from patients are often vague and difficult to characterise[9].

Afferent neurons innervating the alimentary tract can be divided into two groups: 1) intrinsic sensory neurons that originate in the myentric plexus or submucosal plexus and 2) the extrinsic sensory neurons. The first group (intrinsic sensory neurons) are a part of the enteric nervous system, while the second group supply the central nervous system with information about electrolyte homeostasis, tissue integrity and sensation of pain. Additionally they follow the autonomic nervous system and consist of vagal and spinal afferents.[2;8] Afferent fibres in the oesophagus have free nerve endings and are either non-myelinated (70-90%) or thinly myelinated fibres belonging to the C or Aδ class, respectively[10]. Mucosa, submucosa, muscles, myenteric plexus and serosa are supplied by the vagal and spinal fibres and constitute 10-30 % of all nerve fibres[8].

The conscious sensation information carried by sensory nerves travel together with the spinal nerves[8]. The motor innervation of the oesophagus is predominantly mediated via the vagus nerve. The cell bodies of the vagal efferent fibres innervating the upper oesophageal sphincter and the proximal striated muscle arise in the nucleus ambiguous. Fibres destined for the distal smooth-muscle segment and the lower oesophageal sphincter originate in the dorsal motor nucleus of the vagus nerve.[2]

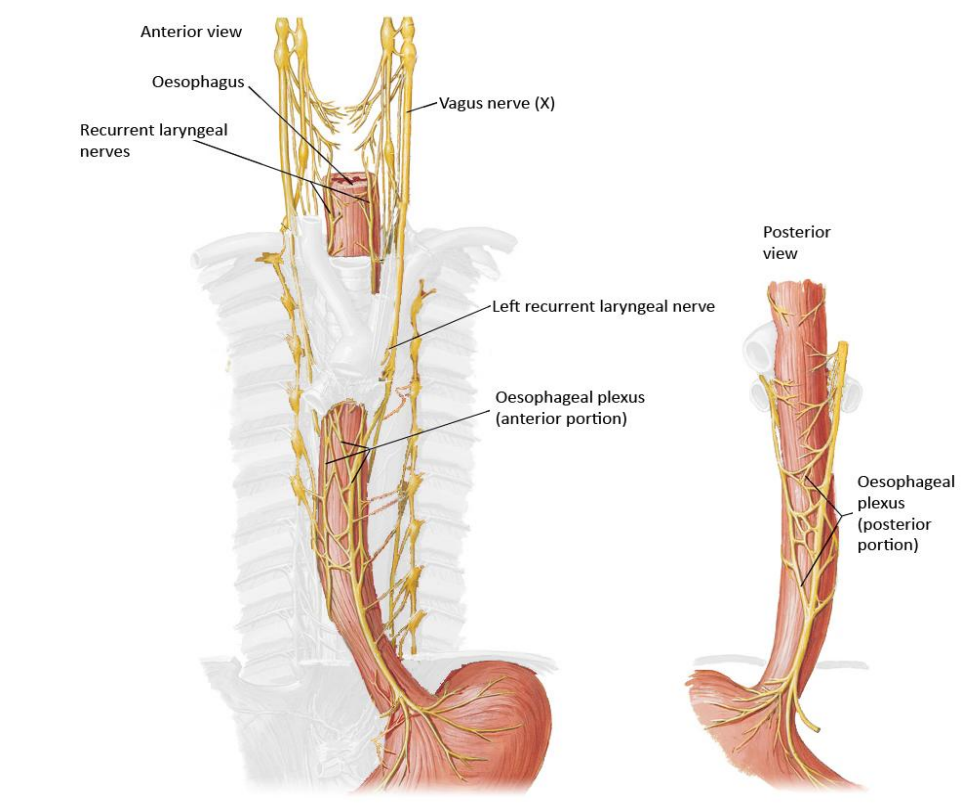


Figure 1.2: Innervation of the oesophagus. Note that both vagal and spinal nerves innervates. Image adopted and modified from Netter medical illustration. (netterimages.com; Image ID 631/4543).

1.4 Mechanics of oesophageal body during swallowing

The average deglutition frequency in man is 585 times per day with a range of 203 to 1008[1]. Each swallow starts complex coordinated neuro-motor activity and an involuntary cascade of longitudinal and circular muscles contractions. The sequence results in a peristaltic force in the oesophagus pushing the bolus aborally[11]. The interaction between the circular and longitudinal muscles is not fully understood[12]. Measured proximal to distal the oesophageal contraction amplitude increase (62 → 109 mmHg) as do the contraction duration (2.8 → 4.0 seconds)[13]. Circular muscle contractions are considered necessary to generate axial force but the propagating velocity or manometric measurements do not correlate very well with axial force[14;15]. This has lead to a theory that the relative thick longitudinal muscles play an important role in the generation of axial force and it has been supported in studies using various techniques[14;16-19]. As the axial force is generated on the basis of very complex interaction between the circular muscle, longitudinal muscle, mucosa and the bolus itself, it is very difficult to verify the function of each components role in axial force generation.

The interaction between the longitudinal and circular muscles is interesting and has been studied to some degree. Using mathematical models Brasseur and co-workers discovered that longitudinal muscle contractions reduced the tension on circular muscle fibres 10 times compared to generating the same force using circular muscles alone[20;21]. Electromyography (EMG) used in animal studies have shown that longitudinal contractions were followed by circular contractions[12;22]. Later in-vivo human

studies using mucosal clips and high frequency ultrasound confirmed that longitudinal muscle contractions starts before circular muscle contractions, but the duration was longer. Thus longitudinal contractions envelops circular muscle contraction[11;23;24].

Using high frequency ultrasound and axial force parameters related to longitudinal muscles have been found to correlate with axial force amplitude[11]. That included maximal contraction of the segment distal to the balloon and extended aboral movement. In relation no association was found for axial force amplitude and maximal circular muscle contractions quantified by manometry[11].

1.5 Oesophageal motility related disorders

Oesophageal motility related disorders are difficult to diagnose and examinations only provides indications of a certain disorder except for achalasia. Manometry is primarily used to classify the different groups of patients[5]. This is most often used as it is easy to apply but the manometric findings are nonspecific, thus there are often more than one diagnosis associated with a specific functional manometric pattern[25]. Motility related disorders are listed in Table 1.1 with a short description.

Table 1.1: Description and typical manometric pattern for motility related disorders. The table is a summary of the paper by J Ritcher in 2001[26] unless specified. LOS=Lower oesophageal sphincter.

Disorder	Description	Typical manometry findings
Achalasia	It has an unknown cause and is the only motility disorders with an established pathology. It results in failure to LOS relaxation.	Absent distal peristalsis Abnormal LOS relaxation Can have raised LOS pressure (>45mmHg)
Diffuse oesophageal spasm	Characterised by normal peristalsis intermittently interrupted by simultaneous contractions. Rarely defined by manometry.	Simultaneous contractions 20% of wet swallows Can have repetitive or multi peaked contractions (three peaks) Can have spontaneous contractions not associated with swallows Contraction amplitude >30 mm Hg but usually not high amplitude
Impaired oesophageal motility	Characterised by low amplitude, some simultaneous contractions or failed peristalsis. Heart burn and mild dysphagia. Most patients also suffer from gastro-oesophageal reflux disease[27].	30% or more low distal amplitude <30mmHg or failed non-transmitted contractions.
Nutcracker	Hypercontracting oesophagus. The high pressure zones occur within the oesophageal body. Chest pain is the main complain. Usually symptom free when the diagnosis is established by oesophageal manometry	Mean distal amplitude >180mmHg Normal peristalsis

Manometry is by many considered to be the “gold standard” when assessing oesophageal motor function[25] and is currently the best commercial available tool to classify motility disorders. Despite is status as being the “gold standard” even expert practitioners has poor inter-observer agreement in the analysis of clinical manometry[28;29]. Emerging technologies such as high resolution manometry is starting to show up in motility classifications[5] and it includes more advanced criteria such as transition

window and contractile front velocity[30]. It has enable achalasia to be sub-grouped into achalasia with aperistalsis, pan-oesophageal or vigorous achalasia[5]. The following sections describe different motility modalities used primarily in research.

1.6 Methods for evaluating the motility function

How the oesophagus transports a bolus has been the subject of investigations for a long time[31]. There are multiple techniques available. This is natural as the oesophageal function is very complex and it is not likely that a single technique can provide all relevant information. If it was possible to combine more examinations into one it would relieve patient discomfort while providing more information. Searching for a better technique, which facilitates more knowledge, might improve the characterization of motility related diseases. The following subsections describe different modalities used for motility evaluation.

1.6.1 Manometry

Manometry is the modality by which pressures is measured at different levels on a luminal catheter to determine the (radial) force applied by oesophageal squeezing. It is either measured by solid state transducers or water perfused system with external transducers.

Manometry has evolved very much in the last decade from being very simple with a few recordings into a procedure with more than 36 recordings separated by one centimetre intervals along the catheter (high resolution manometry). In effect, it shows radial activity from above the upper oesophageal sphincter to below the lower oesophageal sphincter[29]. The activity is not always related to muscle contractions as intrabolus pressure can interact[32]. Due to the introduction of pressure topography colour plots (Figure 1.3) it has very rapidly been adopted in both research and clinic thus the first classification system is already available[5].

A manometric system measures any change in pressure at the level of the transducer or side hole if water is perfused. The change can arise from both muscles and liquid running past the transducer. If liquid is present it is a measure of the intraluminal pressure, which is a measure of the hydrodynamic pressure[33] and not the direct work of the circular muscles. Mathematical models of bolus transport in the oesophagus have shown that changes in geometry of the liquid column changes intrabolus pressure. This is especially present at the liquid tail[34]. A non-occlusive contraction with liquid in the oesophageal body will show up as a mixture of intrabolus pressure and muscle contractions and make an interpretation difficult. In other words when the oesophagus occludes around the catheter the measured pressure is a reasonable indication of the degree of muscle force. Manometry is a measure of force per unit area. When the oesophagus is not occluded (little open or wide open) manometry measures the pressure in the space/air directly connected to the pressure sensor.

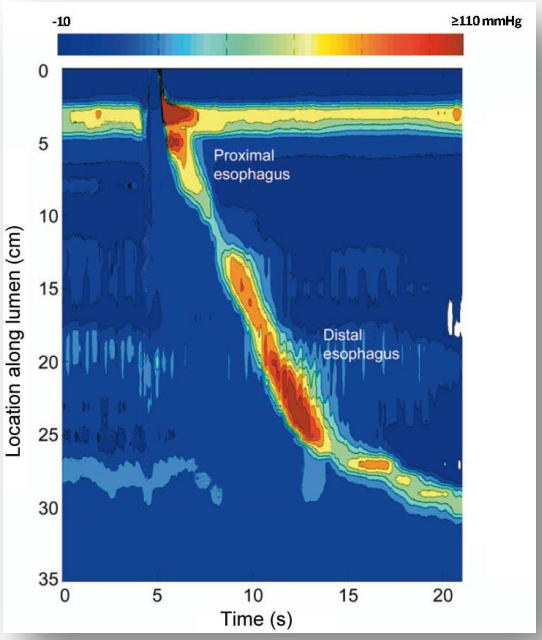


Figure 1.3: A typical colour typography generated on the basis of 36 solid state pressure recordings along the oesophageal body including clear markings of the upper and lower oesophageal sphincter during a swallow. The pressure amplitude is marked with colours with low pressures being blue and high being red (>110 mmHg). The successive contractions, which push the bolus aborally, are visible as red/orange/yellow tracings. Image adopted and modified from [Kahrilas & Sifrim 2008][35].

1.6.2 Fluoroscopy, ultrasonography and electromyography

Fluoroscopy of the gastrointestinal tract is based on radiographic examination. After swallowing contrast medium visible to x-rays (Barium sulphate) the mucosa is coated and visible as a hollow organ. This makes fluoroscopy examination essential when looking for anatomical abnormalities that change the mucosa[36]. Flow of the fluid/bolus will be controlled by oesophageal movements allowing radiologist to gain some knowledge of oesophageal motility. Fluoroscopy can show abnormal, normal and absence of peristalsis. Unfortunately the examination does not provide any quantitative muscle information. Additionally the images are only in 2D where a 3D rendering of the oesophagus would be better to reveal information that is hidden. As a result of these limitations the use of fluoroscopy requires skilled radiologists and even then it can be limited. The clear disadvantage of the method is exposure to radiation[4;37]. As a research tool, video fluoroscopy has been used to examine the shortening of the oesophagus, during swallows using radiopaque metal clips attached to the oesophageal wall[11;38].

High-frequency intraluminal ultrasound (HFIU) displays the oesophageal lumen and the different layers in real-time. HFIU provides images of the oesophagus with geometric information compared to standard manometry[23].This includes the thickness of the circular and longitudinal muscle layers[37]. Unfortunately a high inter-observer variability is present when inspecting HFIU images and further validation and standardisation are needed before it can be used in clinical practice[37;39]. Nevertheless some interesting results start to emerge in this area. In a recent HFIU study, Mittal and co-workers[40] examined 40 normal subjects and 94 patients using HFIU and manometry concurrently. They found an

increased oesophageal muscle thickness in patients with well-defined spastic motor disorders, i.e., achalasia, diffuse oesophageal spams, and nutcracker oesophagus compared to normal subjects. Also of interest is that 24% of the patients with increased wall thickness had normal manometry findings[40].

Electromyography (EMG) records the electrical activity of muscles from intramuscular electrodes or surface electrodes. Despite technical difficulties with artefacts from movements and blood flow[41], some studies have been accomplished. EMG is primarily used in the upper oesophagus and pharynx. Manometry and concurrent EMG recordings have shown that muscle activity can occur without any manometric activity. Pope and co-workers interpreted this as longitudinal muscle contractions without activity of the circular muscles.[42]

1.6.3 Multichannel intraluminal impedance

High resolution manometry lacks the ability to measure reflux and bolus travelling direction. To improve this manometry was combined with multichannel intraluminal impedance as it can detect bolus passage and its direction. The principle of intraluminal impedance is measuring electrical impedance between metal ring electrodes on a catheter and relating the signal deflections to the presence of liquids and gasses with various impedance characteristics. Using multiple detection electrode pairs it is possible to determine whether the bolus/gas is travelling orally or aboral. Depending on the content/material surrounding the electrodes potential difference (resistance) will change. The potential change will also depend on the current frequency and strength. Content includes oesophageal wall, air (belch, air swallowed) and liquids such as saline and gastric reflux each will change the impedance in a certain pattern. From the tracings it is possible to differentiate liquid, air and an occluded oesophagus. The direction of the material can be deduced from multiple measurements.[43]

Combining multichannel manometry and multichannel intraluminal impedance together provide information about oesophageal contraction and bolus transit. This is valuable information and used for motility testing, monitoring reflux and evaluation of bolus transport[44]. It has been used as a research tool and normal range data have been recorded and shown to serve as a better tool for diagnostic[29;45].

1.7 Impedance planimetry

Impedance planimetry (IP) is a technique developed within urology and later modified for bag distensions in the gastro intestinal tract by Gregersen and co-workers[46]. Impedance planimetry technique modified for axial force measurement is a modified way to make use of impedance planimetry (IP). The principle and theory are described in the following sections.

1.7.1 Principles of impedance planimetry

Impedance planimetry can be used to measure cross sectional area (CSA) in an inflatable bag. If the bag is placed inside the oesophagus the CSA will provide an estimate of luminal CSA of the oesophagus. Consider four electrodes and a bag mounted on a catheter as depicted in Figure 1.4. Electrolyte solutions obey Ohm's law similar to metallic conductors. When the bag is inflated with conductive fluid and a constant current (I) is induced between the two outer most (excitation) electrodes the potential difference (V) between the two inner (detection) electrodes is given by Ohm's law:

$$V = I \cdot R \tag{1.1.}$$

If the excitation electrodes are sufficiently far away from the detection electrode the electric field seen by the detection electrodes can be assumed uniform. The resistance, R is defined as in equation (1.2.), where d is the distance between the detection electrode, CSA is the cross-sectional area and ρ [Ohm m] is the resistivity while σ [1/(Ωm)] is the electrical conductance. The equation assumes a homogeneous body of uniform cross section and at constant temperature. The situation is sketched in Figure 1.4.

$$R = \frac{d \cdot \rho}{CSA} = \frac{d}{CSA \cdot \sigma} \tag{1.2.}$$

Combining equation (1.1.) and (1.2.) output voltage can be expressed as in equation (1.3.), but since electrode distance and conductivity of the fluid can be considered constant the equation can be reduced to equation (1.4.). As shown the voltage output will change as the CSA changes. The only unknown variable in the equation is the calibration factor K.

$$V_{output} = \frac{I \cdot d}{\sigma \cdot CSA} \tag{1.3.}$$

$$V_{output} = K \cdot CSA^{-1} \tag{1.4.}$$

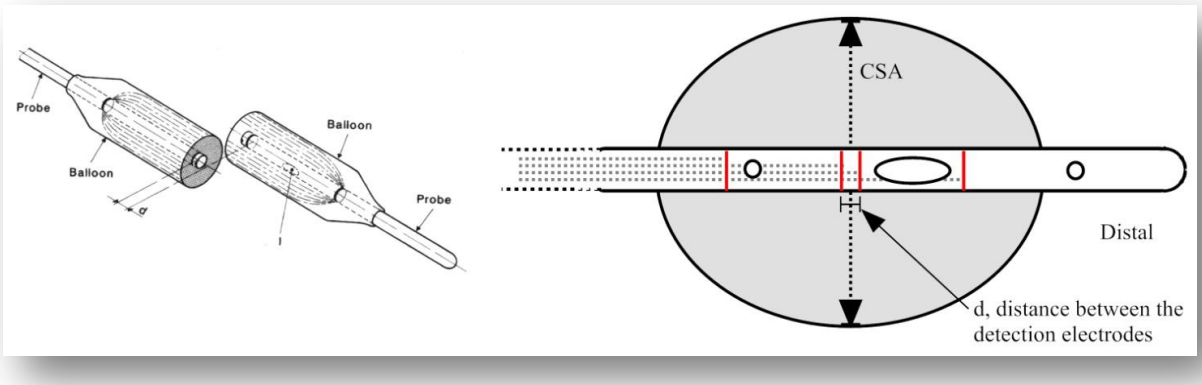


Figure 1.4 Left: Rotated view of the electrodes placed inside a bag with conductive fluid. Right: A transverse view of four electrodes place inside a bag. Left is adapted from [Gregersen 2003][47].

1.7.2 Sources of error

Different parameters result in errors when using traditional impedance planimetry. These include among others the slope of the bag wall between the sensing electrodes, temperature changes, and radial placement of the electrodes[46]. The sources of error related to the modified design are described below.

1.8 Axial force recordings techniques

In 1967 Winship and Zboralske were the first to describe a method to record axial force generated in the human oesophagus[17]. They used an external force transducer connected to a plastic sphere placed in the oesophagus. The setup enabled assessment of the oesophagus' ability to propel a bolus against a known resistance. In 1972 Pope and Horton used a mercury-in-silastic strain gauge which also had a plastic sphere mounted distally[14] (Figure 1.5Figure 1.2). This setup was used later by Schoen *et al*[48] to

examine peristalsis modulation in response to mechanical and pharmacological alterations. To minimize temperature dependency a mercury-in-silastic strain gauge was used by Russell and co-workers[15]. The last series of publications were based on a miniature strain gauge and published in the period from 1992 to 1997[11;19;49-51]. The strain gauge was not described in detail. The strain gauge techniques are summarized in Table 1.2.

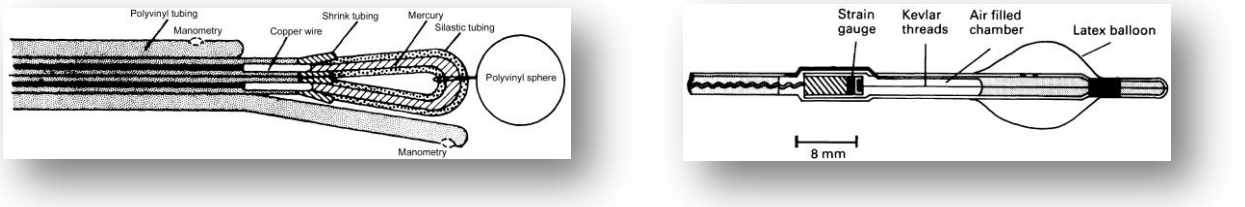


Figure 1.5: Left sketch shows the strain gauge construction used by Schoen and co-workers[48] in 1977. The construction did not enable in-vivo change of bolus diameter. The assembly had to be re-intubated to change the polyvinyl sphere size. Right: The miniature strain gauge construction used by Williams and co-workers in 1992-94[19;49-51].

The method used in paper (I), (II) and (III) is based on impedance technology. This approach is different from the techniques described briefly above. Our method could have been based on modern strain gauges as they are very small and can be found in many different shapes and types. There are, however, some issues that must be considered. Standard strain gauges are temperature dependent, sensitive to bending and to radial squeeze if not protected from outside. Additionally strain gauges can be difficult to mount hence make the construction difficult. These considerations are similar to those discussed in paper (I, II, III) when using a modified impedance approach. The construction of an axial force probe using strain gauge technique includes difficulties such as mounting of the gauges and material selection. The difficulties are similar when using impedance technique but as we in the research group have great expertise using impedance this was chosen.

1.9 Summary

High frequency ultrasound can provide information about muscle geometry which correlates with longitudinal shortening. The shortening can be used as an indirect measure for axial force (the function of the oesophagus) under normal conditions. It is clear that high frequency ultrasound is limited in measuring motor function as it does not incorporate the friction between the mucosa and bolus. Likewise fluoroscopy provides a visualisation of anatomical changes but lacks objective data. Manometry, on the other hand, provide data but is merely a proxy for oesophageal squeeze and it has been shown that the pressure amplitude does not correlate well with axial force generated by the oesophagus[11;14;15;49]. Despite the fact that axial force has shown good clinical results and differentiating it from manometry the method never gained widespread use and it is not commercially available.

Table 1.2: Summary of previous studies using axial force.

Authors and year	Technique	Size of obstruction	Examined
Winship & Zboralske[17] 1967	External force transducer (unspecific)	Air inflated bag (3-25ml) proximal transducer	Acute Obstruction Primary and secondary contractions
Pope and Horton[14] 1972	Strain gauge (mercury-filled silastic tubing) No active radial protection	Sphere 6.9-10.6 mm in diameter proximal transducer	Primary contractions. Frictional forces Obstructing diameter versus force Force versus oesophageal level Force versus Manometry
Schoen et al[48] 1977	Strain gauge (mercury-filled silastic tubing No active radial protection	Sphere 6 - 13mm In diameter proximal transducer	Primary contraction Force and pressure versus oesophageal level Force during drug administration (bethanechol, atrophine)
Russell et al[15] 1992	Force transducer (saline filled tubing) Capsule protection No bag mounted on probe	0 (probe 9 mm in diameter)	Primary contraction Force and pressure versus swallowed bolus
Williams et al[49]	Miniature strain gauge (unspecific)	0-12 ml inflation proximal transducer	Secondary contraction Threshold for inducing contractions
Williams et al[19;50] 1993	Miniature strain gauge (unspecific)	Distension of bag (0ml – 14 ml of air)	Secondary contraction (response to distension) Force versus oesophageal level Threshold for inducing contractions Propagation velocity
Williams et al[51] 1994	Miniature strain gauge (unspecific)	0-16 mm in diameter	Primary contraction Effect of bag volume Effect of swallowed bolus Force and pressure versus oesophageal level
Pouderoux et al[11] 1997	Miniature strain gauge	0-20 mm in diameter	Primary contraction Effect of bag volume Timing of oesophageal shortening versus force

Chapter 2 *Hypothesis & aims*

Today oesophageal motility is quantified by use of manometry. It is done by placing a catheter in the oesophagus where it measures radial pressure at multiple locations (squeeze of probe). Several studies have shown that manometry only is a proxy of the oesophageal propulsive force[11;14;15;49] and manometry patterns used to classify patients are overlapping. Hence, more than one diagnosis can be associated with a particular functional pattern[5;25;52]. Motility could in a more meaningful way physiologically be quantified with a measure of the force generated in the bolus by peristaltic contractions. This is the idea from which axial force recordings has emerged. Previous papers have referred to this phenomenon as:

- Propulsive force[11;15;17;53;54],
- Traction force[11;19;49-51] and
- Peristaltic force[14;48]

This thesis and paper (I), (II) and (III) have defined these concepts as axial force as this term includes both direction and content. It was hypothesised that forward propagated bolus by peristalsis in the oesophagus can be measured by a new axial force probe, and that the outcome is reproducible in healthy volunteers giving additional information about the motor function of the oesophagus compared to manometry alone.

2.1 Main objectives

The overall objective was to construct and test a probe capable of simultaneously measure axial force and multiple pressures in the oesophageal body. The probe should record force generated in axial direction, thus including the "grip" and push/pull effects in human volunteers and in patients with motor disorders of the oesophagus (supplementary data).

2.2 Specific aims

1) To develop an oesophageal probe capable of measuring axial force and pressure simultaneous
2) To verify the accuracy and reproducibility of the axial force measurement technique in vitro
3) To verify the reproducibility and measurement value of the axial force and pressure measurements for the evaluation of the human oesophageal function in vivo
4) To study the effect of bolus viscosity on axial force in the oesophagus during primary peristalsis
5) To study how axial force in combination with manometry can contribute to a better understanding in the examination of patients (preliminary data)

Chapter 3 *Methodological aspects*

This chapter will briefly describe how impedance planimetry was modified to measure axial force. Additionally there will also be a brief description of the handmade probes, the hardware and the developed software.

3.1 Impedance planimetry modified to measure axial force

The impedance planimetry technique can be modified in such a way that the distance between the electrodes is the variable, while other parameters of importance can be maintained constant. The modified construction of the probe is shown in Figure 3.1. This design will maintain a constant CSA and the original approach have changed as shown in equation (2.). The modification makes the calibration linear.

$$V_{output} = \left(\frac{I \cdot d}{\sigma \cdot CSA}\right) = d \cdot K \tag{3.1.}$$

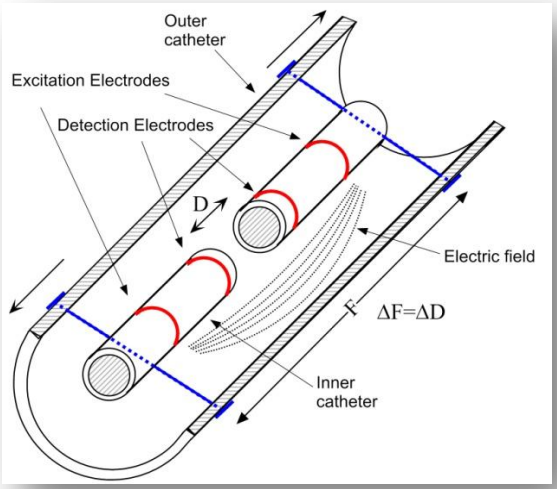


Figure 3.1: Axial force concept sketched in 3D. It shows how impedance planimetry was modified to measure axial force. If the elastic catheter filled with conductive fluid and force is applied to the end of the outer catheter it will move the inner catheter and thus the detection electrodes apart, while maintaining the CSA. The will results in a change of impedance that can be related to the force.

The distance between the excitation electrode and the detection electrode must be long enough to secure that the electric field is homogenous in the measurements range (between the detection electrodes). This is important when using the setup for CSA measurements because the distribution will be non-linear as the CSA increase. When using impedance in the modified version to measure axial force, the CSA does not change. Thus the excitation and detection electrodes can be short circuited. To prevent measurement instability around zero (when the electrodes are positioned close together) a resistor is put in between the excitation and detection electrode. This approach simplifies the construction and was used in paper (II) and (III).

3.2 Manometry

Pressure measurements were incorporated into the probes used in paper I-III. It consisted of a low compliance perfused system connected to external transducers (Edwards TruWave, Edwards Lifescience, Irvine, CA, USA) which were connected to the acquisition system. To be able to compare manometric measurements in (I), (II) and (III) the same tubes and perfusion rate was used.

3.3 Probe construction

A first version of an axial force probe was developed and tested in-vivo (I). It was tested using different in-vitro test setups and a single in-vivo experiment worked as a proof of concept. The relative long axial force section (10 cm) was needed to gain a sufficient voltage output range. This resulted in a long section where radial force and bending would have an influence.

The second version had a shorter section involved in the axial force measurements but to obtain a sufficient output voltage range a more elastic catheter was found (II, III). To obtain a reliable and reproducible measure of elongation and minimize the creep effect an elastic piece of catheter was found. The new design posed challenges to the choice of elastic material and a trip to the NATVAR facility in Belgium resulted in the selection of a proper material with minimized creep while maintaining its elasticity. Using the new material the transducer length was reduced from 10 cm to 1.5 cm. A sliding cylinder principle was found to be a good solution. The rigid cylinders prevented radial force and bending to influence the measurements, though still able to move apart in the axial direction. If a less rigid material was chosen the two cylinders could touch each other and the friction affect the axial force. This would compromise the linearity of the axial force recordings. This double cylinder construction had better temperature protection, hence decreased temperature fluctuations. A sketch of the second version is shown in paper II and in Figure 3.2. A picture of a probe before and after assembly is shown in Figure 3.3. The probe diameter was decreased from 6.1mm to 4.6mm providing better patient tolerance.

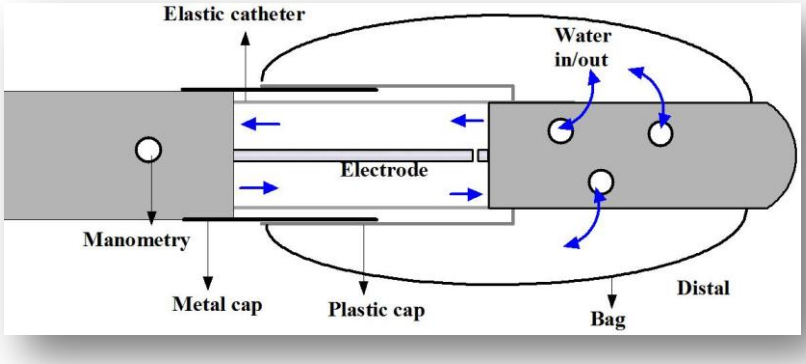


Figure 3.2: Schematic representation of the second axial force probe. Note the rigid metal and plastic cap. They are able to slide apart when axial force is applied to the distal part of the probe. Inside the elastic catheter the electrode moves apart when axial force was applied, thus the impedance measured between the electrodes increases.

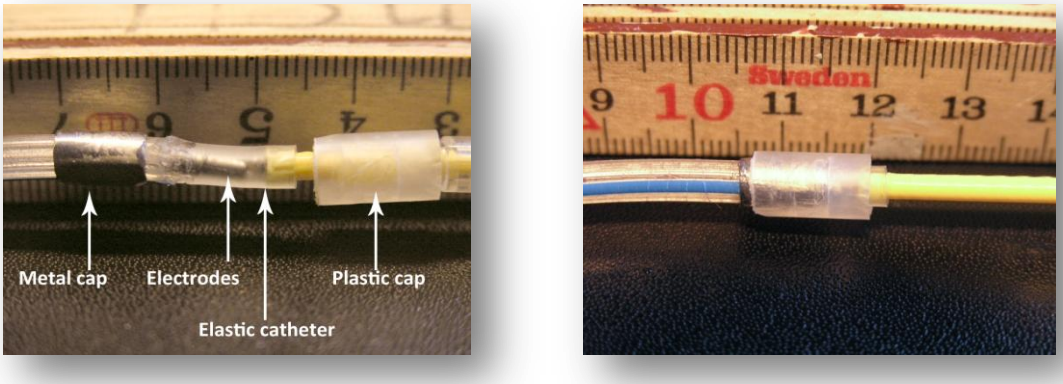


Figure 3.3: Left: The force section before assembly. The labels correspond to the schematic representation in Figure 3.2. The rigid cylinders are moved aside showing the elastic tube with the electrodes inside. Right: Force section after assembly. The bag is not mounted to enable better view.

The axial force probe layout used in paper (II) and (III) is shown in Figure 3.4. The longitudinal and cross section layout is shown together with the design of the bag and the dimensions of the force section.

3.3.1 Bag construction

The bag, mounted on the proximal part of the force section (Figure 3.2), was made of thin inelastic polyurethane. The inelastic property was chosen to optimize the force transfer from the bag to the transducer. The bag was made small to avoid the fluid inside to slosh around and thereby create an imprecise grip/obstruction. The bag could still not be too small as the bag should contain a minimum volume (6ml). The dimensions of the bag in flat dimension (two layers soldered together) are shown in Figure 3.4. The effective volume when inflated can be calculated as follow:

$$V_{effect} = V_{bag} - Vol_{Catheter1} - Vol_{Catheter2} \\ = \pi \cdot h_{bag} \cdot r_{bag}^2 - \pi \cdot h_{cat1} \cdot r_{cat1}^2 - \pi \cdot h_{cat2} \cdot r_{cat\_2}^2 \quad (3.1.)$$

The radius of the bag can then be calculated from circumference of the bag. The circumference of the bag is 2x the flat diameter, thus the effective volume is 12.1mL:

$$V_{effect} = \pi \cdot \left(\frac{\left(\frac{2 * 36mm}{\pi} \right)}{2} \right)^2 \cdot 30mm - \\ \pi \cdot \left(\frac{4.5mm}{2} \right)^2 \cdot 15mm - \pi \cdot \left(\frac{2.2mm}{2} \right)^2 \cdot 15mm = \mathbf{12.1mL} \quad (3.2.)$$

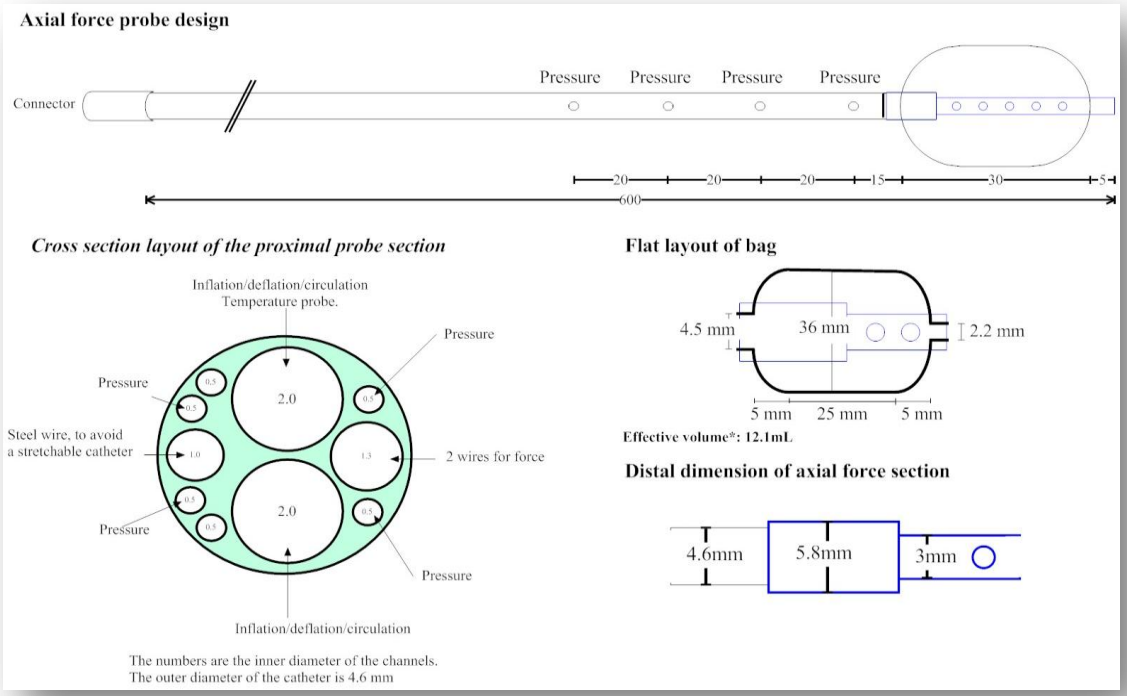


Figure 3.4: The axial force probe design. Top: Longitudinal layout with four manometric side holes, the axial force section and the bag. Left: Cross section layout of the channels in the proximal catheter. Right middle: The dimensions of the bag. The bag consists of two flat pieces of polyurethane soldered together. Right bottom: The dimensions of the force sections pieces without bag mounted.

3.4 Sources of error

The sources of error for impedance planimetry in general (also described in section 1.7.2) can only in minor degree be applied to this modified use of impedance. With the original version of impedance planimetry the errors arise from the change in cross-section area and its geometry. The cross-sectional area is constant in this modified version thus the related errors are minimized. The general and modified impedance techniques are temperature dependent. The dependency arise from the conductivity of the fluid with is temperature dependent[47]. The relationship between conductance and temperature can be described by the following equation:

$$\sigma_T = \sigma_{T_0} * [1 + \alpha_\sigma * (T - T_0)] \quad (3.3.)$$

where σ_0 is the conductivity at a given temperature T, and α_σ =2.14%/°C is the relative variation in conductance expressed in percentage of temperature change of one degree Celsius. For example standard saline (0.9% NaCl) has a conductivity of 1.5S/m at 25°C, at body temperature this conductivity will be increased to $\sigma_{37°C}$=1.89S/m. The temperature dependency is linear and can be minimized by measuring the temperature and correcting for any deviations from the calibrated values. The final probe design included a temperature sensor in the proximity of the electrodes; hence the influence was corrected for and minimized. The temperature will also influence the elastic properties of the tube but this influence is considered minimal when temperature fluctuations are between 32°C and 37°C.

Bending or twisting the force section result in erroneous measurements. As reported the probe designed and used in (I) was sensitive to exactly this but improved in (II) and (III). The elastic catheters properties, such as creep will also influence the results.

The choice of an in-elastic bag instead of an elastic balloon cause a changed in the way the oesophagus grips the bag. The bag construction enables the fluid inside to move around when the volume is low (2 ml). This will delay the grip of the peristaltic wave, as the fluid will be trapped in the distal part of the bag. At 4 ml and 6 ml the bag is filled to a level where this only influences minimally. Choosing an elastic material the volume would also be able to move around but would probably be less varying.

3.5 Data acquisition hardware and software

Commercial available data acquisition system was used to record both the axial force and manometry (GMC Medical, Hornslet, Denmark). The data flow chart is shown in Figure 3.5. The equipment provided a constant current of 100 μA at a frequency of 10 kHz between the electrodes. The measured voltage was amplified, rectified and sampled at 10 Hz by the data acquisition system. It was then transmitted to the PC through a serial connection (RS232 standard). The external pressure transducers were powered by the acquisition system and processed as axial force signals. The data were displayed online using custom-made data acquisition software programmed in LabVIEW® version 6.1 (National Instruments, Austin, TX, USA). The axial force data was calibrated to be recorded in grams and pressure in mmHg. The software enabled markers, with time and text information, to be added to the recorded data. The text information could be the bolus swallowed, volume in the bag or patient related events such as cough or initiated swallow. Finally the data for each study was exported to Matlab® format for later analysis.

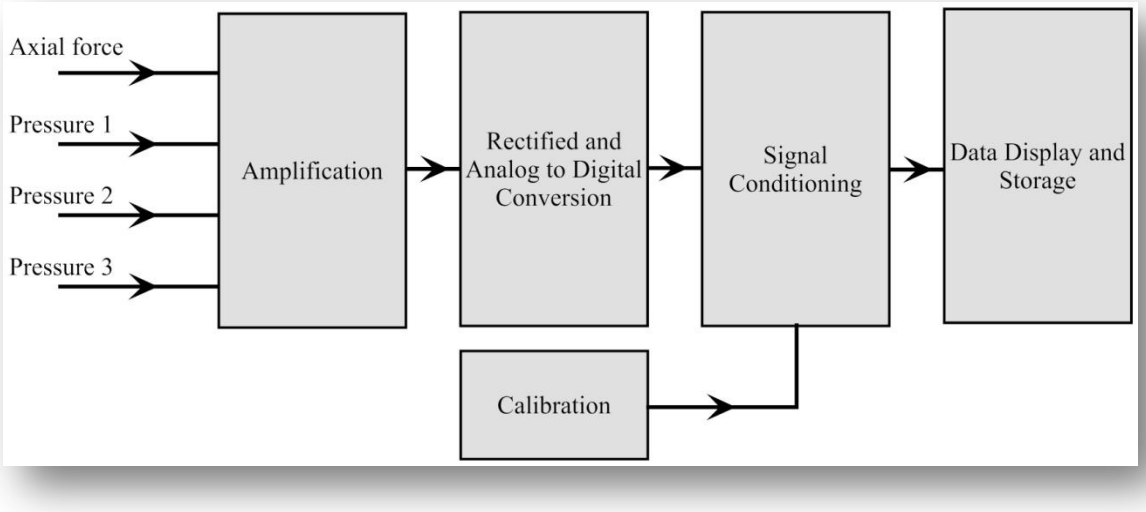


Figure 3.5: Data flow diagram of the axial force and pressure signals from recording site to display on-screen.

3.6 Data analysis software

The number of curves analyzed in paper (I), (II) and (III) exceeds 3000 as each swallows comprised one axial force and three manometric measurements. To optimize the analysis a custom made program was developed in MatLab® version 7.0 (MathWorks, Natick, MA, USA). The program took a semi-automatic approach for optimized performance. Each data set was first cut into pieces by the markers made in the acquisition program and verified manually on-screen. Hereafter the onset and offset of each swallow was defined by mouse clicks. The amplitude was automatically calculated by the software and stored together with the bag and bolus volume. After publication and in relation to patient data each curve was also categorized to fit different shapes. Each shape is described in section 5.2, Table 5.2. A flow chart of the analysis is shown in Figure 3.6.

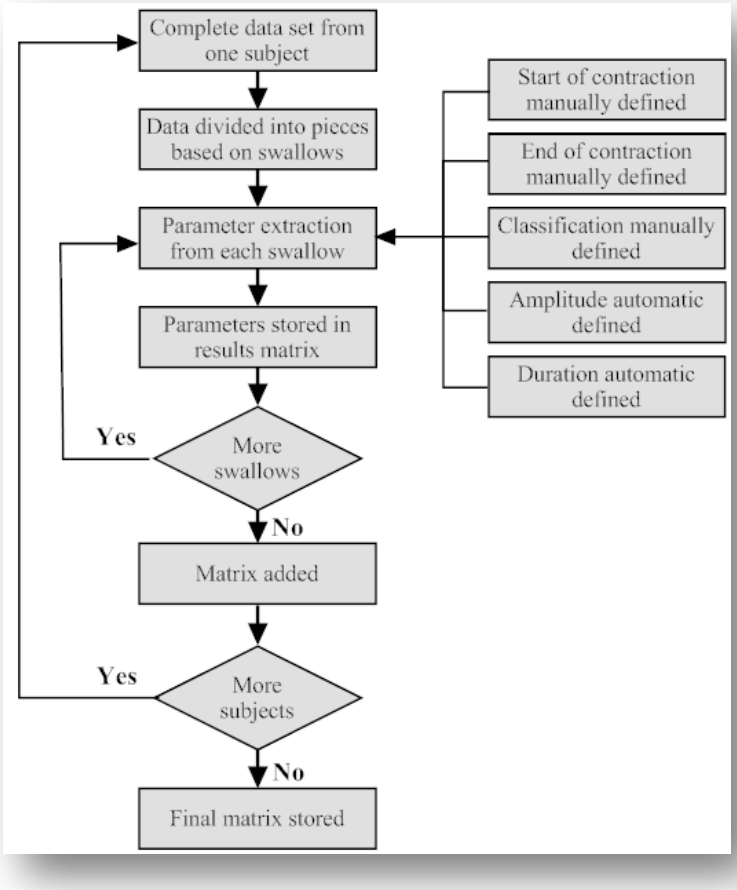


Figure 3.6: Flow diagram of the data analysis.

Chapter 4 *In vitro and In vivo studies*

Before starting in vivo studies probe must be verified in vitro. This chapter starts out discussing some of the in vitro results and leading to further discussion of the results from the in vivo studies.

4.1 In vitro studies

The first developed axial force probed described in paper I was tested in vitro to confirm its usefulness. In vitro tests for creep, bending, frequency response and dispersion were described and validated the method. It should be noted that the tests at 36.4°C was carried out in a whole room heated. This was made possible as we were able to borrow a small room at the Stem Cell Research Group at Aalborg University. It was necessary at least to heat that segment entering the body during the in vivo studies. It is believed that it does not to make a difference whether the entire probe or only the force section was heated, but this room enabled a stable temperature during the in vitro setup.

Similar in vitro tests of the optimised probe used in paper II and III was carried out. These were described in paper II. The axial force transducer was compared to a strain gauge recording as described in paper II. Normally the apparatus is used to measure samples of intestines from laboratory animals. The probe was suspended at each side of the apparatus and it was possible to control the speed of displacement using a computer. A sample of the recorded data recorded is shown in Figure 4.1. The clear difference between the two recording methods is the little time lag of strain gauge incline compared to the axial force recording. Additionally the shape at the resting point is different. The strain gauge recording shows some noise while the axial force recording shows slowly inclining curve. This is however not considered troublesome as the peak value was only about 30 g. Estimated the inclines are in the range of 1-2 g and therefore considered insignificant. As documented in paper II the amplitude, incline and decline rates are similar for both recording methods. A critique to the setup is the speed of the displacement which was too low compared to in vivo conditions, but it was not possible to change this further. The recording method was considered valid and the in-vivo studies were initiated.

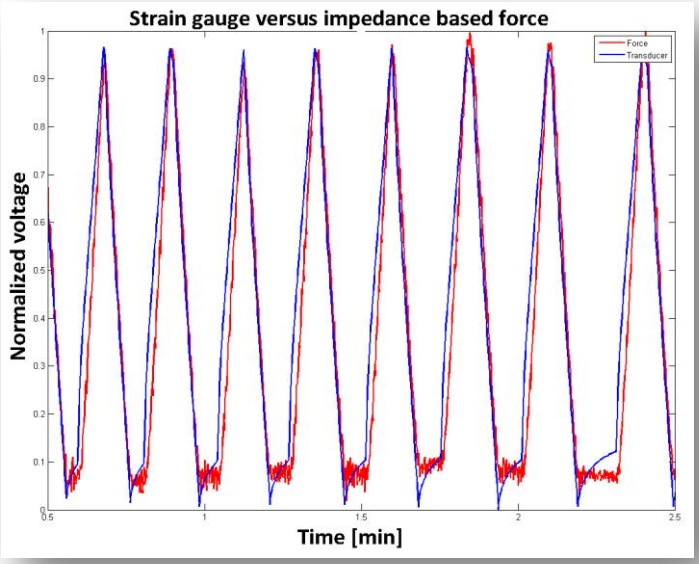


Figure 4.1: Red tracing shows the recorded signal from the strain gauge implemented in the recordings apparatus. The blue tracing shows the simultaneous recorded voltage from the axial force probe. The y-axis represents normalized voltage.

4.2 Healthy subject studies

4.2.1 Oesophageal response to bolus obstruction

In paper II we aimed to minimize the diameter of the probe. It is important as it minimizes intubation discomfort but is also more physiological. Mathematical models have shown that merely putting down a probe will change the way the liquid flows from the mouth to the stomach and thus recordings made with a catheter will become a rather indirect measure for the real physiological process[55]. A bag mounted on a probe placed in the oesophagus might not be physiologic, but it can enable us to investigate how a normal oesophagus response to an obstructing intraluminal bolus[17]. If the diameter of the bag is increased beyond a threshold it will trigger secondary contractions[49;54]. Williams and co-workers found the threshold for secondary peristalsis for healthy subjects to be 7ml (range 5-7ml). This threshold is very close to the maximum bag volume of 6 ml used in Paper II and III. The maximum volume was found in pilot studies and looking into the literature. As expected we did not see any secondary peristalsis due to distension in our data though multi peaked and sustained axial force contractions was seen (see discussion in section 4.2.4). This is most like due to a different choice of bag material. This is described in details[49]. In our studies we choose polyurethane for bag material as it is non-elastic and thin walled (in contrast to e.g. latex). The drawback of a bag compared to a balloon is that that diameter is less precise and we cannot exclude that this may influence the variation of the contraction durations.

4.2.2 Contraction duration

The contraction duration recorded with axial force is longer than the duration recorded with manometry (II). This physiologically relates to the contraction of the longitudinal muscles where longitudinal muscle

contraction envelops circular muscle contraction[11;23;24](and section 1.4). This indicates that axial force also includes the contribution from longitudinal muscles hence more information. An example of this is shown in Figure 4.2 (right) where raw data shows the onset of the axial force is simultaneous with the more proximal manometry recording (1.5cm).

4.2.3 Dynamic range of contraction amplitude

The contraction amplitude recorded with axial force increased with up to 129 % when comparing swallows during bag volumes 0 ml and 6 ml. For manometry this increase was only up to 28%. The difference might have been decreased if the intra bag pressure was measured and an even more direct comparison between pressure and axial force during distensions could have been made. To the best of our knowledge no studies measures intra bolus pressure during primary peristalsis.

4.2.4 Sustained force

Besides secondary peristalsis we also had to consider avoiding the peristalsis wave to turn into a sustained contraction at the site of the obstructing bag. The triggering of sustained contraction have been studies previously with manometry, axial force and a bag placed in oesophagus[17], thus a setup similar to paper II and III. Winship and Zboralske[17] found that if the bolus was big enough the peristaltic wave created a persisting force on the bag placed in the oesophagus. That force would sustain until the bag volume was removed. Sustained oesophageal contraction is not recorded by manometry and could represent longitudinal muscle contraction of the oesophagus[56].

In paper II sustained axial force response was observed for five subjects (23 swallows in total) but only when the bag was filled with either 4 or 6ml, thus during the biggest obstruction/challenge as expected. The sustained force complicated the duration and amplitude analysis in (II) and an example of this is shown in Figure 4.2 (left). In the literature a limit to which a contraction is considered sustained have not been found. In our studies a sustained contraction was defined to be any contraction lasting longer than 10 seconds. This limit was set to avoid sustained contractions influencing normal contractions. Sustained contractions were not included in the subsequent analysis of paper II and paper III, but it became an interesting factor in the preliminary clinical data (Chapter Chapter 5)

High-resolution ultrasound can measure sustained muscle contractions but it lacks the information about the direction (squeeze, a push or both). It can be used as an indirect method to record sustained contractions. Pouderoux and co-workers have shown, with a force transducer and high resolution ultrasound, that longitudinal muscle contractions correlate well with axial force measurements[11]. In patients suffering from non-cardiac chest pain sustained oesophageal contractions correlates with the pain events[56-58]. The duration of the sustained contractions was in patients reported to 32 seconds[57] and 124 seconds[58]. The sustained force recorded in healthy volunteers in paper II lasted from 10-30 seconds. The decreased duration compared to the patient studies is likely due to our borderline volume. E.g. if we used 8 ml we might have recorded longer or increased number of sustained contractions. This leads to another interesting discussion of the bag volume and how it challenges the oesophagus.

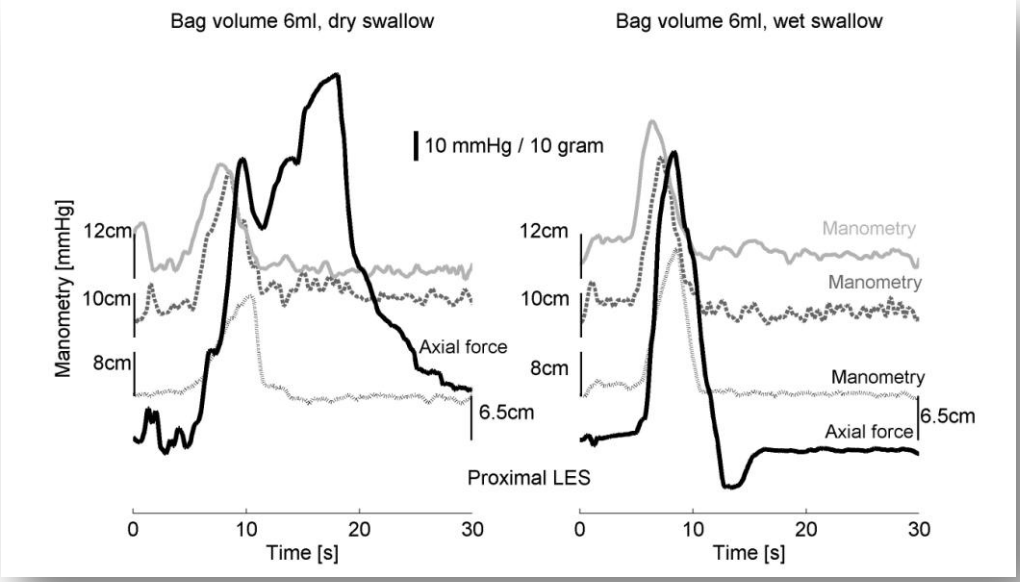


Figure 4.2: A swallow started a time zero from two subjects. In both swallows the bag was filled with 6mL. Left: A swallow with normal manometry but sustained and powerful axial force (duration >10s). Right: A swallow with normal manometry and normal axial force.

4.2.5 Bag volume and multiple swallows (oesophageal challenge test)

The standard clinical procedure with manometry during swallow tests does not include a bag being inflated as this only to a minor degree affects the manometric data[59;60]. On the other hand, increasing the bag volume presents a challenge to the oesophagus similar to an electrocardiogram recorded during exercise. During exercise the electrocardiogram can reveal abnormalities not seen at rest[61]. Thus, a "stress test" likely will provide a more sensitive test when recorded with axial force. We have initiated a study to examine this phenomenon and the preliminary data are described and discussed in Chapter 5. An indication of its use have been shown in a study by Williams and co-workers[49] where the bag volume for triggering secondary peristalsis in patients suffering oesophagitis was found. The patients generated weaker contraction and the threshold for triggering secondary peristalsis was increased compared to healthy controls. It is though unknown whether this is the cause or effect for oesophagitis.

Another way to stress or challenge the oesophagus is to make multiple rapid swallows. It has been shown that 70% of patients suffering from ineffective oesophageal motility had abnormal manometry pattern during multiple rapid swallows despite normal manometry[62]. A similar examination including axial force recording would be interesting as it primarily was the manometric amplitude that was affected.

4.2.6 Number of swallows

Traditionally subjects are asked to do 10 wet swallows during a manometric motility examination[5;63] and fatigue has not been found for 50 sequentially swallows[63]. In another study 5-8 wet swallows was found sufficient to obtain reliable and reproducible manometric parameters in healthy subjects[64]. The minimum number of sufficient swallows has not yet been examined with high resolution manometry. In studies examining the viscosity 10 swallows have been used[44;45]. In paper I, II and III we used 5 dry

swallows and 5 wet swallows for each bag volume level this was a borderline number as the relative few swallows at each level increased the variation. Especially for the dry swallows as non-propagating contractions (failed) sometimes occurred in 40-50% of the swallows leaving only 2-3 swallows to include in the analysis. In future it is suggested to increase the number of swallows at each level to improve the basis of the analysis.

4.2.7 Bi-directional axial force

The probe design facilitates axial force to be measured in two directions; aborally and orally. Axial force generated in the oral direction, that is negative force, was observed in paper II. Contractions generating more than 10 g of push in the oral direction were found in eight of the health volunteers and in a total of 18 contractions. As shown in Figure 4.3 (left) a bi-directional axial force pattern can co-exist with normal manometry pattern. A purely negative force (orally) co-existed with ineffective manometry pattern as shown in Figure 4.3 (right). This indicates that additional information is gained from using the axial force probe compared to manometry alone. The analysis of negative axial force can however not be too strong as the probe is not fixed distally and the probe therefore can bend rendering the negative axial force amplitude lower than what is actually happening. Additionally purely negative axial force could be the consequence of oesophageal shortening thus the lower oesophageal sphincter is pushing the probe in oral direction.

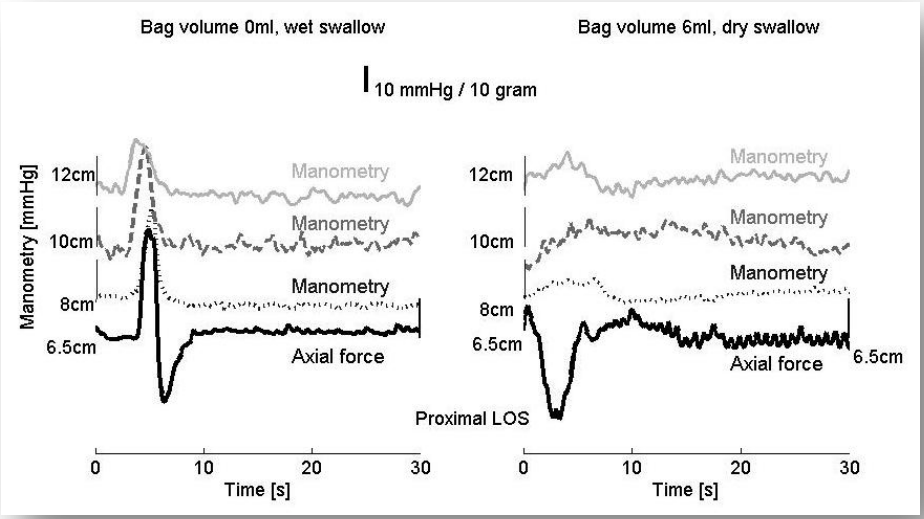


Figure 4.3: A swallow started a time zero from two subjects. Left: Swallow with normal manometry but as positive (aborally) and negative (orally) axial force. Right: A swallow at time 0 with ineffective motility manometry pattern but a negative orally axial force (-37 grams).

4.2.8 Bolus properties (viscosity)

Many studies have sought to investigate how different parameters are able to modulate the peristalsis. It has been shown that bolus volume modulates the peristaltic contraction velocity and duration[65;66]. Additional parameters like the interval between swallows[67;68], body position[66;69] and bolus temperature[70] have also shown to modulate peristalsis. Previous studies have found that the pressure amplitude was unaffected by increasing bolus viscosity whereas the duration decreased and velocity

reduced[70;71]. In paper III we found similar results, as not difference in amplitude during 5 and 10 ml swallows was found for manometry recordings. For axial force recordings the amplitude was marginally increased with increasing viscosity. Axial force has not before been used to examine how viscosity alters the peristalsis. The contraction duration was prolonged for manometry and axial force recordings as found in other studies[70;71].

The complexity of fluids mechanism can explain lack of clear results. Fluid motion is not only determined by its viscosity but also the friction between the bolus itself and the mucosa. It has been shown, with mathematical models, that a coating, which decreases the friction to the mucosa, will decrease the forward pushing effect of peristalsis[33]. To support this argument swallowing salad oil, with a low frictional resistance, decreased axial force amplitude by 50% in subsequent swallows[14]. This implies that frictional force is of greater importance than bolus viscosity.

4.2.9 Reproducibility

Any robust method should be both valid and reliable. Reproducibility had been documented for 24-h manometry[72;73] and secondary peristalsis[74] but to the best of our knowledge no data exists on reproducibility during ambulatory swallowing studies neither for manometry nor axial force. This is interesting as manometry is a standard clinical test and widely used and accepted. In paper II we examined the reproducibility of manometry and axial force. Two statistical validation tools for reproducibility were chosen. The intra-class correlation coefficient (ICC), which reflects individual variance at repeated sessions and repeated measure analysis of variance (rmANOVA) which measures systematic bias over time relating to the method.

The best reproducibility was found at lower bag volumes for both modalities. This is most likely due to the limited number of valid swallows at bag volumes of 4 ml and 6 ml. Some of these swallows were multi peaked and therefore not included in the analysis. A third way to consider reproducibility is by visual data inspection and Figure 4.4 shows the duration and amplitude from examination day 1 and day 2. The data is from ten subjects (paper II). The optimal results would have been that all the data was on top of each other, but some variance is present. The variation between the patients does not seem be related to the examination day nor vice versa. The variation seems equal for axial force and manometry amplitude while duration recorded with manometry seems to have less variation. The variations can be due to changed saliva production, latency, measurement artefact and/or neuro-hormonal control[13]. For one subject the raw axial force and manometry data is shown in Figure 4.5. The curves are aligned.

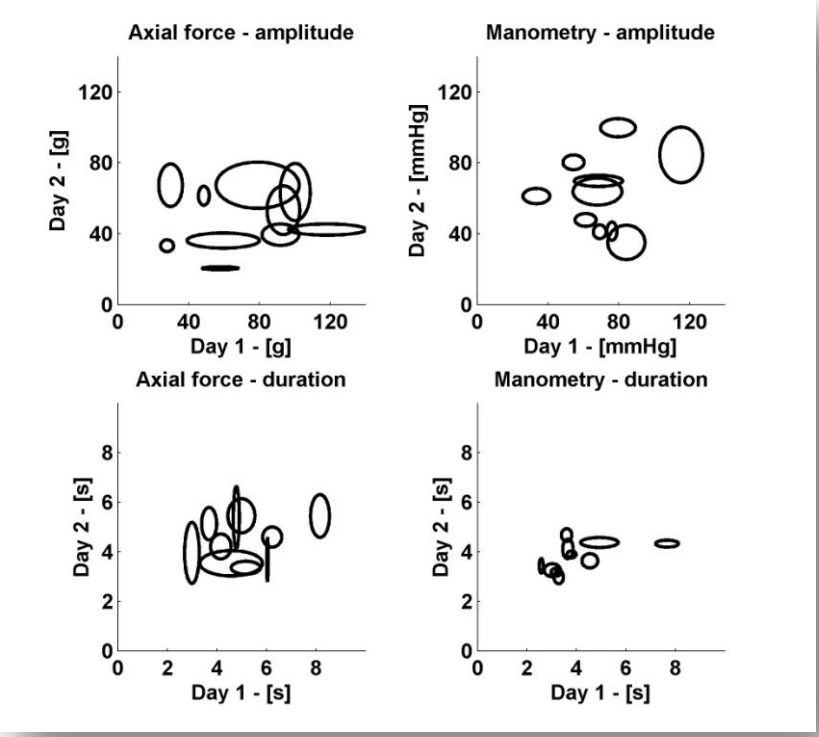


Figure 4.4: Top row is amplitude and bottom row is duration. Left column is for axial force recordings and right column is for manometry recordings. Each ellipsoid represents one subject. The centre of the ellipsoid is the average value for (x) day 1 and (y) day 2. The size of the ellipsoids shows the SEM value for both day 1 and day 2. The SEM values are calculated as several swallows done at each day. The data is calculated for bag volumes of 2 ml during wet swallows.

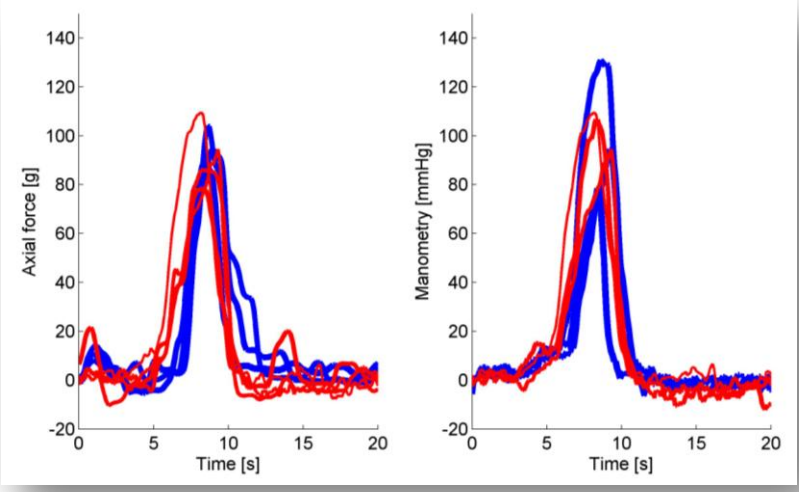


Figure 4.5: Four wet swallows on examination day 1 (red) and three wet swallow on day 2 (blue) in one subject. The bag volume was 2 ml both days. Only swallows rated as normal was included. Left graph show axial force recordings and right graph manometric recordings.

Chapter 5 *Preliminary clinical studies*

As a result of the success with this new measurement technique we were able to carry out preliminary clinical studies at the Centre for Gastroenterological Research in Leuven, Belgium. The probed used for this clinical study was identical to the one used in Paper II and Paper III. As data analysis is not yet completed preliminary results are presented here.

5.1 Aims and objectives

Patients with upper gastrointestinal motility disorders can go through manometric examinations without a clear diagnosis. The objective of the clinical studies was to investigate how axial force combined with manometry can provide information not found with manometry alone. The specific aims were to examine the amplitude, duration and the shape of the contractions for both manometry and axial force.

5.2 Methods

The protocol and equipment was the same as that described in Paper II. In brief the bag volume levels were 0, 2, 4 and 6ml and for each bag volume five dry and five wet swallows were done. As some of the patients had difficulties timing the swallowing we changed to protocol from being 45 seconds between to vary in an interval of 20-40 seconds. This allowed a more natural rhythm and they did not swallow in between the protocol swallows. One axial force and three pressure measurements were recorded simultaneously.

5.2.1 Patient groups

The patients had a variety of motility related disorders. In total 20 patients (57±14.8 years) were included. These were seven patients suffering from diffuse oesophageal spasms (DES), six patients suffered from achalasia and seven belonged to a miscellaneous group. Table 5.1 provides an overview of the information about the patients.

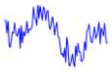
Table 5.1: A list of patient information enrolled in the study. The numbers in () designate the number of patients. *the median years (75% quartile). **Note that one patient can have had several treatments.

Group	Disease(s)	Symptoms duration*	Treatments**
DES	DES (7)	3.5 (5.5) years	Botox(4), Adalat(3), surgery(1)
Achalasia	Unspecified Achalasia (5)	2.2 (6.25) years	Dilatation(3), Botox(1), None(2)
Miscellaneous	Steinert disease (1), Unspecified Reflux(4), Systemic sclerosis and hypomotility (1), GERD (1)	N/A	PPI(5), Surgery(2), None(1)

5.2.2 Analysis - Categories

The recorded contractions were categorised using nine different types of contractions (Table 5.2). This categorizing scheme was also used to re-analyse the data from Paper II. To enable a comparison between the patient groups and to the healthy controls the number of swallows in each category was normalized by dividing with the total number of swallows within that group. Each recorded contraction could only be assigned to one type although more types could apply to the same contraction hence some categories were combined in the subsequent analysis. As multi peaked contractions (category 6) often had a longer duration than 10 seconds (category 5) these two were combined.

Table 5.2: Description of 9 categorizes used to classify each contraction. Each recorded contraction was classified using this table. It was used for both axial force and manometry recordings.

#	Description	Sketch of force recordings	#	Description	Sketch of force recordings
1	One positive (aborally) deflection		6	Multi peaked contraction Can also be presented during sustained force and vice versa.	
2	One positive deflection followed by a negative deflection		7	Failed or diminished contraction	
3	One negative deflection followed by a positive deflection		8	Invalid contraction Air bubbles are found in the system, coughs etc.	
4	One negative (orally) deflection		9	One negative, then positive and ending with negative deflection	
5	Sustained force Minimum duration of 10seconds				

5.2.3 Analysis – Swallow parameters

As in paper I, II and III the amplitude and duration were analysed for each swallow and compared for each group. Additionally this preliminary analysis included an analysis of some of the categories. In the amplitude and duration analysis only contractions with category 1 was used. To be able to compare with normal data from healthy subjects, data recorded for Paper II were included in the analysis.

5.3 Results

All patients completed the study without adverse events. The patients coughed or made movements during a swallow more often than the healthy subjects. These events were marked in the recorded file and rated as not valid and left out of the analysis. The duration from positioning the probe to the end of the study was 61 (range 42–71) minutes. The temperature was 36±0.4°C during examinations. In total 890 swallows were recorded which rendered 3560 curves to analyse.

The preliminary data shown here is without statistical analysis because the relative low number of patients and their diversity. The manometric data shown are only for the recordings 8 cm proximal to the lower oesophageal sphincter.

5.3.1 Results – Amplitude

Axial force (Figure 5.1 left*):*

As shown in paper II the contraction amplitude for healthy subjects increased with more than 100% when the bag volume increased from 0 ml to 6 ml. The group of achalasia patients had no increase when the bag volume increased and was in general much lower than the healthy subjects. This corresponds well to the typical manometry findings of absent distal peristalsis. It should be noted that the number of successful swallows (category 1) for the achalasia patient was relative low as most of their swallows was failed. The group of miscellaneous and diffuse oesophageal spasm patients had a tendency to increased amplitude but when the oesophagus was challenged both groups failed to show an increase. Again this could be compared to the manometric findings for patients suffering diffuse oesophageal spasm described in Table 1.1 page 10. In general the group of healthy subjects had higher amplitude when the bag volume was 6 ml compared to any of the patient groups.

Manometry (Figure 5.1 left*):*

The manometric amplitude for healthy subjects increased some for the group of healthy subjects as previous documented (Paper II). This tendency (level of amplitude and increase) was also seen for the miscellaneous group. The group of patients suffering from achalasia had a little lower amplitude and did not increase with increasing bag volume. The amplitude recorded with manometry for the group of patients suffering from diffuse oesophageal spasm decreased when the bag volume increased. This is in contrast to the axial force amplitude in the same group where it increased with increasing bag volume. In general the manometric amplitude was not much different when comparing the healthy controls to the other patients groups. This might be due to the lower dynamic range of the manometric recordings.

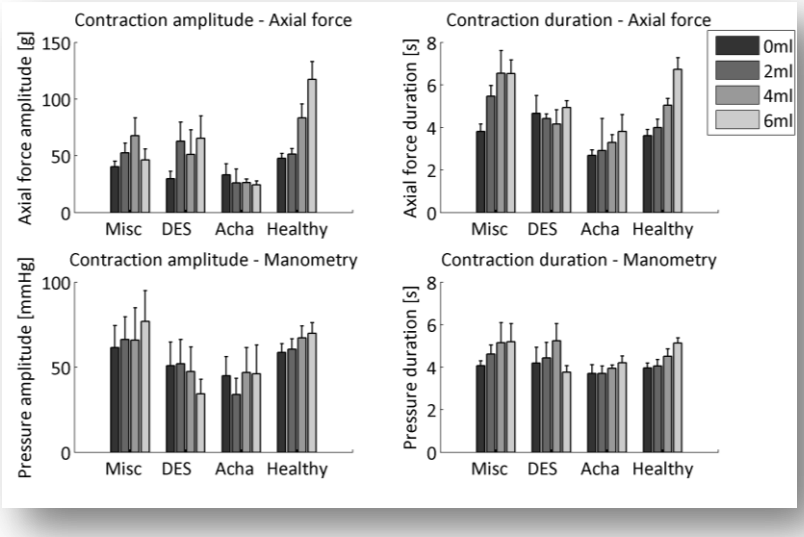


Figure 5.1: Top row is axial force and bottom row is manometry. Left column is the contraction amplitude and the right column is the duration. Mean±SEM pressure and axial force amplitude and duration with increasing bag volume (0-6ml). Patient data are shown together with the groups of healthy subjects. Wet and dry swallows are combined. DES=Diffuse Oesophageal Spasm, Acha=Achalasia, Misc=Miscellaneous.

5.3.2 Results – Duration

Axial force (Figure 5.1 right*):*

The contraction duration recorded with axial force increased with increasing bag volume for the group of healthy subjects, achalasia patient group and the miscellaneous group. The diffuse oesophageal spasm group did not shown any increase. In general the dynamic range for all groups was small and no clear difference was found, except between the group of healthy subjects and the achalasia group. The achalasia group had a decreased duration for all bag volumes.

Manometry (Figure 5.1 right*):*

The contraction duration recorded with manometry was very similar for all groups. This is most likely due the small dynamic range. In general the duration recorded with manometry was not altered with increased bag volume.

5.3.3 Results – Categories

Axial force (Figure 5.2 top*):*

It is clear that the number of multi peaked and sustained contractions increased with bag volume for the group of healthy subjects. In general not many sustained contraction was recorded (15 swallows for the patients and 23 for healthy subjects). The number of failed contractions decreased a little when the bag volume increased. In general the number of failed contractions was lower compared to the patient groups.

The achalasia group had a low number of multi peaked contractions but a high number of failed contraction. The miscellaneous group showed similar pattern for multi peaked contractions as the group of healthy subjects when the bag volume increased. The number of failed contractions did not change with increasing bag volume but was more frequent compared to the group of healthy subjects. The groups of patients suffering from diffuse oesophageal spasm had a relative high level of multi peaked contraction and a little increased with increased bag volume. The number of failed contractions did not seem to be affected by increasing bag volume.

Manometry (Figure 5.2 bottom*):*

No swallows was categorized as sustained contraction when measured with manometry. The number of multi peak contractions was for all patient groups higher than the group of healthy subjects. Comparing the number of failed contractions, recorded with manometry, in the group of patients suffering from diffuse oesophageal spasm to the number of failed contractions recorded with axial force in the same group shows a similar pattern. The same conclusion can be made for the group of miscellaneous patients. A difference is seen when comparing the number of failed contractions for manometry and axial force in the group of patients suffering from achalasia. Failed contractions are more frequent when recorded with axial force.

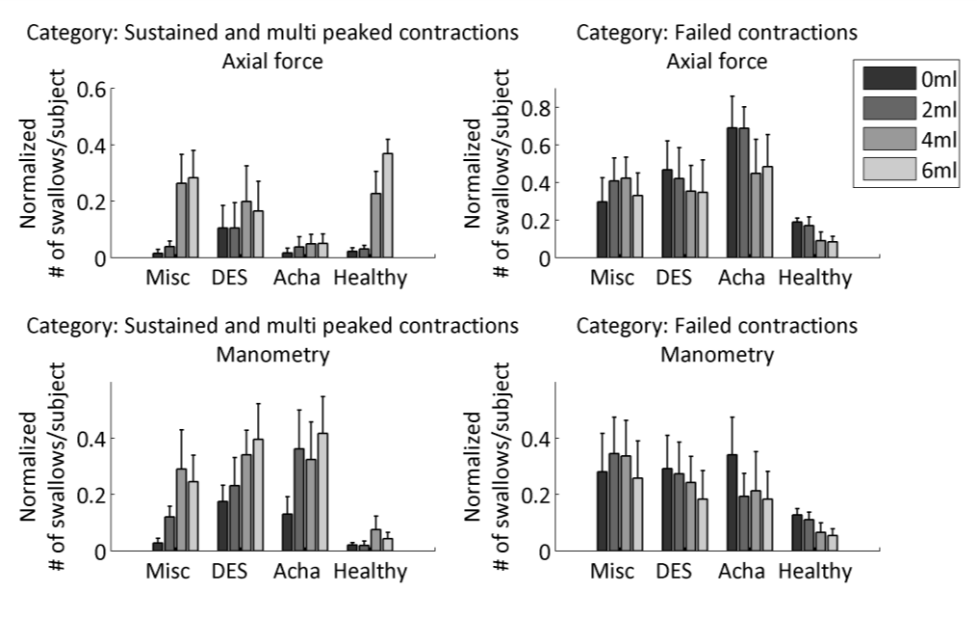


Figure 5.2: Normalised numbers of contractions±SEM in relation to increasing bag volume. Top row is axial force and bottom row is manometry. Left column is the number of contraction categorized as multi peaked and sustained. Right column is the number of failed contractions. Patient data are shown together with the group of healthy subjects. Wet and dry swallows are combined. DES=Diffuse Oesophageal Spasm, Acha=Achalasia, Misc=Miscellaneous.

5.4 Discussion

In this preliminary study we have documented that axial force and manometry are able to show a difference between healthy subjects and patients and that axial force provide information critical to differentiate patients from healthy subjects.

The most interesting result is how the group of patients suffering from achalasia are different from the group of healthy subjects but also the two other groups of patients. The differences are clearest for the axial force recordings. The amplitude was must lower and the number of failed contraction much higher for the group of patients suffering from achalasia compared to the other groups.

Despite being a preliminary study with very different patients and no homogenous disease or treatment axial force have provided a clearer picture of the patients' defects compared to manometry alone, hence additional and important information compared to manometry alone was found. The groups were made on the basis of manometry and patients specific symptoms. This is in favour for manometry to show a difference, but clearly this was not the case when using the developed axial force probe.

5.4.1 Amplitude and duration

The amplitude is interesting as previous work with axial force measurements have shown that using manometry and axial force together increased the number correctly classified patients[51]. Williams and co-workers examined 30 patients suffering from oesophagitis and six patients showed normal

manometry but decreased axial force amplitudes[51]. The same study also included a group of gastro-oesophageal reflux patients and found, as we also did, decreased axial force amplitudes.

In general, when the oesophagus is challenged (4-6ml in bag) axial force amplitudes lower for patients compared to healthy subjects. This corresponds, as described above to a previous study[51]. The difference for manometry is more mixed which could be due to the lower dynamic range. The group of patients suffering from achalasia had lower axial force amplitude compared to the group of patients suffering diffuse oesophageal spasm. This was not the case for manometry. The axial force amplitude was unaltered for the achalasia group when bag volume was increased; this is in contrast to the large dynamic range seen in the group of healthy subjects.

5.4.2 Failed and multi peaked contractions

The three patient groups showed different results compared to healthy subjects, but between groups there were less variation, especially for the number of failed contractions. The few multiple contractions, recorded by axial force in the achalasia patient group, are interesting in contrast to the high number of failed contractions and this differentiates this patient group to the other groups. This is as expected as this group of patients have difficulties creating a useful contraction. Making the same comparison between multiple contractions and failed contraction with manometry shows a less clear picture as these are quite similar. For diffuse oesophageal spasm group the number of failed contractions measured with manometry had a tendency to increase with the bag volume while this was not the case for the axial force. This is consistent with the disease description, which describes un-coordinated contractions and therefore not able to create any forward driving peristaltic wave. How effective the contractions are can directly be measured with axial force.

Manometry does not record sustained contractions and if it is used without axial force this information would not be provided. The results might have been different if the pressure was measured inside the bag as the sustained contraction would have been recorded.

The decreasing number of failed contractions for the healthy subjects was expected and is probably caused by a changed neuro-feedback mechanism. Naturally it an advantage if the number of failed contractions decreased as the bolus present in the oesophagus increase.

Chapter 6 *Conclusion & Perspectives*

6.1 Summary

This work demonstrates for the first time that axial force, based on electrical impedance measurements and pressure recordings in the oesophageal body can be used to measure oesophageal motility. The research follows a journey through device development in three published papers. Paper I demonstrates how the already established technique of impedance planimetry can be modified to measure axial force in vivo, and used as a short study on volunteers to shows its safety and efficacy. From the lessons learn the technique was further modified and the axial force transducer was improved to minimized bending and temperature dependency in paper II. Paper II also demonstrates the validity and reliability of these new measurements, their appropriateness for use in oesophageal body and its comparable reproducibility to manometry. Paper III indicates how the measurement could be used practically. It is clear that axial force recordings are a more physiologic related measurement than standard manometry.

6.2 Achieving aims and objectives

6.2.1 Paper I

In paper I it was shown how axial force and pressure simultaneously could be measured in the oesophageal body during bag distension. For the first time axial force has been measured in the human oesophagus, thus representing a new application of the impedance planimetry technique. It was approved and thus tested in-vivo in a single healthy volunteer to demonstrate that pressure and axial force data could be measured. Paper I documented the development of a probe that were capable of measuring axial force and pressure simultaneously (**aim 1**). Additionally it verified the accuracy and reproducibility of the axial force recordings in-vitro (**aim 2**).

6.2.2 Paper II

Paper II represents the verification and achievement of the concluding and improved probe design (**aim 1**). It compared well to an in-vitro strain gauge setup which confirms its usefulness as an objective measuring tool in the oesophageal body (**aim 2**). Paper II also demonstrated the reproducibility of axial force and manometry developed by the human oesophagus in healthy volunteers **(aim 3)**. This has never been reported for a swallow test with increasing probe bolus with simultaneous manometry and axial force recordings. To emphasize that manometry is not a valid measure of axial force the association between these two measurements was examined. The correlation between axial force and manometry became weaker as the probe bolus increased. This have previously been confirmed with other axial force technologies[11;14] and indicated by mathematical models[20]. The protocol, in terms of changed “grip” effect (increasing bag volume) is an important factor when comparing axial force recordings to manometry. Axial force showed a much bigger dynamic range for both duration and amplitude compared to manometry. The protocol also included a variation of the swallowed bolus (none vs. 5 ml). A difference in amplitude was found for both manometry and axial force though this difference was clearer for axial force.

6.2.3 Paper III

Paper III sought to investigate peristaltic parameters; amplitude, duration and the association with altering bolus viscosity using axial force and manometric measurements. Both techniques showed a prolonged duration with increased viscosity, indicating that peristalsis in some degree is modulated by viscosity. As in paper II the association between manometry and axial force decreased with increasing viscosity. This underlines the importance of having both measures. The paper document achievement of **aim 4**.

6.2.4 Preliminary clinical studies

Having started recording patient data is important to show axial force true potential. The most important test is how axial force will present itself when it is recorded in patients and how this relates to data recorded in healthy subjects. The preliminary patient data shows promising results for axial force. Despite this broad group of patients axial force amplitude recorded in achalasia patients showed differences to the two other groups and clearly was different from that recorded in healthy subjects. The physiological deficits found in patients with diffuse oesophageal spasm and achalasia was clearer when using axial force, manometry and the ratings combined. The added information was achieved in the same examination as manometry would have alone and it documents fulfilment of **aim 5**.

The rating of the contractions indicates a potential. To the best of my knowledge the rating has not been used before. The design of the protocol where the oesophagus is being challenged is also not seen before and we believe it will reveal new information, which could be similar to a stress test of the heart.

This project came to a successful conclusion and the hypothesis was confirmed. All aims were reached and in fact it was possible to add further clinical relevant data. The clinical results may in the future change how the patients are categorized and treated.

6.3 Perspectives

This study is the first to confirm reproducibility of a simple axial force measurement in man. It represents the opportunity to obtain superior diagnostic information compared to conventional manometric examinations without additional discomfort for the patient.

Future work and improvement have initiated to add multiple axial force transducers along the same catheters. Multiple axial force recordings combined with multiple manometric measurements and multiple intraluminal impedance measurements, will provide unique information about the oesophageal function. The information will be more useful than measuring high resolution manometry alone and it is still only one examination for the patient. Adding multiple measurements create a problem with in amount of data to be analysed. The probes are currently handmade and could benefit dramatically from being manufactured on a purpose-built production line. With better material and more standardized building process the design in terms of probe diameter and length of the axial force transducer will also improve.

In Paper II, III and the preliminary patient study more than 7000 contraction curves have been analysed. Even though the analysis was made semi-automatic it was still rather time consuming. A more

automatic analysis process would be of great value and increase the usefulness of the technique. This process have been started but will last for some time to come as no consensus has been made on how to categorize the contraction.

Previous patients studies by Williams et al. using axial force measurements have shown good results in relation to secondary peristalsis[19] and clearance function[50]. We have initiated a study where patients suffering from Barrett's oesophagus are examined with axial force, manometry and pH during induced acid perfusion. The time for clearance (related to pH) in combination with axial force will show how much the disease have changed their muscle function - and whether this have pathophysiological impact for the disease.

Axial force measurement provides fundamental and direct information about oesophageal function. It may in future help to further define and classify motility related disorders and improve the classification of motility patients. A bigger patient study with more homogenous patients may help us find out precisely how much information is gained by combining axial force and manometry, compared to manometry alone and such studies are also in the planning phase.

Chapter 7 *Summary in Danish*

Mennesket synker i gennemsnit 585 gange i døgnet. Hvert synk involverer spiserøret, der ved komplekse mekanismer transporterer f.eks. spyt og mad gennem munden og ned i mavesækken. Transportmekanismen kaldes peristaltik. Peristaltiske bevægelser måles konventionelt med manometri der registrerer trykændringer. Målingen foretages på sonden hvor der gennem små huller langsomt flyder væske ud. Når der fremkommer peristaltiske bevægelser klemmes sonden og væskestrømningen påvirkes. Denne påvirkning kan måles som et trykændring, og retningen af dette er normalvis radial, dvs. vinkelret på sonden og derved på spiserøret. Denne måling er kun et indirekte mål for hvordan spiserøret fungerer. Det er i præliminære studier vist, at det er muligt at måle spiserørets funktion direkte. Det betyder, at det er muligt at måle kraften i aksial retning som er den retning hvormed maden transporteres ned i maven. Målene for dette studie var derfor: at udvikle og teste en sonde, der måler den aksiale kraft af de peristaltiske bevægelser i spiserøret samtidig med manometri; at verificere reproducerbarheden af målene i mennesker; at studere hvorledes peristaltikken moduleres ved ændringer i en sunket væskes viskositet; og at undersøge hvorledes aksial kraftmåling og manometri kan bidrage til en bedre forståelse i patientundersøgelser (præliminært data).

En sonde, der kan måle den aksiale kraft, baseret på brug af impedans, og flere trykændringer samtidig, blev udviklet. Den første version blev påvirket af bøjning og temperaturændringer og en videreudvikling var nødvendig. Den optimerede sonde reducerede længden af den aksiale kraftmåler fra 10 cm til 1,5 cm, samtidig med at diameteren af sonden blev reduceret til 4,6 mm fra 6,1 mm. Sonderne havde en ikke-elastik pose monteret nedenfor den aksiale kraftmåler. Posen skulle efterligne et stykke mad liggende i spiserøret. Den videreudviklede sonde blev også testet i forhold til tidligere studiers strain gauge-teknologi (strækmåler). Forskellene blev fundet acceptable. Ved forsøg i mennesker bestod forsøgsprotokollen af fem tør-synk og fem våd-synk. Disse synk blev gentaget ved 0 ml, 2 ml 4 ml og 6 ml væske i den monterede pose.

Ti raske frivillige personer blev undersøgt to gange og reproducerbarheden af den aksiale kraft af trykmålingerne blev verificeret. Den aksiale kraftmåling steg med 129% og 117% ved våd og tør synk når væsken i posen steg fra 0 ml til 6 ml. For den gængse trykmåling var den tilsvarende stigning kun 28 % og 25 %. Dette indikerer at aksiale kraftmålinger er mere følsomme overfor fysiologiske ændringer i fødebolus end manometri. Generelt blev der ikke fundet nogen sammenhæng mellem aksiale kraftmålinger og trykmålingen ved højere pose volumina (4 ml og 6 ml), og man må derfor formode at de to målemetoder giver forskellige informationer.

Den udviklede sonde blev brugt til at undersøge hvorledes peristaltikken ændres når væsken, der synkes, ændrede viskositet. Seks raske frivillige personer sank 5 ml og 10 ml væske med varierende viskositet (1mPa·s til 10kPa·s) mens den aksiale kraft og manometri blev målt i spiserøret. Både den aksiale kraft- og manometri-målingerne viste længere kontraktioner ved en højere viskositet. Amplituden af de manometriske målinger blev ikke påvirket af øget viskositet, mens amplituden på de aksiale kraftmålinger blev påvirket marginalt. Aksial kraft og manometri viste en relativ høj korrelation

ved lave viskositeter og denne korrelation mindskes da viskositet øges. Det vil sige at aksiale kraftmålinger viste nogle ændringer, der ikke kunne måles ved hjælp af manometri.

Et præliminært studie med den udviklede sonde inkluderede 20 patienter, der led af varierende spiserørssygdomme relateret til peristaltikken. De præliminære data viste, hvordan samlet information fra begge modaliteter kan højne informationsniveauet i forhold til den gængse trykmåling alene. Kombinationen af modaliteterne i samme sonde mindsker ubehaget for patienten da denne kun skal gennemgå en undersøgelse. Dette forventes at kunne give bedre muligheder for at klassificere patienter og dermed også kvalificere behandlingen i fremtiden.

Konkluderende kan den nyudviklede sonde bidrage væsentligt til fremtidig forståelse af den peristaltik der genereres i spiserøret. Metoden vil kunne anvendes til at nærme sig en mere fuldstændig forståelse af de parametre, der har indflydelse på synkebevægelsen i spiserøret. En øget forståelse vil kunne bidrage til bedre og mere validerede behandlingsmetoder.

Chapter 8 *References*

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Chapter 9 *Appendix: Paper I-III*

Paper I

"***Measurement of the axial force during primary peristalsis in the oesophagus using a novel electrical impedance technology***"

Published in *Physiological Measurement*

Paper II

"***Reproducibility of axial force and manometric recordings in the oesophagus during wet and dry swallows***"

Published in *Neurogastroenterology & Motility*

Paper III

"*The viscosity of food boluses affects the axial force in the oesophagus*"

Submitted to Digestive Diseases and Sciences, December 2009