TIMING OF RESPIRATION AND SWALLOWING EVENTS DURING DEGLUTITION

Katarina Bodén

Karolinska Institutet

Karolinska Institutet

From **Department of Molecular Medicine and Surgery**

Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Background Dysphagia is a common symptom that can be due to disease, but can also occur without a known cause. Today, we know that the coordination of swallowing and respiration is essential for a safe swallow. Swallowing consists of several subsecond events. To study these events, it's important to use modalities with high temporal resolution. In the first study in this thesis, we examined young healthy individuals with simultaneous videofluoroscopy, videomanometry and respiratory recordings, all with high temporal resolution.

We know that dysphagia is more common in elderly and in patients with gastroesophageal reflux disease, (GERD).Whether this increased incidence of dysphagia in elderly is due to a disease process or is part of normal ageing is somewhat unclear. Furthermore, we believe that the increased incidence of dysphagia in GERD patients is due to reflux of gastro-duodenal content into the pharynx and larynx, which likely alter the sensory nerves of the mucosa which might deteriorate the sensitivity.

To evaluate these two groups, we used our young healthy controls as a reference. However, to be able to use this control group, we used the same technique, modalities and protocol as in the study with young healthy volunteers.

All of the above described studies were mostly experimental studies. Of this reason we wanted to perform a more clinical study and as swallowing maneuvers are the main treatment for dysphagia, caused by functional (neuromuscular) dysfunction. The aim of this study was to evaluate different swallowing maneuvers by intraluminal pharyngeal manometry in healthy volunteers.

Material and Methods We examined all volunteers in our first three studies, with simultaneous videofluoroscopy, videomanometry and respiratory recordings, all with high temporal resolution.

In the young group, the onset of 13 predetermined swallowing and respiratory events and the surrounding respiratory phase pattern were studied in different body positions and different respiratory drives, which were induced by breathing 5% CO_2. In the elderly group we did not induce hypercapnia. However, six of the included 26 volunteers were examined in both the upright and the decubitus position, to evaluate whether posture had any effect on swallowing and respiratory coordination or on the swallowing safety. Our results demonstrated a highly repeatable and fixed temporal coordination of the swallowing and respiratory events despite position and respiratory drive.

In our last study we only used simultaneous videofluoroscopy and videomanometry. Ten healthy volunteers without any swallowing complaints were included in the study. They started with three normal swallows without using any swallowing maneuvers and then they performed three swallows using each maneuver - the supraglottic, the super-supraglottic and the Mendelsohns maneuver. The supraglottic and the super-supraglottic swallows were explained during the examination. Subjects were instructed and trained in the Mendelsohns maneuver.

Results

Our results demonstrated a highly repeatable and fixed temporal coordination of the swallowing and respiratory events in the young individuals, despite position and respiratory drive

We could demonstrate that swallowing and respiratory coordination in elderly individuals did not differ significantly comparing the upright and decubitus position. The most significant results were several manometric values that were altered in the elderly individuals compared to the young. Even in the GERD patients, we could demonstrate almost the same results, with several impaired manometric values.

In our study of swallowing maneuvers, we could demonstrate a few altered manometric values, preferable with the Mendelsohns maneuver and with the super-supraglottic swallow.

Conclusions

We believe that these differences in the manometric values in the elderly mainly are due to age-related changes with decreased sensitivity in the mucosa of the mouth and pharynx. We speculate that the altered muscle force in the mouth and pharynx are age-related. In the GERD patients, we believe that the impaired manometric values are due to reflux of gastro-duodenal content into the pharynx which ought to result in decreased sensitivity, that might cause an impaired force in the muscles of the mouth and pharynx.

The reason why we only could confirm a few statistically significant manometric changes when healthy volunteers performed three different swallowing maneuver, might be explained by the need of more extensive training of the swallowing maneuvers or it could be due to the fixed pattern of the normal swallow.

LIST OF PUBLICATIONS

I.   Boden, K, Hardemark Cedborg, A, Eriksson L.I, Witt Hedstrom H, Kuylenstierna, R, Sundman, E, Ekberg O

Swallowing and respiratory pattern in young healthy individuals recorded with high temporal resolution

Neurogastroenterology and Motility. 2009 Nov;21(11)1163-e101

II.   Boden, K. Hardemark Cedborg, A. Eriksson L. I. Witt Hedstrom, H. Kuylenstierna, R. Sundman E, Ekberg O.

Swallowing and respiratory pattern in elderly healthy individuals recorded with high temporal resolution.

Manuscript in print

III.   Boden, K. Hardemark Cedborg, A. Eriksson L. I. Witt Hedstrom, H. Kuylenstierna, R. Sundman E, Ekberg O.

Swallowing dysfunction in patients with gastroesophageal reflux disease, GERD, compared with a group of historical controls.

Manuscript

IV.   Boden, K. Hardemark Cedborg, A. Eriksson L. I. Witt Hedstrom, H. Kuylenstierna, R. Sundman E, Ekberg O.

Effects of three different swallowing maneuvers analyzed by videomanometry

Acta Radiologica, April 7, 2006, 47:7; 608-633

CONTENTS

LIST OF ABBREVIATIONS

AS   Apnea start

AE   Apnea end

SA   Swallowing apnea

SAD   Swallowing apnea duration

PhCM   The middle part of the pharyngeal constrictor

PhCL   The lower part of the pharyngeal constrictor

TB   The tongue base

BOT   The base of tongue

UES   The upper esophageal sphincter

PhCs   The superior part of the pharyngeal constrictor

PCi   The inferior part of the pharyngeal constrictor

GERD   Gastroesophageal reflux disease

1 INTRODUCTION

Dysphagia (difficulty in swallowing, implying difficulty of passage of the bolus) is a surprisingly common symptom and, often, an extremely troublesome one. It can be long-standing, frustrating and all-consuming and can interfere with one of the most enjoyable social interactions, namely eating. In addition, dysphagia is a symptom that may not be given due attention by friends or relatives, or may be dismissed as psychogenic or psychosomatic. Dysphagia is a symptom that spans all ages, being common in the young and otherwise healthy, the middle –aged and the elderly; swallowing disorders in all stages of life will be discussed in the following text.

The act of swallowing seems simple and it is something we do not consciously think about. Yet, its successful execution requires the intricate coordination of several cranial nerves and thirty to forty muscles of the face, mouth, pharynx and the esophagus. Neurological and neuromuscular diseases, head and neck surgery and trauma, cancer in the head and neck area, gastrointestinal disorders etc, can all produce problems with swallowing. The resulting impairment may range from mild discomfort to life-threatening disability.

Many patients adjust to slowly progressive disease by modification of their diet or speed of eating. They may be unaware of such compensatory behavior. In more advanced dysphagia, sensory perception in the mouth, pharynx or larynx may be lost, resulting in silent aspiration without coughing or subjective awareness. This can cause aspiration pneumonia, which might be life threatening, especially in elderly individuals.

1.1 DYSPHAGIA AND COMPENSATORY SWALLOWING MANEUVERS

Apart from these involuntary compensatory mechanisms, there are several voluntary compensatory swallowing techniques that are used in the rehabilitation of oropharyngeal dysphagia. To analyze the swallowing dysfunction and to determine the appropriate technique for each patient, a barium swallow examination is considered the gold standard, (1-10). However, today, pharyngeal manometry, with high temporal resolution can be performed simultaneously with videofluoroscopy. The manometry curve is superimposed on the videofluoroscopic images and displayed and recorded together on a monitor. Techniques for treatment of oral and pharyngeal dysfunction, often used, are the supraglottic, super-supraglottic, Mendelsohns maneuver, effortful swallow and the chin

tuck. By using these techniques, the patients learn to swallow in a more safe and efficient way. The supraglottic swallow involves breath holding before and during swallowing, by closing the true vocal cords before and during swallowing to prevent entry of food into the airways. The super-supraglottic technique requires breath holding while bearing down, which pulls the arythenoid cartilage forward to the base of the epiglottis and closes the laryngeal entrance at the level of the false vocal folds. The Mendelsohns maneuver is designed to prolong the laryngeal elevation and thereby prolong the opening of the UES. The patient is instructed to swallow normally and when the larynx is fully elevated, to hold the larynx up voluntary, for several seconds, (1-2).

1.2   SWALLOWING AND RESPIRATORY COORDINATION

As described above, swallowing dysfunction may cause dysphagia, and also is considered to be a potential cause of aspiration of ingested food or liquid, which might lead to pulmonary contamination. As the pharynx is the shared route for food, liquid and air, a good coordination between breathing and swallowing is vital for a safe swallow. Cessation of breathing (swallowing apnea, SA) and airway closure during swallowing must occur to prevent entrance of food or liquid into the trachea, (11-14).

1.3   BRAIN STEM AND SWALLOWING

Swallowing is a complex sensorimotor behavior involving the coordinated contraction and relaxation of the musculature, located around the mouth, tongue, larynx and pharynx bilaterally and the longitudinal and circular muscles of the esophagus. During swallowing, different levels of the central nervous system, from med cerebral cortex to the brain stem are involved and many of the striated muscles innervated by the cranial nerves (CN) are excited and/or inhibited sequentially for the performance of the passage of the bolus from the mouth to the stomach. We know that breathing and swallowing are physiologically connected to each other, (3-4). Respiration and swallowing are temporally coordinated during feeding, to avoid aspiration and to permit sufficient respiration during the passage of bolus into the esophagus. This has been demonstrated clinically by the swallowing apnea during the pharyngeal phase of swallowing, and resumption of the respiratory cycle in expiration, after swallowing, (16)(5)

Almost all of our knowledge about how swallowing is controlled from the brain stem, is due to experimental deglutition studies, except for some information that was generated by clinical studies. Therefore, most of the information related to the brain stem and swallowing has been obtained from non-human mammals.
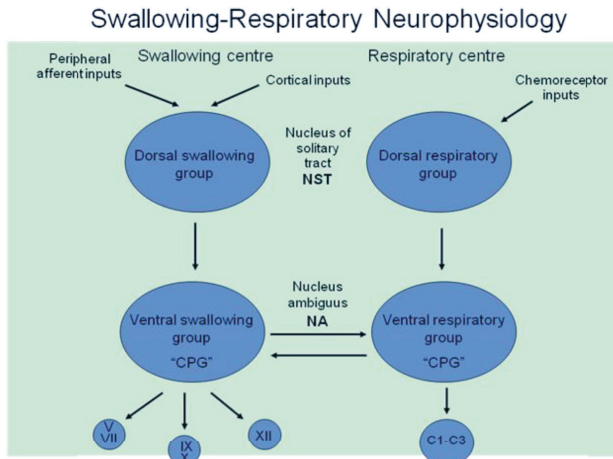
The precise pattern of muscle contraction and inhibition sequentially, as mentioned above is dependent on brain stem neural structures that conceptually consist of 3 levels:

1. An afferent and/or descending input level that corresponds to sites of termination of peripheral and central swallowing afferent fibers, mainly from the superior laryngeal nerve (SLN) and cerebral cortex.

2. An efferent level that corresponds to the motoneuron pools of the cranial motor nuclei that provides innervations to swallowing muscles, as tongue base, pharyngeal contrictors and upper esophageal sphincter.(6)

3. An organizing level that consists of an interneuronal network of "premotor" neurons in contact with both afferent and efferent levels

These premotor neurons or interneuron, which can initiate or organize the swallowing motor sequence are known as the swallowing central pattern generator, CPG, (17-19). Experimental electrophysical studies have demonstrated that swallowing premotor neurons are located in the adjacent reticular formation surrounding "nucleus tractus solitaries, (NTS), and in the reticular formation around and just above the "nucleus ambiguous", (NA).

Since both the respiratory cycle and the pharyngo-esophageal sequence of swallowing, consists of involuntary activation of cranial and spinal motor nuclei, coordination have to involve interaction between the two CPGs for respiration, and swallowing, which both are located in the brain stem,(3)(1).Fig 1.

Figure 1.

Swallowing and Respiratory center: Afferent sensory input to swallowing centre comes from peripheral nerves, i.e. the glossopharyngeal nerve (GN) and the superior laryngeal nerve (SLN), and from the cerebral cortex. Afferent input to the respiratory center comes from chemoreceptors in the aorta and in the carotid arteries, which are sensitive to low O_2 and high CO_2 and send signals to the respiratory centre.

1.4   PERIPHERAL EVENTS AND THE DIFFERENT PHASES OF SWALLOWING

Historically, swallowing has been divided into three phases: oral, pharyngeal and esophageal. The three phases of swallowing are related to their pattern of innervations. The oral phase is often accepted as voluntary, while the pharyngeal phase is automatic and considered a reflex response and the esophageal phase is mainly under dual control of the somatic and autonomic nervous system, (18) (20-21).

However, the pharyngeal phase does not only involve pharyngeal and laryngeal muscles but also the muscles in the oral cavity, such as tongue, suprahyoid- and submandibular muscles. Even the periorbital muscles actively contribute to the involuntary swallows. This phase can best be described as being composed of an oropharyngeal phase and is followed by an esophageal phase, (20-21). In normal human subjects, it is evident that there is usually a gradual accumulation of prepared food on the posterior surface of the tongue and this solid food reaches the valleculae in advance of the initiation of the

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swallow, (22-23). However, the initiation of the swallow can be expected from the posterior part of the oral cavity to the hypopharynx, depending on the different kinds of bolus.

When the movement of the bolus from the oral cavity to the pharyngeal space triggers the swallowing reflex or response, the following physiological events occur in rapid overlapping sequence. All of the events, until the esophageal phase are mainly controlled by the swallowing and respiratory CPG's of the brain stem.

The oral phase of the swallowing is mainly voluntary and highly variable in duration, depending upon taste, environment, hunger etc. Its primary function is the movement of the tongue, pressing the bolus against the hard palate and initiating the movement of bolus to the posterior part of the tongue and toward the oropharynx

The oropharyngel phases of swallowing are anatomically separated but functionally integrated regions. When the movement of the bolus from the oral cavity to the pharyngeal spaces, triggers the swallowing reflex or response, the following physiological events occur in rapid overlapping sequence.

1. Nasal, laryngeal and tracheal airways are, protected by several "reflex" events.

2. The tongue thrusts posteriorly to push the bolus throughout the pharynx and into the esophagus. A sequential wave of contraction of the pharyngeal constrictor muscles clears any remaining material into the esophagus.

3. The upper esophageal sphincter (UES) relaxes and opens for the bolus transport into the esophagus. The UES consists primarily of the tonically contracting striated cricopharyngeal muscle. During a swallow this muscle relaxes and is opened and the sphincter is pulled cranially and anteriorly by contraction of the suprahyoid/submental muscle group. Then the pharyngeal phase is completed and the UES closes until the next swallow.

1.5   CLINICAL STUDIES OF SWALLOWING AND RESPIRATORY COORDINATION

Swallowing is a complex motor event that is difficult to investigate in man by neurophysiological experiments. For this reason, the characteristics of the brain stem pathways have been studied in experimental animals. However, the sequential and orderly

activation and inhibition of the swallowing muscles, with the monitoring of the laryngeal excursion can be recorded during deglutition. Although influenced by the sensory and cortical inputs, the sequential muscle activation does not alter from the perioral muscles caudally to the cricopharyngeal sphincter muscle. This is one evidence for the existence of the central pattern generator, CPG, for human swallowing.

Clinical studies of swallowing and respiratory coordination has increased the last decade. It is well known that disordered oropharyngeal swallowing may cause dysphagia, this has been implicated as a potential cause of aspiration of ingested foods and liquid, leading to pulmonary contamination and infection. Furthermore, the incidence of dysphagia and pneumonia (16, 20, 25-26) rises sharply with advanced age.

Clinical and some experimental evidence support the existence of neurophysiological, structural, and functional interdependence between the upper respiratory and digestive systems, (27). Clinical observations reveal that breathing and swallowing functions are well coordinated in the healthy adult, (21, 28). The protection of the airway, and ultimately the respiratory system, during and around the time of swallowing is dependent on the integrity and coordination of breathing and swallowing. Although, the coordination of oral, pharyngeal and cervical esophageal swallowing physiology, has been studied, using video-fluorography, (7-8, 29), fiber-optic endoscopy, (26) and submental EMG, (26, 29) the temporal integration of these events with respiratory cessation has not been scrutinized and is not well understood. Further examination with simultaneous investigation of respiration and swallowing with high temporal resolution, is important, mainly for evaluation of the respiratory phase in regard to the swallowing apnea (SA). Furthermore, the temporal location and duration of the SA is important as this is the main protection against aspiration.

1.6   OROPHARYNGEAL DYSFUNCTION IN ELDERLY

As the pharynx constitutes a common pathway for air, food and liquid, this requires a high degree of coordination between swallowing and respiration to reduce the risk for laryngeal penetration and tracheal aspiration. The incidence of dysphagia rises sharply with advanced age, (30-31). Several studies are performed in elderly, but the result has been quite variable. Shaker et al. (26) and Hirst et al. (32), demonstrated that elderly initiated the swallowing more often in the inspiratory phase. Others could only

demonstrate that swallowing apnea duration was increased with increased age (24). The main question about dysphagia in elderly is whether this is due to normal ageing, so called presbyphagia, or is part of any underlying disease. To increase our knowledge of how swallowing changes with age, further studies of dysphagia in elderly is required.

2 AIMS

The *overall* aim of this study was to better understand the coordination between the swallowing and respiration and to find methods to examine this coordination clinically. A better understanding of the coordination between swallowing and respiration might improve the treatment of dysphagia.

2.1 STUDY I

The aim of this study was to evaluate the coordination of swallowing and respiration and to define timing of swallowing and respiratory events with high temporal resolution and with simultaneous modalities, in a group of young healthy individuals, to define a normative data for swallowing and respiratory coordination.

2.2 STUDY II

The aim of this study was to evaluate the coordination of swallowing and respiration and to define timing of swallowing and respiratory events with high temporal resolution and with simultaneous modalities, in elderly individuals, to be compared with our historical normal controls.

2.3 STUDY III

The aim of this study was to evaluate swallowing dysfunction in patients with gastroesophageal reflux disease, GERD, to be compared with our historical normal controls

2.4 STUDY IV

The aim of this study was to evaluate three different swallowing maneuvers in healthy volunteers by combining intraluminal pharyngeal manometry with videoradiography

3   MATERIAL AND METHODS

3.1   STUDY I

3.1.1   STUDY SUBJECTS

Thirty-two healthy volunteers were included in the study (16 male and 16 female, mean age 25 years, range from 20-35 years). None of the subjects had any history of dysphagia, gastro-esophageal reflux disease or surgery to the pharynx, larynx or the esophagus. None of the subjects were on any medication at the time of the study. None used tobacco. The study was approved by the Regional Ethical Committee on Human Research at the Karolinska, Institutet, Stockholm, Sweden (Dnr: 2005/926-31/1) and the study was performed according to the Declaration of Helsinki. Written informed consent was obtained from each study participants.

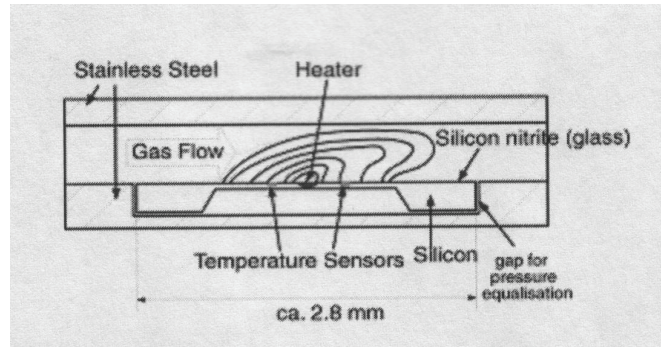### 3.1.2   MATERIAL AND METHODS

Respiratory recordings

A bidirectional air flow meter (ASF 1420; Sensirion AG, Staefa, Swizerland) was used to measure the inspiratory and expiratory oral and nasal air flow using a dual temperature compensated thermistor (CMO Sens®; Sensirion AG). The sensor had an internal flow integration time of 5 milliseconds (ms). This made it possible to determine the start, end and duration of flow or apnea (ms), as well as direction of flow (inspirations and expirations). The air flow meter is validated by comparing it with diaphragmatic and abdominal electromyography, (EMG) and was proven to be accurate and reliable (30). Fig 2.

Furthermore, a nasal pressure transducer (Response™; SynMed Medicinteknik, Spånga, Sweden) was inserted in one of the nostrils. This non-calibrated pressure transducer delivered an analogue signal that, due to variable built in time delay, was suitable for monitoring direction of flow but not the exact timing of flow or apnea. The oral and nasal air flow signal was Digital/Analogue converted, then digitized and sampled (Polygraf®; SynMed Medicinteknik) together with the nasal pressure signal. Using these two

techniques, the respiratory events, surrounding the swallow, were recorded in relation to bolus location and pharyngeal muscle contractions. Fig. 3

Figure 2

A controllable heater element is mounted in the middle of this pressure-stable membrane and temperature sensors are mounted symmetrically upstream and downstream from this heater element in the direction of flow. Any flow over this membrane causes a transfer of heat and thus generates a precise measurable signal. Thanks to the low thermal mass of the membrane, the sensor reacts to changes of gas flow within 1,7 ms
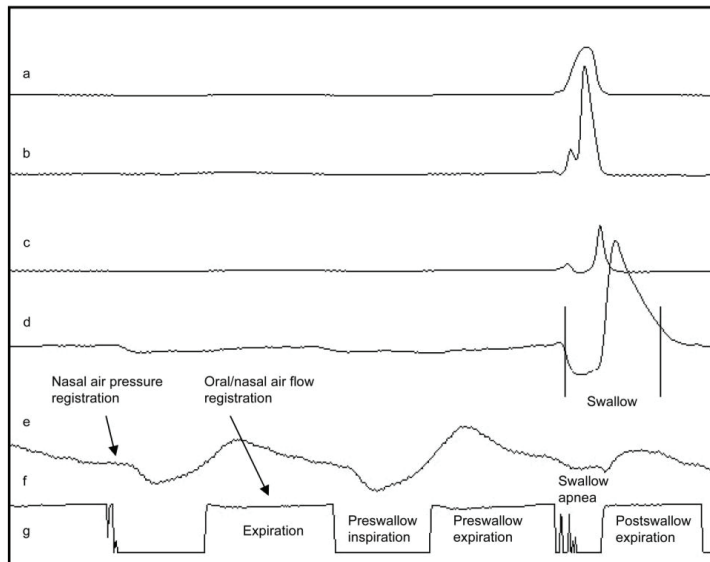
Figure 3.

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Fig 3: Simultaneous pharyngeal manometry and respiratory registration during swallowing.The manometric registrations were performed on four levels where a) refresent the tongue base level, b) the middle pharyngeal constrictor level c) the lower pharyngeal constrictor level and d) the upper esophageal sphincter

Respiratory registration was done with two modalities where e) represent the nasal pressure registration and f) the oral/nasal registration. On the nasal pressure registration, a positive registration indicated expiration while a negative registration indicated an inspiration and a flat line indicated swallowing apnea. On the oral/nasal air flow registration, an upward horizontal line indicated expiration, a downward horizontal line indicated inspiration and swallowing apnea was indicated by an oscillating signal. Registration from the flow meter clearly determined the start and end of expiration and inspiration as well as apnea start (AS) and apnea end, (AE).

Manometric recording

The manometry system is an intraluminal solid state transducer system. The manometry catheter has a diameter of 4,6 mm with four solid state pressure transducers positioned 2 cm apart. The two proximal sensors were standard microtransducers with a single recording site, oriented radially to measure 120°, while the two distal transducers were circumferential, allowing 360° measurements. All sensors were radiopaque and easy to identify during fluoroscopy. The transducer system was extremely non-compliant with a low volumetric compliance and a pressure rise rate of more than 2000 mm/Hg/s. The sampling frequency was 64Hz. The analog signal was converted to a digital signal (Polygraf®; SynMed Medicinteknik, Spånga, Sweden). The videofluoroscopy image and the videomanometric registration were mixed using a Microeye Video Output Card, and recorded together on the videotape (S-VHS) The computer was IBM compatible with Polygraf Upper-GI edition software by gastrosoft. Inc. (SynMed Medicintektni, Spånga, Sweden). All pressure values were registered in mmHg and referred to atmospheric pressure. The system was calibrated at 0 and 50 mmHg and carried out at 37°.

The manometry catheter was introduced through the nostril and positioned with the tip in the proximal esophagus and the distal transducer in the upper esophageal sphincter, UES (positioned 5 cm above the tip of the catheter). The three proximal transducers were each positioned at the level of the inferior pharyngeal constrictor, PhCM, the middle pharyngeal constrictor muscles, PhCL and the base of the tongue, BOT, respectively. During swallowing the pharynx-larynx elevation moves the UES in a cranial direction, so

that when the catheter is correctly positioned in the cranial part of the UES a characteristic M-shaped configuration of the manometry appears during swallowing, as described by Castell (34) and Olsson, (35), see Fig 4.
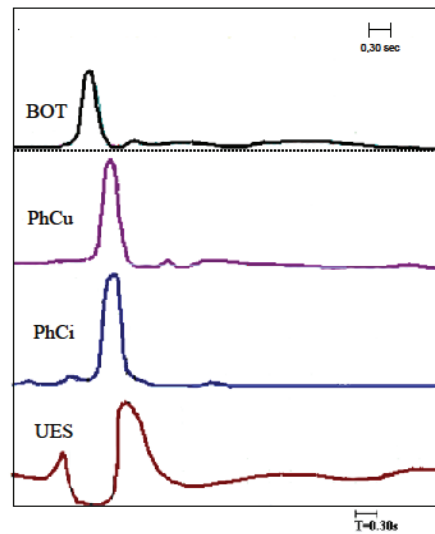
Figure 4.

Fig.4.Schematic of normal manometric tracings. The sensors are positioned at the base of the tongue (BOT), at the level of the superior pharyngeal constrictor (PgCM), at the level of the inferior pharyngeal constrictor (PhCL), and the cranial aspect of the upper esophageal sphincter (UES).When the catheter is correctly positioned in the cranial part of the UES, a characteristic M-shaped configuration of the manometry appears during swallowing.

Videofluoroscopy equipment

A Philips digital system (Multi Diagnost 4;Philips Digital System,Brest, The Netherlands) was used for fluoroscopy. Videofluoroscopic recordings was done with a resolution of 50 fields (25 frames) per second.Video analyses was performed by slow motion and frame-by-frame analyses. Timing of events was done by comparing the fluoroscopy with the manometry registration as these were displayed on the same monitor.

3.1.3 PROTOCOL

 Simultaneous videoradiography, solid state intraluminal pharyngeal manometry (videomanometry) and respiratory registration were performed in both the upright lateral and the left decubitus position. The left decubitus position was chosen to obtain a lateral fluoroscopy image.

The volunteers were studied during three conditions:

1. Upright lateral position, breathing normal air, *normocapnia*

2. Left decubitus position, breathing normal air, *normocapnia*

3. Left decubitus position, breathing air with an addition of 5% CO_2, hypercapni
   Hypercapnia was used to increase the respiratory drive by induce hyperventilation

After a 10 minutes adaptation period, with all equipment installed, during which swallowing and respiration were monitored, all participant performed three repetitions of swallows. Ten milliliters (ml) of water soluble contrast medium (Omnipaque® 240 mg mL -1, Nycomed Imaging, Oslo, Norway) was given as an orally administered bolus via syringe. Subjects were informed before the contrast medium was given and instructed to swallow when comfortable.

In each participant, 13 swallowing and respiratory events were selected for analysis, to determine their exact order during swallowing. We defined the start of the ventral movement of the hyoid bone as the indicator of the starting point of the pharyngeal swallowing and this event was selected as the time 0, (t_0), all other events were then referred in time to this particular event. The 13 events are defined in Tab 1 and Fig 5a and 5b.

Table 1 Definition of (A) 13 radiographic, manometric och respiratory temporal events and (B) 11 manometric variables

A. Temporal Events	Definitions
Radiographic temporal events	
Hyoid ventral	First ventral movement of the hyoid bone (
Bolus at faucial isthmus	Head of bolus passed the posterior aspect of the ramus of the mandible
Bolus at vetibular inlet	Head of bolus at the level of the vestibular inlet
Max vestibular closure	Total eliminatin of air contrast in the vestibular inlet
Bolus below UES	The tail of the bolus have passed the upper esopgageal sphincter (UES)
Vestibular opening	First appearance of air contrast in the vestibular inlet
Manometric temporal events	
TB start	Start of the contraction of the tongue base
UES relaxation start	Start of the relaxation of the upper eosophageal sphincter
PhCM start	Start of the contraction of the middle pharyngeal muscle
PhCL start	Start of the contraction of the lower pharyngeal sphincter
UES contr start	Start of the contraction of the upper oesophageal sphincter
Respiratory temporal events	
Apnea start	End of stable airflow
Apnea end	Start of stable airflow
B. Manometric Events	
Tongue base contraction peak (Tbpeak)	Peak contraction pressure (mmHg) at the tongue base level
Tongue base contraction rate (Tbrate)	Mean contraction rate (mmHg-1s) at the tongue base level
Tongue base contraction duration (Tbdur)	Duration (ms) of the contraction at the tongue base level
Pharyngeal contraction pressure (PhCLpeak)	Peak contraction pressure (mmHg) at the lower pharyngeal constrictor level
Pharyngeal contraction rate (PhCLpeak)	Mean contraction rate (mmHg-1s) at the lower pharyngeal constrictor level
Pharyngeal contraction duration (PhCLdur)	Duration (ms) of the contraction at the lower pharyngeal constrictor level
Tongue base contraction to pharyngeal muscle contraction (TB-PhCL)	Velocity (cm/sec) from the peak contraction of the tongue base to the peak contraction of the lower pharyngeal constrictor
UES relaxation duration (UESdur)	Duration (ms) of the UES relaxation duration
UES relaxation pressure (UESrel)	Mean pressure value (mmHg) during the UES relaxation
Coordination of the UES and the lower pharyngeal contraction (UES-PhCLcoord)	Duration (ms) between the start of the lower pharyngeal contraction and the relaxation of the UES
UES contraction pressure (UESpeak)	Peak contraction pressure (mmHg) at the UES

Table 1; 13 swallowing and respiratory events were selected for analysis, to determine their exact order during swallowing. We defined the start of the ventral movement of the hyoid bone as the indicator of the starting point of the pharyngeal swallowing and this event was selected as the time 0, (t_0), all other events were then referred in time to this particular event

Eleven manometric events were selected for analyses and are defined in Tab.1

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Respiratory phase related to swallowing was measured from registration of the air flow meter (thermistor) and from the nasal pressure transducer, as described in Fig. 3.Registration from the air flow meter, clearly determined the start and end of expiration and inspiration as well as apnea start (AS) and apnea end (AE).

Swallowing-respiratory phase relationship was defined as E-E, expiration before and after swallowing, I-E, inspiration before and expiration after swallowing, E-I, expiration before and inspiration after swallowing and I-I, inspiration before and after swallowing.

From the same registration, swallowing apnea duration, SAD, and the respiratory cycle surrounding the swallowing apnea, SA, was analyzed. To compare the durations in the upright and left decubitus position and during normocapnia and hypercapnia, we selected only swallows with the E-E phase pattern for analyzes, as this was the predominant pattern. During swallows with E-E phase pattern the respiratory cycle includes the last inspiration before swallowing until the last expiration after swallowing, Fig 3

Three respiratory durations were analyzed:

1. Preswallow inspiration

2. Preswallow expiration
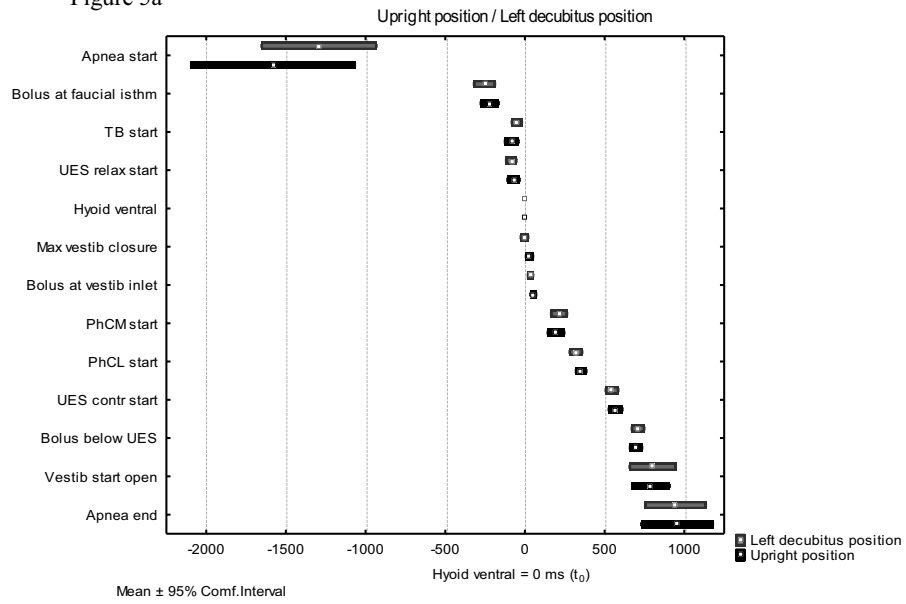
3. Postswallow expiration

Figure 5a

Upright position / Left decubitus position

Apnea start
Bolus at faucial isthm
TB start
UES relax start
Hyoid ventral
Max vestib closure
Bolus at vestib inlet
PhCM start
PhCL start
UES contr start
Bolus below UES
Vestib start open
Apnea end

-2000 -1500 -1000 -500 0 500 1000

Left decubitus position
Upright position

Hyoid ventral = 0 ms (t_0)

Mean ± 95% Comf.Interval

Figure 5a

Left decubitus, normocapnia / Left decubitus, hypercapnia

Apnea start
Bolus at faucial isthm
TB start
UES relax start
Hyoid ventral
Max vestib closure
Bolus at vestib inlet
PhCM start
PhCL start
UES contr start
Bolus below UES
Vestib start open
Apnea end

-2000 -1500 -1000 -500 0 500 1000

Left decubitus hypercapnia
Left decubitus normocapnia

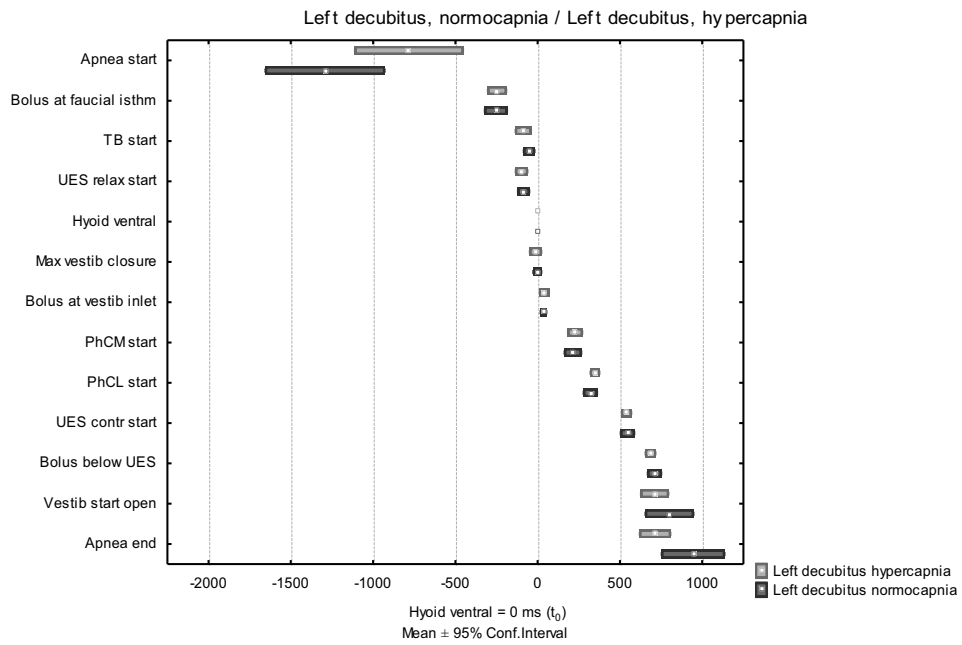Hyoid ventral = 0 ms (t_0)
Mean ± 95% Conf.Interval

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Fig 5a och b: Temporal coordination of swallowing and respiratory events in the upright and the left decubitus position (5a) and with normocapnia and hypercapnia (5b).TB, tongue base, UES, upper esophageal sphincter, PhCM, middle pharyngeal constrictor, PhCL, lower pharyngeal constrictor. For explanation, see Table 1.

Respiratory phase related to swallowing was measured from registration of the air flow meter (thermistor) and from the nasal pressure transducer, as described in Fig.3.Registration from the air flow meter, clearly determined the start and end of expiration and inspiration as well as apnea start (AS) and apnea end (AE).

Swallowing-respiratory phase relationship was defined as E-E, expiration before and after swallowing, I-E, inspiration before and expiration after swallowing, E-I, expiration before and inspiration after swallowing and I-I, inspiration before and after swallowing.

From the same registration, swallowing apnea duration, SAD, and the respiratory cycle surrounding the swallowing apnea, SA, was analyzed. To compare the durations in the upright and left decubitus position and during normocapnia and hypercapnia, we selected only swallows with the E-E phase pattern for analyzes, as this was the predominant pattern. During swallows with E-E phase pattern the respiratory cycle includes the last inspiration before swallowing until the last expiration after swallowing, Fig 3

Three respiratory durations were analyzed:

4. Preswallow inspiration

5. Preswallow expiration

6. Postswallow expiration

Comparisons of the manometric values, timing of swallowing and respiratory events and respiratory durations in the upright versus the left decubitus position and during normocapnia versus hypercapnia, were made using ANOVA repeated measurements and presented as mean values ± standard deviation (SD) or with 95% confidence interval (CI). The mean value of three consecutive swallows was calculated for each parameter and each individual, P-values **< 0,05** were considered statistically significant. Correlation analysis was used to calculate the correlation coefficient of the swallowing and respiratory events. P-values **< 0,005** were considered statistically significant to avoid mass significance. STATISTICATM 7.1 (Statsoft® Inc, Tulsa, OK, USA) was used for statistical analyzes.

3.2   STUDY II

3.2.1   STUDY SUBJECTS

Twenty-six healthy elderly volunteers were included in the study (14 men and 12 women) with a mean age of 73 years (aged 66 - 85 years). To be included in the study the volunteers should be over 65 years of age. None of the subjects had any history of dysphagia, gastroesophageal reflux disease or surgery to the pharynx, larynx or esophagus. None of the subjects were on any medication that might have any influence on the study. All volunteers included in the study had to fill out a health declaration to exclude any serious diseases, such as heart disease, epilepsy, serious lung diseases or any malignant disease.

The study was approved by the Regional Ethics Committee on Human Research at the Karolinska Institute, Stockholm, Sweden (Dnr: 03-255 and 2006/509-31/4) and the study was performed according to the Declaration of Helsinki. Written informed consent was obtained from each study participant.

3.2.2   MATERIAL AND METHODS

Respiratory, manometric and vidoradiographic recordings

are described in **STUDY I**

3.2.3 PROTOCOL

A total of 26 elderly individuals were examined. Six of the included 26 volunteers, (3 women and 3 men) with a mean age of 71 years, (aged 66-84 years) were studied in both the upright and the left decubitus position to evaluate if posture had any effect on swallowing-respiratory coordination in elderly individuals.

Simultaneous videoradiography, solid-state intraluminal manometry (videomanometry) and respiratory registration was performed in both the upright lateral and the left decubitus position (head of the table tilted 8-9° upward). The left decubitus position was chosen to obtain a lateral fluoroscopy image.

The remaining 20 volunteers were only studied in the left decubitus position, together with the above described 6 individuals, a total of 26 individuals were thus studied in the left decubitus position, from now on called "decubitus position". The reason for choosing this position was that 17 of the 26 volunteers, studied only in the decubitus position, also were included in a study, carried out by a research group from our department of anesthesiology, with whom we collaborate. The purpose of their study was to evaluate the effect of partial neuromuscular block on pharyngeal function. This study will be presented as a separate study from the Anesthesiology department.

In our previous study, (36) we examined 32 young healthy individuals with the aim to define timing of respiratory and swallowing events in young healthy individuals. In this study, swallowing and respiratory coordination were measured in both the upright and the decubitus position. In the present study we have used the same equipment, modalities, technique and protocol as in our previous study, in order to be able to compare these results. All elderly, (26 individuals), as well as all young individuals (32 individuals) were examined in the decubitus position, subsequently, we choose that position to be able to compare the young and the elderly individuals.

The remaining **PROTOCOL** is described in **STUDY I**

Statistical Analysis

Evaluating the manometric values, the timing of swallowing and respiratory events and of the respiratory durations, we calculated the mean value of three consecutive swallows. Comparisons of the manometric values, the timing of swallowing and respiratory events and of the respiratory durations in the upright versus the decubitus position were made using Wilcoxon signed rank test, matched pairs, as all these variables were non parametric values. These values were presented as median with 95% confidence interval (CI). Comparison of the manometric values, the timing of swallowing and respiratory events and respiratory durations in the elderly versus the young individuals (parametric values) were made using paired t-test with independent groups and presented with mean values ± standard deviation (SD) or 95% confidence interval (CI). In cases where the above described values were non parametric, the comparisons were made using Mann-Whitney U-test and presented with median values with 95% CI. P-values < 0,05 were generally considered statistically significant.

Correlation analysis was used to calculate the correlation coefficient of the swallowing and respiratory events in the young and elderly individuals. P-values < 0,005 was considered statistically significant to avoid mass significance. Calculating the correlation coefficient for the upright and decubitus position (non-parametric), we used Spearman rank order correlation, p-values < 0,05 were considered statistically significant. StatisticaTM 10 (Statsoft® Inc.,Tulsa, OK, USA) was used for analysis,

3.3   STUDY III

3.3.1 STUDY SUBJECTS

Fifteen volunteers, eight male and seven female (age 43 - 64 y, mean 51 y) entered the study after oral and signed informed consent. Inclusion criteria included age less than 65 years, BMI less than 30 and ongoing symptoms of heartburn and regurgitation since more than one year. In addition, gastroesophagoscopy should demonstrate a reflux esophagitis. Exclusion criteria were history of cardiac disease, including heart fibrillation, severe lung disease, diabetes, ongoing malignancy or history of surgery to the pharynx, larynx or esophagus. Prior to inclusion, all volunteers had to fill out a health declaration to

document the inclusion criteria. All volunteers were asked to make a pause with their proton pump inhibiting medication, one week before the study. If this caused severe symptoms they should continue the medication. None of the subjects were on any other medication that would influence the study.

The study was approved by the Regional Ethics Committee on Human Research at the Karolinska Institutet, Stockholm, Sweden, Dnr: (03-255) and the study was performed according to the Declaration of Helsinki.

3.3.2 MATERIAL AND METHODS

Respiratory, manometric and videoradiographic recordings;
Are described in **STUDY I**

3.3.3 PROTOCOL

Simultaneous videoradiography, solid-state intraluminal manometry (videomanometry) and respiratory registration was performed in the upright lateral position.

In our previous study (36) we examined 32 young healthy individuals with the aim to define timing of respiratory and swallowing events, with high temporal resolution. In the present study we used the same equipment, technique and protocol, in order to be able to compare these results. After a 10 minutes adaptation period, with all equipment installed, during which swallowing and respiration were monitored, all participants performed three consecutive swallows of 10 ml of water soluble contrast medium (Omnipaque® 240 mg/ml, Nycomed Imaging, Oslo, Norway) given as an orally administered bolus via a standard 30 mL syringe. Subjects were informed before the contrast medium was given and instructed to swallow spontaneously when comfortable.

The remaining **PROTOCOL** is described in **STUDY I**

Statistical analyses

Evaluating the manometric data, the timing of swallowing and respiratory events and the respiratory durations, we calculated the mean value of three consecutive swallows. Comparison of the manometric data from the GERD patients versus the young, (32 individuals, parametric values) were made using paired t-test with independent groups and

presented with mean values ± standard deviation (SD) or 95% confidence interval (CI), p-values < 0,05 were generally considered statistically significant. Correlation analysis was used to calculate the correlation coefficient between the swallowing and respiratory events in the GERD patients and the normal historical controls, p - values < 0,05 were considered statistically significant. To evaluate the categorical data of swallowing dysfunction, chi^2 test was used. StatisticaTM 10 (Statsoft® Inc.,Tulsa, OK, USA) was used for analysis

4 RESULTS

4.1 STUDY I

The temporal coordination of the physiological swallowing events was stable comparing all three conditions, the upright with the left decubitus position and the normocapnia with hypercapnia, Fig 5a and 5b. Only the vestibular closing time was significantly earlier (p < 0,004) in the left decubitus position compared to the upright position. There were no differences in swallowing events comparing normo-and hypercapnia.

Respiratory coordination demonstrated a higher degree of variability comparing the three conditions. SAD was significantly decreased during hypercapnia compared to normocapnia (p = 0,003). Furthermore the apnea end, AE, was earlier during hypercapnia compared to normocapni (p = 0.043).

The UES resting pressure was significantly lower during hypercapnia compared to normocapnia. None of the remaining manometric values showed any significant differences comparing the upright and the left decubitus position or during normo- or hypercapnia.

There were no differences comparing the qualitative radiographic evaluation. Pharyngeal spill-over was present in 10-19% of the swallows in all three conditions. Subepiglottic penetrations were present in only 2-4% of the swallows in all conditions. Only one supraglottic penetration was found in the left decubitus position during normocapnia. Retention was only seen in three swallows. All penetrations were totally cleared during swallowing. Tab 2.

Table 2

Swallowing dysfunction	Upright position	Decub position	Decub position CO_2
	n = 90	n = 92	n = 92
Pharyngeal spill.over	17 (19%)	9 (10%)	12 (13%)
Subepiglottic penetration	2 (2%)	3 (3%)	4 (4%)
Supraglottic penetration	0 (0%)	1 (1%)	0 (0%)
Tracheal aspiration	0 (0%9	0 (0%)	0 (0%)
Retention	2 (2%)	1(1%)	0 (0%)

Swallowing dysfunctions in young healthy individuals upright versus decubitus position and with normos-versus hypercapnia. Swallowing dysfunction was the most common, dysfuction,
ranging from 10% to 19% in all three conditions.

Swallow-respiratory phase pattern, was analysed in 288 swallows in the upright and left decubitus position and during normo- and hypercapnia. In this study we demonstrate the E-E phase pattern in 286 out or 288 swallows. Only in one individual, we found one I-E and one E-I swallow in the left decubitus position. In all other individuals, we found only E-E swallowing in the upright and the left decubitus position as well as during normo- and hypercapnic breathing.

4.2   STUDY II

Comparing young and elderly individuals, there were good correlation between the 13 respiratory, manometric and videofluoroscopic events in both the young and the elderly individuals. In the young group there was a strong correlation between the contraction start of the PhCM and PhCL, (p = 0,002) as well as with the UES contraction start (p = 0,001 and p = < 0,001), respectively. Correlation analyses could demonstrate that the elderly partly had a similar pattern as in the young group, where the contraction starts of the PhCM and the PhCL, (p = 0,004), PhCM and the UES (p < 0,001) and the PhCL and the UES, (p = 0,001) were highly correlated with each other. In contrast to the young group, there was no correlation of the time when bolus reached the vestibular inlet and the maximal closure of the vestibule. Comparing the temporal coordination of the swallowing and respiratory events between the young and elderly individuals, only the maximal vestibular closure was significant earlier in the old group (p = 0,006).

In the elderly group in the decubitus position we could not demonstrate any correlation between the contraction start of the middle and lower pharyngeal constrictors or with the contraction start of the UES. Only two correlations was found in the decubitus position, a high correlation between the start of the UES relaxation and the maximal closure of the vestibular inlet (p = 0,02), Furthermore we could demonstrate a high correlation between the opening of the vestibular inlet and the time when bolus had passed the UES (p = 0,02)
.

However, in both the young and the elderly groups, the AE was correlated with the opening of the vestibular inlet. Thus, there was no correlation of the apnea start, AS, to any other events in the young group. AS was also highly variable in time.

The most important results were the manometric values, comparing the elderly with the normal controls, where we could demonstrate several altered contractions and UES relaxations and contractions.

The UES resting pressure was lower before swallowing in the elderly compared to the younger group. There was no difference in the resting pressure after swallowing comparing the two groups. The TB peak contraction was decreased and the contraction rate was slower among the elderly compared to the young. Furthermore, the contraction duration of the PhCL was prolonged in the elderly compared to the young.

The velocity of the contraction wave in the pharynx was slower in the elderly compared with the young group. Tab 3.

Table 3

Manometric values in young and elderly individuals in decubitus position		Young		Elderly	
		N	Mean (SD)	N	Mean (SD)
UES resting pressure before swallowing	mmHg	31	85 (40)*	25	64 (45)*
UES resting pressure after swallowing	mmHg	30	77 (47)	26	61 (43)
TB contraction pressure	mmHg	31	286 (111)*	26	230 (174)*
TB contraction rate	mmHg/s	31	1525 (758*)	26	848 (590)*
TB contraction duration	ms	31	736 (148)	26	763 (191)
PhCL contraction pressure	ms	31	286 (124)	26	311 (139)
PhCL contraction rate	mmHg/s	31	1347 (535)	26	1344 (743)
PhCL contraction duration	ms	31	559 (99)*	26	658 (140)*
TB-PhCL contraction velocity	cm/s	31	13,2 (6)*	26	7,4 (2,3)*
UES relaxation duration	ms	31	593 (134)	26	591 (128)
UES relaxation pressure	mmHg	31	15,1 (10,5)	26	12,9 (9,7)
Coordination of UES and PhCL	ms	31	(-)277 (143)	26	(-) 300 (109)
UES contraction pressure	mmHg	30	365 (87)	26	379 (144)

UES = Upper esophageal sphincter; TB = Tongue base; PhCL = Lower part of the
 pharyngeal constrictor;

* significant differences

Swallowing-respiratory phase pattern was analyzed, in the upright and the decubitus position. We analyzed 34 swallows in total, 18 in the upright position and 16 in the decubitus position. In both positions there were 100% E-E swallowing phase pattern. The swallowing-respiratory phase pattern did not show any differences between the young and the elderly. In the young group, 91 out of 93 swallows (98%) were E-E swallows compared to 69 out of 75 swallows (92%) in the elderly group.

There were no I-I swallow in any of the groups. In the young group there were one I-E (1%) and one E-I (1%) swallows and in the elderly group there were two I-E (3%) and four E-I (5%) swallows.

Qualitative radiographic events in upright and decubitus position did only demonstrate one difference in the supepiglottic penetration which was somewhat more common in the upright position with five subepiglottic penetrations compared to one in the decubitus position. The other radiographic events were more or less the same. Tab 4

Table 4

Swallowing dysfunction	Position	
	Upright	Left decubitus
	n= 18	n=16
Pharyngeal spill over	4 (22%)	3 (19%)
Subepiglottic penetration	5 (28%)	1 (6%)
Supraglottic penetration	1 (6%)	0 (0%)
Tracheal penetration	0 (0%)	0 (0%)
Retention	0 (0%)	0 (0%)

Qualitative radiographic variables were analyzed in respect to swallowing dysfunction, in a total of 18 swallows in the upright position and 16 swallows in the decubitus position.

In the elderly group there was a significantly shorter expiration after SA compared to the young group (p = 0,002). There were no other differences in respiratory durations or SAD.

Pharyngeal spill over was more common in the elderly compared to the young group, 18% and 10% respectively. Even subepiglottic penetration was more common among the elderly compared to the young group, 9% and 3% respectively. Supraglottic and tracheal penetrations as well as retention were rare in both groups, Tab 5.

Table 5

Swallowing dysfunction	Age	
	Young	Elderly
	n=92	*n*=76
Pharyngeal spill over	9 (10%)	14 (18%)
Subepiglottic penetration	3 (3%)	7 (9%)
Supraglottic penetration	1 (1%)	0 (0%)
Tracheal penetration	0 (0%)	0 (0%)
Retention	1 (1%)	1 (1%)

Comparing swallowing dysfunction in the elderly individuals,(76 swallows) with the young individuals (92 swallows), pharyngeal spill over was more common among the elderly (18%) compared to the young, 9%

4.3   STUDY III

The GERD patients showed good temporal coordination of the 13 temporal swallowing and respiratory events, (Fig 7). This implies that the registered events occurred in a sequential order. Only the contraction start of the PhCM occurred earlier compared to the normal controls (p = 0,04). Furthermore, comparing the GERD patients and the normal historical controls, there were an earlier closure of the vestibular inlet (p = 0,02).

Figure 7.

Fig 7: Temporal coordination of 13 swallowing and respiratory events in GERD patients compared to the normal controls. Only the vestibular closure and the contraction start of the PhCM was significantly earlier in the GERD patients compared to the normal controls. For definitions; see Table 1

As mentioned above, in our group of normal controls, we could demonstrate a high correlation between the contraction start of the PhCM and the PhCL (p < 0,001) and both the pharyngeal constrictors had a high correlation to the contraction of the UES (p < 0,001). However, in the group of GERD patients, we could demonstrate a correlation of the PhCM and PhCL (p = 0,01). Likewise, there was a correlation between the contraction start of the PhCL and the UES (p < 0,007), Thus, there were no correlation between the contraction start of the PhCM and the UES. Consistent with our normal controls, there was a correlation between the apnea end, AE, and the start of the opening of the vestibular inlet (p = 0,002). This is in accordance with the correlation in our historical controls (p < 0,001).

The main findings in this study were the manometric values, where several values differed significantly comparing the GERD patients with the normal controls. Subsequently, the TB peak contraction was decreased (p < 0,04) and the contraction rate was slower (p < 0,001) compared to the normal controls. Furthermore, the PhCL contraction rate was slower in the GERD group (p < 0,001) compared to the normal controls. However, the PhCL contraction duration was prolonged (p < 0,05) compared to the normal controls.

Furthermore the wave speed, which is the velocity of the contraction wave in the pharynx, was much faster (p < 0,0001) in the GERD group compared to the normal controls.

Further, the UES resting pressure was lower after swallowing (p < 0,004), compared with the normal controls, and the UES residual pressure was lower in the GERD group (p < 0,04) compared to the normal controls, see Tab 6.

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Table 6
Comparing manometric values between patients with GERD and normal controls

		GERD n = 17		Normal n = 30	
Manometric values					
		Mean	SD	Mean	SD
TB amp	mmHg	212*	85	288	132
TB slope	mmHg/s	522*	204	1430	793
TB dur	ms	801	118	778	165
PhCL amp	mmHg	281	262	298	119
PhCL slope	mmHg/s	739*	510	1404	476
PhCL dur	ms	647*	114	568	134
Wavespeed	cm/s	23*	16	9	2,6
Coord PhCLstart-UES start	ms	-354	151	-310	122
UES amp	mmHg	481*	156	402	99
UES dur	ms	644	184	583	153
UES res	mmHg	8*	10	15	11

Several manometric values were deteriorated in the GERD patients
compared to the normal controls.

*p= < 0,05
For definitions, see Table 1

There were no differences in respiratory durations or in apnea durations comparing the GERD group with the normal controls. There were no differences in swallowing-respiratory phase pattern comparing the GERD group with the normal controls. The most prevalent swallowing dysfunction was the "pharyngeal spill-over, which did not differ between the GERD patients and the normal controls and occurred in 15% of swallows in the GERD patients compared to 10 % in the normal controls. However, retention (p = 0,003) and subepiglottic penetration (p = 0,001) was significantly more common among the GERD patients, see Tab 7.

Table 7

Swallowing dysfunction	GERD	Normal controls
	n = 45	*n= 93*
Pharyngeal spill-over	7 (15%)	9 (10%)
Retention	5 (11%)*	1 (1%)
Subepiglottic penetration	5 (11%)*	3 (3%)
Supraglottic penetration	0	1 (1%)
Tracheal penetration	0	0

n = numberof observed swallows
* p< 0,05

The retention (p< 0,003) and the subepiglottic penetration (p< 0,01) were more frequent in the GERD group compared to the normal controls.

4.4 STUDY IV

The main findings in this study were an increased peak contraction pressure (p < 0,05) and an increased contraction duration (p < 0,05) of the PhCi with the Mendelsohns maneuver, compared to the control swallow. Furthermore, the relaxation pressure of the UES was significantly increased in the super-supraglottic swallow compared to the control swallow (p < 0,05). The peak value of the UES contraction was decreased in both the Mendelsohns maneuver (p < 0,05) and the supraglottic swallow (p < 0,05).
Videoradiographic evaluation demonstrated a longer duration of the bolus transit time in the super-supraglottic and the Mendelsohns maneuver.

Table 8

Seven manometric variables were analysed during 3 different swallowing maneuvers	Control	Supraglottic	Super-supraglottic	Mendelsohns maneuver
Manometric parameters				
Pharyngeal peak contraction (mmHg)	178 ± 17,7	177 ± 26,9	171 ± 19,6	201 ± 16,3 *
Pharyngeal peak duration (msec)	665 ± 64	751 ± 105	822 ± 101	2619 ± 207 *
Pharyngeal contraction rate (mmHg/msec)	916 ± 178	887 ± 135	829 ± 90	945 ± 94
UES relaxation pressure (mmHg)	6,67 ± 0,8	6,16 ± 1,55	15,1 ± 2,37 *	6,5 ± 1,62
UES relaxation duration (msec)	509 ± 24,1	502 ± 21,2	435 ± 34	497 ± 33,3
Coordination of PhCi-UES (msec)	−246 ± 26,2	−226 ± 13,4	−233 ± 33,9	−239 ± 25,3
UES peak contraction (mmHg)	301 ± 23,6	260 ± 23,7 *	259 ± 26,2	230 ± 16,5*
Videoradiographic parameters				
Bolus transit time (sec)	0,77 ± 0,09	0,8 ± 0,10	0,86 ± 0,15*	0,87 ± 0,14 *
Maximal hyoid movement (mm)	19,6 ± 3,56	20,2 ± 0,78	19,8 ±7,38	18,32 ± 3,97

*= p <0,05

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5 DISCUSSION

The true prevalence of dysphagia is unknown but epidemiologic studies estimate the prevalence in individuals over the age of 50 to be in the range of 16% to 22 % , (2, 37) A survey study of all ages in a Midwestern population estimated the prevalence of dysphagia to be 6% to 9%, (38). More important is the fact that up to 60% of occupants in nursing home, have feeding difficulties, (5) and nursing home occupants with oropharyngeal dysphagia and aspiration have a 45% 12-months mortality, (3)

The management of oropharyngeal dysphagia often involves a multidisciplinary evaluation with the aims to identify and characterize oropharyngeal dysphagia as well as diagnose the underlying cause whenever possible. The major symptoms indicative of oropharyngeal disease include dysphagia (difficulties in swallowing), odynophagia (painful swallowing) regurgitation, pyrosis (heartburn) and chest pain. Prominent pulmonary symptoms include chronic cough, wheezing and recurrent pneumonias which may indicate swallowing disorder.
Dysphagia is clinically classified into functional (neuromuscular) motor dysfunction or mechanical dysfunction. A mechanical dysfunction might be a cricopharyngeal strictures, posterior hypopharyngeal diverticulum (Zenker), oropharyngeal tumors and cervical osteophytes. Dysphagia due to mechanical disorders can usually be treated by dilatation or surgery. The management of dysphagia due to motor dysfunction has no well-controlled treatment studies, instead, treatment is supportive and empiric. However, in most patients with oropharyngeal dysphagia, symptoms are from neuromuscular causes. If neuromuscular dysphagia is suspected, treatment may be directed by the specific cause of dysfunction and the degree of functional impairment. Swallowing therapy with diet modification, swallowing posture and swallowing technique may improve symptoms and oral nutrition, (39-40)

The primary objective of this thesis was to describe the exact temporal coordination of swallowing and respiratory events in young healthy individuals, using modalities with high temporal resolution. The last decades, several neuromuscular studies have been performed, which have increased the understanding of the coordination of the swallowing and respiration in the brain stem. Also the clinical studies of this coordination have increased significantly. The sequential and orderly activity of swallowing muscles can be

demonstrated by EMG methods. The submental and suprahyoid muscles are easily recorded by surface electrodes and demonstrate the onset and duration of the oropharyngeal phase of swallowing.

In our studies, we used pharyngeal manometry to demonstrate the onset, offset and duration of the tongue base, TB, pharyngeal muscles and the cricopharyngeal muscle. The manometry catheter had transducers with a transducer system that was extremely non-compliant with a low volumetric compliance and a pressure rise rate, more than 2000 mmHg/s. Furthermore, the technique for respiratory recordings, we used a bidirectional air flow meter, developed by our research group, measuring both oral and nasal air flow with high temporal resolution. This made it possible to assess a precise measurement of inspiration and expiration in correlation to the exact position of contrast bolus and to the contractions and relaxations of the pharyngeal and cricopharyngeal muscles. The air flow meter was validated by comparing it with diaphragmatic and abdominal electromyography, EMG, and was proven to be accurate and reliable, (33)

In this thesis, the objective was to describe a normal swallowing and respiratory pattern with high temporal resolution. We decided to use young healthy volunteers to correspond to a healthy population. This group of young healthy volunteers consisted mainly of medical students of the Karolinska Insititutet. This material would later be used as a normal control group to the elderly healthy volunteers and a group of patients with gastroesophageal reflux disease, GERD.

As described above, dysphagia with a neuromuscular cause does not have any specific treatment except for supportive treatment as swallowing therapy with diet modification and swallowing posture or technique. However, with the knowledge of the importance of swallowing and respiratory coordination for a safe swallow, we believe that it is important to investigate how the swallowing and respiratory coordination functions. If the patient have an impaired coordination of swallowing and respiration, it might be easier to teach the patient to alter the respiration rather than to change the swallowing, which has a fixed pattern from the brainstem. Respiration is also controlled from the brainstem but still you can voluntarily influence the respiration (inspiration or expiration) and voluntarily, hold your breath.

5.1 STUDY I

The primary objective of the study with young healthy individuals was to obtain normative data on respiratory and swallowing coordination in young healthy individuals, using simultaneous modalities with high temporal resolution. The technique of air flow recordings, made it possible to asses a precise measurement of inspiration and expiration in correlation to the exact position of contrast bolus and to the contractions and relaxations of the pharyngeal and cricopharyngeal muscles.

To further challenge the interaction between respiration and swallowing, the study was designed to determine whether body position or respiratory drive influenced swallowing physiology or swallowing-respiratory coordination. This is the first in a series of studies with the aim to define normal and abnormal respiratory and swallowing patterns.

We could demonstrate a well-timed correlation of the respiratory and pharyngeal-laryngeal swallowing events in the young healthy individuals, despite position.

Several swallowing and respiratory events were highly correlated to each other, with one exception, the AS which was highly variable with a range from 50 to 5000 ms prior to the pharyngeal swallow. AS always occurred before pharyngeal swallowing and vestibular closure in both the upright and the decubitus position, which is consistent with previous studies, (21, 28). This implies that AS is not due to vestibular closure and indicates strongly that AS is controlled from the brainstem. Hiss and Charbonneau, (41-42) could demonstrate that in lareyngectomised patients, SA still occurred, even though SA is theoretically no longer needed in individuals with laryngectomi. Subsequently SA ought to be centrally controlled from the brain stem. However, the AE, only correlated with one swallowing event in the upright position, i.e. the opening of the vestibular inlet. The fact that the opening of the vestibular inlet always occurred before the AE, in both the upright and the decubitus position, indicated that even the AE is centrally controlled and not due to laryngeal opening

The temporal coordination of the physiological swallowing events was stable comparing all three conditions, the upright with the left decubitus position and the normocapnia with hypercapnia, Fig 5a and 5b. Only the vestibular closing time was significantly earlier (p < 0,004) in the left decubitus position compared to the upright position. There were no differences in swallowing events comparing normo-and hypercapnia.

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The UES resting pressure was significantly lower during hypercapnia compared to normocapnia. None of the remaining manometric values showed any significant differences comparing the upright and the left decubitus position or during normo- or hypercapnia.

Respiratory coordination demonstrated a higher degree of variability comparing the three conditions. There were no differences comparing the qualitative radiographic evaluation.

According to the swallowing dysfunction, pharyngeal spill-over was present in 10-19% of the swallows in all three conditions. Subepiglottic penetrations were present in only 2-4% of the swallows in all conditions. Only one supraglottic penetration was found in the left decubitus position during normocapnia. Retention was only seen in three swallows. All penetrations were totally cleared during swallowing, Tab 2.

SAD was significantly decreased during hypercapnia compared to normocapnia (p = 0,003). Furthermore the apnea end, AE, was earlier during hypercapnia compared to normocapni (p = 0.043)
.

Swallow-respiratory phase pattern, was analysed in 288 swallows in the upright and left decubitus position and during normo- and hypercapnia. In this study we demonstrate the E-E phase pattern in 286 out or 288 swallows. Only in one individual, we found one I-E and one E-I swallow in the left decubitus position. In all other individuals, we found only E-E swallowing in the upright and the left decubitus position as well as during normo- and hypercapnic breathing.

Consistent with previous studies (21, 24, 28, 42) we could demonstrate that swallowing was initiated during expiration and the predominant respiratory phase pattern was the E-E pattern. In contrast to other studies, we could demonstrate the E-E phase pattern occurred in basically all swallows irrespectively of position and respiratory drive. This fits with the theory that exhalation clears the vestibular inlet from residue before the next inspiration. Saito et al. demonstrated how stimulation of the sensory superior laryngeal nerve in rat resulted in swallowing only if done during expiration or immediately after inspiration. Fig 8.

Figure 8.

Fictive swallowing evoked by stimulation of superior laryngeal nerve (SLN).

Swallowing is monitored by a hypoglossal burst of activity, only when not simultaneous with the inspiratory activity of the phrenic nerve

Saito Y, Brain and Development, 2003 (25), issue 5, 338

5.2   STUDY II

The primary objective of this study was to obtain normative data of respiratory and swallowing coordination in elderly individuals without any swallowing disorders, using simultaneous modalities. In this study we used the same modalities, techniques and protocol as in **STUDY I.**

Consistent with our previous study, examining young, healthy individuals, we could demonstrate a well timed coordination of the respiratory and pharyngeal-laryngeal swallowing events even in the elderly individuals. However, comparing the elderly with the young group, only the maximal vestibular closure was significant earlier among the elderly. Comparing our normal, healthy controls with the elderly healthy volunteers, we could not demonstrate any differences in swallowing-respiratory phase pattern. This is in accordance with Martin Harris, (28, 32, 42), who nor could demonstrate any differences in swallowing-respiratory phase pattern in the elderly. On the other hand, Shaker et al. (29), demonstrated that the elderly initiated the swallowing more often in the inspiratory phase. However, in accordance with Shaker, we could not demonstrate any differences in respiratory phases according to different position.

We could demonstrate that the swallowing and respiratory coordination in the elderly individuals did not differ significantly comparing the upright and the decubitus position. Comparing the elderly individuals in this study with our young healthy controls, we could only demonstrate a few changes in temporal swallowing and respiratory coordination; however, we could demonstrate several differences in the manometric values and swallowing dysfunction. We believe that these differences mainly are due to age-related changes in sensory nerve function, we speculate that even the muscle strength of the mouth, pharynx and the UES may weaker due to age-related changes.

Other correlations that existed in the young group but not among the elderly were the correlation between the time when bolus reached the vestibule and the maximal closure of the vestibule. Furthermore, the AE was highly correlated with the vestibular opening in the young group. Nonetheless, we could not find this correlation among the elderly. The lack of these correlations may have a negative impact on the safety of the swallowing

According to the qualitative radiographic variables, we could demonstrate that there were no difference in pharyngeal spill-over comparing the upright position and the decubitus position. However, supepiglottic penetration was more common in the upright position compared to the decubitus position. Thus, in the upright position the gravity will affect the bolus in an inferior direction and if bolus control is decreased in the elderly, due to decreased sensibility in the mouth and pharynx, (44) this might imply a higher incidence of subepiglottic penetration. Tab 4.

However, comparing the elderly with the young group, we could demonstrate that pharyngeal spill-over was more common among the elderly as shown in Table 5. Supraglottic penetration, tracheal penetration and Retention were rare in both groups. It is to be noted, however, that all recordings were performed on healthy elderly individuals and that changes in the swallowing pattern most likely could be anticipated when pathological conditions are encountered.

5.3   STUDYIII

The aim of this study was to define the timing of respiratory and swallowing events with high temporal resolution in patients with gastroesophageal reflux disease, GERD, to evaluate whether swallowing and respiratory coordination differs compared with a group of normal controls.

We have previously studied respiratory and swallowing coordination in young healthy individuals in the upright position (36) and these results will be compared with the above described patients with GERD. The young group was studied with the same equipment, technique and protocol as the present study.

GERD is a highly prevalent gastrointestinal (GI) disorder that usually presents with the typical manifestation of heartburn and regurgitation. This is associated with a reverse flow of gastric contents through the esophagus that occasionally reaches the pharynx and potentially might cause laryngo-pharyngeal reflux, (LPR), hereby irritating tissues in both the pharynx and the larynx.

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While we know that reflux affect long-term outcome and is associated with several laryngeal disorders such as laryngitis, hoarseness, granulomas, stenosis and carcinoma of the larynx, (45-46), we lack a more comprehensive understanding on the effect of how the oropharyngeal swallow may be affected by leaking duodeno-gastric contents in GERD patients.

This study was designed to examine whether swallowing disorders are more common in GERD patients compared to a group of normal controls. We examined the temporal coordination of thirteen respiratory and swallowing events by videofluoroscopy, pharyngeal manometry and respiratory recordings, all with high temporal resolution, Tab 1.

Our main findings in the GERD patients were several altered manometric values, such as tongue base contraction which was both weaker and slower compared to our historical controls.

The lower pharyngeal constrictor was slower but with prolonged contraction duration, probably as a compensation for the decreased an slower TB contractio. Other altered manometric values were a lower residual pressure in the UES. Furthermore the GERD patients had a decreased resting pressure after swallowing, which might increase the risk of reflux through the UES. Finally we could demonstrate a faster contraction wave through the pharynx. There are few previous studies concerning GERD and swallowing dysfunction where pharyngeal manometry has been used to study pharyngeal swallow.

Table 9

Comparing manometric values between patients with GERD and normal controls

Manometric values		GERD $n = 17$		Normal $n = 30$	
		Mean	SD	Mean	SD
TB amp	mmHg	212*	85	288	132
TB slope	mmHg/s	522*	204	1430	793
TB dur	ms	801	118	778	165
PhCL amp	mmHg	281	262	298	119
PhCL slope	mmHg/s	739*	510	1404	476
PhCL dur	ms	647*	114	568	134
Wavespeed	cm/s	23*	16	9	2,6
Coord PhCLstart-UES start	ms	-354	151	-310	122
UES amp	mmHg	481*	156	402	99
UES dur	ms	644	184	583	153
UES res	mmHg	8*	10	15	11

Several manometric values were deteriorated in the GERD patients
compared to the normal controls.

$* = p < 0,05$
For definitions, see Table 1

In one of our previous studies, (manuscript in print) examining elderly healthy individuals, we could demonstrate altered manometric values, very similar to the values of the GERD patients. Most likely the reflux of gastro-duodenal contents will impair the sensation in the superior laryngeal nerve, SLN, (2)(7) which most likely will influence on the contractions of the tongue base, pharyngeal constrictors and the UES.

5.4   STUDY IV

As our first three studies, mostly were experimental studies, we decided to include a clinical study to evaluate if we could demonstrate any differences in manometric values during three different swallowing maneuvers. Swallowing maneuvers are mainly used when the dysphagia is due to a functional (neuromuscular) dysfunction. There are several swallowing maneuvers and we chose; the supraglottic, the super-supraglottic

and the Mendelsohns maneuver. The supraglottic swallow is designed to close the true vocal cords before and during swallowing to prevent entry of food into the airways. The super-supraglottic swallow is designed to close the airway entrance above the true vocal cords and the Mendelsohns maneuver is designed to extend and prolong the UES opening during swallowing. How to perform these swallowing manevers are described in the "Material and Methods."

The main findings in this study were seven manometric values that were significantly changed compared to the control swallow. The PhCi peak contraction and the contraction duration were increased in the Mendelsohns maneuver compared to the control swallow. The UES relaxation pressure was increased in the super-supraglottic swallow, compared to the control swallow. The peak value of the UES contraction was lower in both the Mendelsohns maneuver and the supraglottic swallow compared to the control swallow.

According to the videoradiography, the only two finding were a significantly prolonged transit time in the super-supraglottic swallow and in the Mendsohns maneuver, compared to the control swallow.

Bulow et al. (8), examined patients with dysphagia with simultaneous videoradiography and videomanometry. Supraglottic swallow, effortful swallow or chin tuck were used as swallowing maneuvers. However, they could not reduce the number of misdirected swallows, but effortful swallow and chin tuck, significantly reduced the depth of contrast penetration.

Maintaining an oral intake, with a safe swallow, ensures a good quality of life and is the main goal in the rehabilitation of oropharyngeal dysphagia. The swallowing speech and language pathologist need a thorough understanding of different swallowing techniques. However, Bulow et al. could not demonstrate reduced number of misdirected swallows but effortful swallow and chin tuck, showed a significantly reduced depth of contrast penetration.

It is difficult to understand how these swallowing techniques affect the swallowing physiology. More examinations of patients with dysphagia is needed to determine whether swallowing maneuvers could be improved in any way.

The reason why we could only demonstrate a few manometric differences and two videoradiographic changes compared with the control swallows, could depend upon, that healthy volunteers need more extensive training before they can use the swallowing maneuver properly. Another reason could be that the swallow has a fixed pattern which is difficult to change, especially if the swallow is not impaired.

Our study showed that, in the super-supraglottic swallow, the UES relaxation pressure was significantly increased compared to the control swallow. This is probably due to the effort that is combined with breath holding, which might result in an increased pressure even in the cricopharyngeal muscle causing an increased relaxation pressure. The increased UES relaxation pressure might also explain the prolonged bolus transit time.

6 CONCLUSION

In conclusion, we have studied respiration and swallowing in young healthy individuals, using simultaneous modalities and with high temporal resolution and could demonstrate that young healthy individuals had a well timed coordination of swallowing and respiratory events that was not influenced by different body positions. Basically all swallows occurred during E-E phase pattern. Several events were highly correlated to each other despite body position. Hypercapnia induced a later AS and an earlier AE, subsequently a shorter SAD.

Comparing our young healthy controls with elderly healthy individuals, we could demonstrate that swallowing and respiratory coordination in elderly individuals did not differ, comparing the upright versus the decubitus position. However, comparing the elderly individuals with our young healthy controls, we could demonstrate several manometric differences and a few swallowing dysfunctions. We believe that these differences are mainly due to age-related changes in the sensory nerve function which will imply on the muscle strength of the mouth, pharynx and the UES.

Comparing the GERD patients with our young healthy controls we have demonstrated several impaired variables in the GERD group, according to the pharyngeal swallow which ought to influence on the safety of the swallowing. However, there were only a few swallowing dysfunctions in the GERD patients compared to the normal controls. According to Jones et al. (47) this might be an adjusted act to compensate an impaired swallow. The early start of the vestibular closure might be one of the compensations for a safe swallowing. It is reasonable to believe that the laryngeal-pharyngeal reflux might influence the laryngeal and pharyngeal mucosa, resulting in a deteriorated sensibility. With a decreased sensory input, it seems likely that the connection to the motoneurons also would be weak and possibly the contractions and relaxations would be weaker

In our last study we decided to define manometric values by combining intraluminal pharyngeal manometry with videoradiography, evaluating three different swallowing maneuvers in ten healthy volunteer. This study could only confirm a few statistically significant manometric changes when healthy volunteers used three different swallowing maneuvers. This might be explained by a fixed pattern in the normal swallow or the need for more extensive training of the swallowing maneuvers. We do know from clinical

experience that the described techniques do work in dysphagic patients. Further studies of the swallowing techniques and their effects on the pharyngeal swallow are needed both in patients with impaired swallowing and in healthy elderly volunteers.

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