Laryngopharyngeal reflux - development and refinement of diagnostic tools

Olle Andersson

Institute of Clinical Sciences
at the Sahlgrenska Academy
University of Gothenburg

University of Gothenburg

Correspondence to:
Olle Andersson
Division of Otorhinolaryngology
Sahlgrenska University Hospital
SE-413 45 Göteborg, Sweden
olof.l.andersson@vgregion.se

ISBN 978-91-628-7850-0
Printed by Intellecta DocuSys AB. V. Frölunda, Sweden 2009

Abstract

Laryngopharyngeal reflux (LPR), characterized by symptoms of chronic cough, hoarseness, throat clearing, globus, laryngospasm, throat pain and excessive mucus has in recent years been recognized as an extra-esophageal manifestation of gastroesophageal reflux disease (GERD). There are still many questions to be answered regarding how to diagnose the LPR disease and how to effectively select patients that may benefit from treatment.

The aim of this thesis was to develop and refine diagnostics of LPR. In study I, an upper limit of normality (ULN) for hypopharyngeal acid exposure with a cut-off level of pH5 instead of the traditional pH 4 was established. Re-evaluation of ambulatory two-level 24-hour pH-registrations of 35 healthy volunteers showed an ULN of 1.5% of the pH registration. In study II we investigated the natural history of LPR and if asymptomatic pharyngeal reflux is a risk factor for the development of LPR disease. Twenty-four healthy volunteers were re-evaluated after 13 years with pH-monitoring, symptom registration and a larynx examination. Upper airway symptoms had developed in 10 of 24 (42%) subjects and pathological laryngeal findings in 9 (39%) subjects. However, the portion of subjects with pathological acid exposure at pH 4 in the hypopharynx had decreased from 42 to 13%. Study III describes the Swedish translation and adaption of the questionnaire Laryngo Pharyngeal Reflux – Health Related Quality of Life Questionnaire (LPR-HRQL). LPR-HRQL was psychometrically evaluated in a population of 228 patients with upper airway symptoms. The Swedish translated version of LPR-HRQL proved to be a statistically valid instrument to assess HRQL in patients with LPR disease. Study IV described the development and psychometric evaluation of the Pharyngeal Reflux Symptom Questionnaire (PRSQ) in the same cohort. After analysis and item-reduction it was found to be a valid and reliable instrument.

The present thesis reports that the presence of asymptomatic hypopharyngeal reflux do not constitute a risk factor for future development of LPR. Although upper airway symptoms and pathological laryngeal findings seem to develop over time in a sample of healthy volunteers, there was only a weak correlation between symptoms, laryngeal findings and pH-monitoring results. The thesis also reports on normal values for hypopharyngeal reflux with a pH 5 which may potentially improve upon diagnosis since weakly acidic reflux has been implicated in mucosal damage and symptom generation. The thesis also presents validated questionnaires in Swedish for health related quality of life (LPR-HRQL) and diagnosis (PRSQ) of the LPR disease. Correctly developed and validated patient reported outcome (PRO) questionnaires have the potential to sharpen the diagnosis and to capture a treatment effect, both in research and in the clinic.

List of publications

I. Andersson O, Ylitalo R, Finizia C, Bove M, Ruth M. Pharyngeal reflux episodes at pH 5 in healthy volunteers. Scand J Gastroenterol 2006;41:138-143.

II. Andersson O, Moller RY, Finizia C, Ruth M. A more than 10-year prospective, follow-up study of esophageal and pharyngeal acid exposure, symptoms and laryngeal findings in healthy, asymptomatic volunteers. Scand J Gastroenterol 2009;44:23-31.

III. Andersson O, Rydén A, Ruth M, Moller RY, Finizia C. Validation of the Swedish translation of LPR-HRQL (Submitted).

IV. Andersson O, Rydén A, Ruth M, Moller RY, Finizia C. Development and validation of a laryngopharyngeal reflux questionnaire, PRSQ (Submitted).

Contents

1 Abbreviations

BID	bis in die, Latin for twice daily
EER	Extraesophageal reflux
EGD	Esophagogastroduodenoscopy
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
HRM	High resolution manometry
HRQL	Health Related Quality of Life
LES	Lower esophageal sphincter
LPR	Laryngopharyngeal reflux
LPR-HRQL	Laryngo Pharyngeal Reflux – Health Related Quality of Life
NERD	Non-erosive reflux disease
PPI	Proton pump inhibitor
PRO	Patient Reported Outcome
PRSQ	Pharyngeal Reflux Symptom Questionnaire
RCT	Randomized controlled trial
RSI	Reflux Symptom Index
SF-36 v2	Short Form -36 version 2
TLESR	Transient lower esophageal sphincter relaxations
UES	Upper esophageal sphincter
UGDQ	Upper Gastrointestinal Disease Questionnaire
ULN	Upper limit of normality

2 Introduction

Reflux is the retrograde flow of gastric contents from the stomach into the esophagus. Reflux may in some instances also pass the upper esophageal sphincter and into the hypopharynx/larynx as well as the lower aerodigestive tract [1]. While gastroesophageal reflux disease (GERD) is readily recognised by the typical symptoms of heartburn and acid regurgitation, the symptomatology of laryngopharyngeal reflux (LPR) or extraesophageal reflux (EER) is more diverse and less patognomonic [2,3].

The prevalence of troublesome symptoms of heartburn and/or regurgitations on a weekly basis in the western world vary in different reports between 10-20% [4]. The prevalence of LPR is less established [5,6] and the natural history of the LPR disease is largely unknown, mainly because a golden standard for how to diagnose LPR does not exist. Long-term studies following a GERD population over time have, however, shown it to be a chronic disease [7,8].

The main diagnostic tools are patient reported symptoms, 24-hour pH monitoring, and laryngoscopic examination [9].

The symptoms associated with LPR are chronic cough, hoarseness, throat clearing, globus, laryngospasm, throat pain and excessive mucus [3]. Koufman et al found that patients with these symptoms represent around 10% of the patients presenting in an ENT-clinic [3]. However, the symptoms of LPR may be caused by other conditions such as smoking, allergy, voice abuse or airway infections [10] and according to several studies, lack sufficient diagnostic specificity and sensitivity [11,12]. An important aspect in the process of creating guidelines for diagnosis in this context is to develop and evaluate psychometrically tested, patient reported symptom questionnaires.

24-hour pH monitoring is usually performed in the distal esophagus and either in the proximal esophagus just below the upper esophageal sphincter (UES) or in the hypopharynx within 1-2 cm above the UES. Not only is the optimal positioning of the catheter debated, but also what should be regarded as pathological acid exposure in the hypopharynx [6,13]. The classical cut-off limit at esophageal pH monitoring, pH 4, has traditionally been used also in hypopharyngeal pH monitoring. It has been suggested, however, that a higher limit should be used in the hypopharynx, for example pH 5, as the laryngeal mucosa is reported to be more sensitive to pepsin and acid than the esophageal mucosa [14]. Furthermore, pepsin has been reported to be active up to pH 6 [15].

Typical laryngeal findings associated with LPR are posterior laryngitis including edema and erythema. Others findings are, vocal fold nodules, granuloma or even cancer. However, the signs have shown poor specificity for the LPR-disease [16].

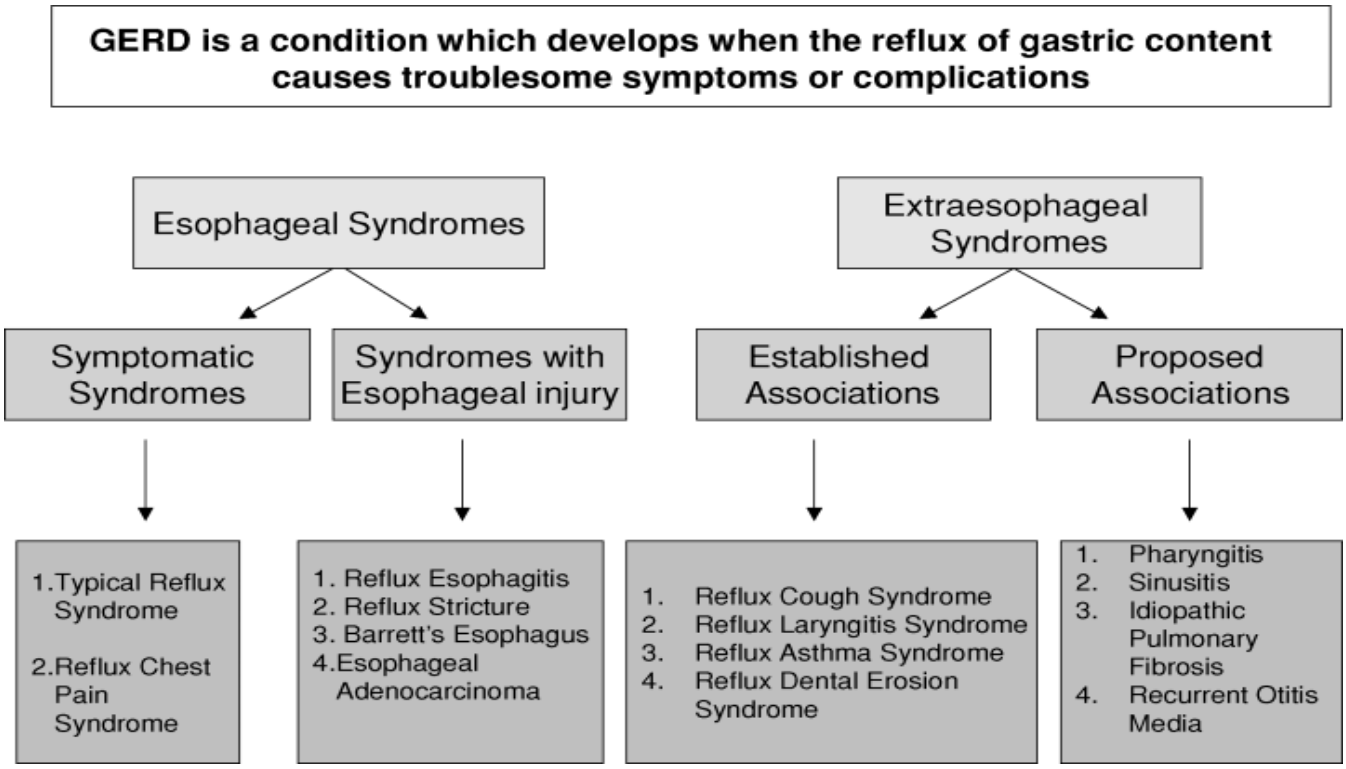
The aim of this thesis was therefore to aid in the understanding of the disease and to develop and refine the diagnostic tools of LPR. This was done by investigating the occurrence of LPR over time in healthy volunteers, by investigating reference intervals of pharyngeal pH monitoring at the pH 5 level, by translating and validating a Swedish version of the Laryngo Pharyngeal Reflux – Health Related Quality of Life (LPR-HRQL) questionnaire [17], as well as by creating and validating a new diagnostic instrument, the Pharyngeal Reflux Symptom Questionnaire (PRSQ).

3 Background

3.1 Definitions and demographics of reflux disease

Heartburn as a predominant symptom has been shown to have a high diagnostic specificity for GERD [18]. The diagnosis of GERD, proposed in the Genval workshop report from 1999 [19], i.e. heartburn at least 2 times a week, was challenged when it was shown that 37% of patients with esophagitis did not have classical reflux symptoms [20]. Therefore the World Congress of Gastroenterology in Montreal, Canada 2005 defined GERD as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" [21]. This definition also includes patients without classical symptoms but with complications or syndromes of both esophageal and extraesophageal nature. Extraesophageal syndromes were divided into established and proposed associations. The established associations were deemed to be reflux cough, reflux laryngitis, reflux asthma and reflux dental erosions while pharyngitis, sinusitis, pulmonary fibrosis and otitis media were deemed as proposed associations,
Figure 1. The existence of GERD increases the likelihood of laryngeal signs and symptoms [2,22]. The reflux up to the hypopharynx/larynx area is referred to as LPR. LPR is a more restricted definition than EER, where the latter also includes the lower aerodigestive tract.

Figure 1. Montreal classification



Adaption from Vakil et al. 2006. With permission from Am J Gastroenterology.

The prevalence of GERD varies with geographical location according to a recently published systematic review of 15 studies. The study showed that 8-27% of the adult population in the western society had heartburn and/or acid regurgitation one or more times per week. In Asia the reported prevalence is significantly lower, i.e. 3-5% [4]. Due to the lack of consensus in how to diagnose LPR and the disparate methodologies used by investigators, the true prevalence of LPR is not well known. Connor et al. reported that symptoms commonly attributed to LPR were as high as 49% in a normal community dwelling [2,6]. In patients with GERD, extraesophageal symptoms were reported by 33% [2].

3.2 Established extraesophageal conditions associated with GERD

3.2.1 Asthma

There is strong evidence linking asthma to GERD [23,24]. Several studies have indicated that acidity in the trachea generates increased pulmonary resistance [25,26]. Harding et al. demonstrated that between 50-80% of the asthma patients also had GERD

symptoms and up to 75% also had pathological acid exposure [23]. A study of over 15.000 primary care patients showed that there was up to a twofold risk of receiving a GERD diagnosis following a first diagnosis of asthma [27].

The cause and effect relationship between asthma and reflux is however not clear as both conditions may be the result of the other. Reflux may cause asthma through microaspirations into the bronchial tree or through a vagal mediated nerve reflex which causes an asthmatic reaction. Furthermore, during an asthma attack you get a negative intrathoracic pressure which may give reflux. [28].

3.2.2 Chronic cough

Chronic cough is defined as cough with a duration of more than 3 weeks. According to Irwing et al. and Pratter et al., GERD together with postnasal drip syndrome and asthma are responsible for over 90% of chronic cough diseases out of which 10-30% of the cases could be directly related to GERD [29,30].
These results are in accordance with double-blind placebo controlled studies with GERD patients, showing a significant improvement in cough scores in the PPI treated patient group [31,32].

3.2.3 Dental erosions

The prevalence of dental erosion among individuals with GERD has been estimated to 20-55%, compared with a prevalence of 2-19% in the general population [33]. Munos et al. showed that GERD patients, verified with pH-registrations and endoscopy, had significantly more dental erosions, compared with controls, 47.5% vs. 12.5% [34].

3.2.4 Reflux laryngitis

Laryngitis or laryngeal inflammation is relatively common, unspecific and often resolves spontaneously [35]. When laryngitis is persistent the underlying causing agent may be allergy, infection, vocal trauma, postnasal drip or LPR.

LPR may be suspected in the presence of symptoms of hoarseness, globus, throat clearing, dysphagia, cough, laryngospasm, throat pain and excessive mucus [3,9,36,37]. Symptoms of heartburn and acid regurgitation are often absent in LPR, i.e. in 60 %

according to Koufman et al. [3]. However, more recently, the Montreal definition stated that unexplained asthma and laryngitis are unlikely to be related to GERD in the absence of heartburn or regurgitation.

Laryngeal findings indicating LPR are posterior laryngitis with erythema, edema and presence of interarytenoid thickening in the posterior wall of glottis [38]. Medical or surgical therapy on reflux laryngitis has in observational trials demonstrated a partial improvement of upper airway symptoms and to some extent of laryngeal findings [39,40]. However, the only randomized controlled trial demonstrating a treatment effect, was on patients with classical GERD symptoms in addition to laryngitis. Whereas other recent trials that excluded patients with frequent heart-burn demonstrated no benefit of a PPI over placebo in treating the laryngitis [41,42].

3.3 Proposed extraesophageal associations with GERD

Adequate evidence of causal linkage is lacking between LPR and sinusitis, pulmonary fibrosis, pharyngitis and recurrent otitis media [43,44].
However, a moderate increased risk for sinusitis (Odds ratio 1.6) and idiopathic pulmonary fibrosis (Odds ratio 1.36) was seen in a epidemiological study on U.S. military veterans with reflux esophagitis [45].

3.4 Physiology and patophysiology of LPR

Physiology: Gastroesophageal as well as gastro-esophago-hypopharyngeal reflux occur due to the pressure gradient between the positive intra-abdominal pressures and the negative pressures in the thorax/hypopharynx.
Gastroesophageal physiological reflux occurs predominantly in conjunction with transient relaxations of the lower esophageal sphincter (TLESR) [46]. TLESR are triggered by gastric distention, mainly in the postprandial period and are activated by stretch receptors in the gastric wall. The reflex arch includes a vagus mediated impulse to the N Tractus Solitarius in the brain stem, vagal efferents to the LES and a non-cholinergic, non–nitergic inhibitory interneurone, which relaxes the sphincter [46]. The role of these relaxations is to release swallowed air by belching [47]. They occur independently from swallowing, are longer (5-30 seconds), and are typically followed by an after-contraction of the LES.

Reflux to the hypopharynx occurs predominantly postprandially and in the upright position [48,49]. LPR is, in contrast with GERD, often not associated with heartburn and regurgitation [50].

Components: The agents responsible for producing upper airway symptoms and laryngeal pathology are acid, pepsin, bile acids and trypsin. The relative importance of the agents is, however, presently under debate. Pepsin combined with acid has been found to be the most injurious agents with a significant association with laryngeal lesions [15]. Pepsin has in animal experiments and in vitro been shown to be active and cause laryngeal cell injury up to pH 6 [14].

The reflux can either be gas, liquid or mixed (gas/liquid). The vast majority of the pharyngeal reflux is gaseous without pH drops and is seen equally in healthy subjects and laryngitis patients, while mixed and liquid refluxes and also gas reflux with pH drops are significantly more common in LPR patients [51]. The nocioceptive damage of biliary reflux on laryngeal structures has also been demonstrated [52,53]. Impedance testing together with bilitec may here improve upon diagnostics.

Protective mechanisms: There are 4 principal protective physiological barriers against reflux

1. The lower esophageal sphincter (LES)
2. Acid clearance, through esophageal motor function and gravity
3. Esophageal mucosal tissue resistance
4. The upper esophageal sphincter (UES)

Active bicarbonate production is pumped into the extracellular space in the esophagus but not into the larynx, which thus has less capacity to neutralize the nocioceptive influence of acid. Recent investigations suggest that laryngeal tissues are also protected from reflux damage by a carbonic anhydrase in the mucosa of the posterior larynx. The carbonic anhydrase enzyme catalyzes hydration of carbon dioxide to produce bicarbonate, which neutralizes the acid in the refluxate. Carbonic anhydrase isoenzyme III, expressed at high levels in normal laryngeal epithelium, was however shown to be absent in 64% of biopsy specimens from laryngeal tissues of LPR patients [54].

Patophysiology: There are two dominating theories about how gastric acid provokes extra esophageal pathological symptoms and/or findings. The first implies direct acid-pepsin injury to the larynx and surrounding tissues [15,26]. The second

proposes that acid in the distal esophagus stimulates vagal-mediated reflexes that result in bronchoconstriction leading to chronic throat clearing and coughing, which in turn provokes mucosal lesions [28,55]. In fact, they may both play an essential part in conjunction [56]. Symptoms may arise either from direct mucosal injury or because of damage to cilias, leading to mucous stasis and chronic throat clearing and cough.
Also the level of acidity corresponds to the degree of mucosal damage where pH 0-4 is the most damaging [15]. Weakly acidic reflux episodes (pH4-pH7), not detected by the classic cut-off limit at pH 4 in 24-hour pH monitoring, may pass through the esophagus without symptoms and signs, but doing harm to the more sensitive mucosa of the larynx [14,15,57]. The ciliated respiratory epithelium of the larynx has been shown to be more sensitive to acid, activated pepsin and bile salts than the esophageal mucosa [14,15].

The time and frequency of acid exposure necessary to create disease is also under debate. Koufman et al. postulated that one single reflux episode is enough [3]. This was concluded after an animal experiment where he subjected the arythenoid region of animal larynx to acid and pepsin 3 times a week and discovered that this was enough to create mucosal damage. In later years however, many investigators agree that a larger amount of reflux is needed to cause disease, (Table 1). This is due to the fact that around 20-50% of healthy symptom-free subjects have, in several studies, been reported to have hypopharyngeal reflux episodes. A recent review by Joniau et al. compared 11 studies with normal controls and 13 studies with reflux laryngitis, and found in the pooled data that reflux events were detected in 23% of the normal controls and in 38% of the LPR-patients [58]. In another meta analysis of upper-probe measurements by Merati et al. the pooled data gave that 31% of the normal subjects had hypopharyngeal reflux events, as opposed to 51% of the LPR patients. Bove et al. found the ULN of acid exposure at pH 4 in 40 healthy subjects to be 0.2% or 6 reflux episodes during the 24-hour pH-monitoring [59].

3.5 Diagnosis of LPR

One challenge in diagnosing LPR is that the symptoms of the LPR disease lack sufficient specificity to confirm LPR and thus to rule out other causative agents.
In fact, several studies have shown a poor correlation between LPR symptoms, laryngeal findings and findings from hypopharyngeal pH registrations [9,13,60,61].

3.5.1 Laryngeal examination.

The most frequently reported signs believed to be caused by LPR are posterior laryngitis with erythema, edema and thickening of the posterior wall of the glottis. Other proposed signs are vocal fold granuloma [62], contact ulcer, subglottic stenosis [63] and chronic laryngitis [11].

The correlations between laryngeal findings, symptoms and pH monitoring have been found to be weak [9,60,64]. It has been reported that findings normally associated with LPR may also be found among healthy controls, even as in the report by Hicks et al., as often as in 86% [35]. However, there are studies proposing pseudosulcus to be a better predictor of LPR. Pseudosulcus is caused by a bilateral infraglottic edema going from the anterior commisure to the posterior wall of the glottis, differentiating it from a true sulcus vocalis which is limited to the membraneous parts of the vocal folds. Belafsky et al. found in a study that pseudosulcus had 70% sensitivity and 77% specificity for LPR-disease [65]. Also Ylitalo et al. showed pseudosulcus to have a 70% sensitivity for LPR disease in a patient with symptoms of LPR [66].

Another problem is the intra- and inter-rater variability. Branski et al. reported that 5 blinded experienced otolaryngologists presented with 120 video segments of fiberoptic laryngeal examinations showed a big variability in both intra- and inter-rater scoring [64].

In an attempt to standardize the larynx examination, Belafsky et al. proposed a validated systematic instrument for assessing the laryngeal findings, the Reflux Finding Score (RFS) [38], which to date is the most recognized and used instrument for evaluating laryngeal findings. In a study of 76 patients with laryngeal symptoms, Oelschlager et al. reported that 83% of patients with a RFS score > 7, together with pathological hypopharyngeal pH monitoring, responded to anti reflux therapy compared to 44% of those with normal RFS score and hypopharyngeal pH monitoring [67]. This suggests that the RFS score together with hypopharyngeal pH monitoring may play a complementary role in identifying patients with upper airway symptoms secondary to GERD.

3.5.2 Histology

Dilation of intercellular space (DIS) between squamous epithelial cells has been put forward as the earliest microscopic marker of acid damage both in the esophagus and the larynx [68,69]. Biopsies from the interarytenoid area in LPR patients were demonstrated to have a significantly larger DIS than in healthy controls [69]. Intracellular concentrations of pepsin and depletion of carbonic anhydrase isoenzyme III has also been demonstrated in laryngeal vocal fold and ventricle biopsies from LPR-patients, whereas the healthy controls had low levels of pepsin and higher levels of isoenzyme III [57].

3.5.3 24-hour pH monitoring

24-hour pH monitoring is considered the most reliable test for LPR. Two pH-electrodes are introduced transnasally and positioned 5 cm above the LES and 0.5-2 cm above the UES with the help of manometry. The probe placed 2 cm above the UES is considered the best at representing this. With the probe placed in the proximal esophagus the amount of reflux is greater and will not accurately reflect the acid exposure of the hypopharynx/larynx [70]. Acid exposure in the esophagus and the hypopharynx is registered by antimony, glass or ISFET probes and is stored on a digital recorder, commonly with a sampling frequency of 0.25Hz. Symptoms, meals and body position may be registered simultaneously by the patient by pressing a button on the same digital recorder and by specifying the event in a manual diary.

Using pH < 4 as the cut-off value, a meta analysis of dual probe pH metry of 16 studies showed that 10-30% of normal subjects had acid reflux events at the upper probe (in the UES or up to 2 cm above the UES) [13]. Of the patients with diagnosed LPR disease, only 51% had demonstrated reflux to pharynx [13]. The mean percentage of acid exposure time in healthy subject was less than 0.01% of the 24-hour pH monitoring. The authors concluded that acid exposure time was the most consistent indicator to detect LPR and that measurements between the UES and 2 cm into the hypopharynx give the most accurate and consistent information [13]. Shaker et al. used a simultaneous 3-site pH monitoring (distal and proximal esophagus and hypopharynx) and demonstrated that hypopharyngeal acid exposure occurred more frequently and in greater amount among LPR patients than in GERD patients or controls. Koufman, in his groundbreaking study,

considered 1 single reflux to be enough to create signs or symptoms. A more recent approach is to consider LPR confirmed when the total acid exposure time (%) < pH 4 during the 24-hour pH monitoring is more than 1% [51].

The sensitivity of esophageal pH-monitoring in the diagnosis of GERD reported in the literature has ranged from 79% to 96% [71-74] and the specificity from 86% to 100% [74,75] with a reproducibility of 89% [76]. The specificity and sensitivity of the hypopharyngeal pH recordings are, however, less impressive. Ahmed et al. reported a sensitivity of hypopharyngeal pH monitoring of only 40% sensitivity as compared to 70% and 50% for distal and proximal esophageal measurements [11], comparing the correlations between clinical diagnosis of GERD and LPR with pH measurements. Table 1 show the degree of reflux found in healthy controls and LPR patients in different studies at 2 cm above the UES.

Table 1. Hypopharyngeal reflux in healthy subjects and LPR-patients

	Hypoph reflux healthy			Hypoph reflux LPR pat		
Study	n	Reflux mean n	Acid expos mean %	n	Reflux mean n	Acid expos mean %
Koufman 91	12	0	0			
Shaker 95	12	0.17	0	14	4.36	0.24
Smit 98	20	1.8	0.01			
Toohill 98				12	2.42	0.009
Ulualp 99	17	0.2	0	20	2.65	0.13
Bove 00	40	1	0			
Ylitalo 01	19	0.7	0	26	1.50	0.034
Powitzky 03	15	1	NR			
Oelschlager 02				76	3.4	NR

n = number, Reflux mean n = mean number of reflux events, Acid expos mean % = mean percentage of acid exposure, NR = not reported

The clinical importance of weakly acidic reflux (pH 4 – pH 7) has gained increasing interest over the recent years, further enhanced with the introduction of 24-hour combined impedance-pH monitoring. Combined multi-channel intraluminal impedance and pH-metry is a technique that enables monitoring of gastroesophageal reflux independent of its acidity and the relation to typical and atypical symptoms. It allows the recognition of major acid, minor acid, non-acid, and gas reflux events

[51,77,78] which may improve on diagnostics. Recorded symptoms can be correlated with all reflux events (e.g. acid, minor acid, non-acid, and gas). Impedance evaluation of bolus transit might also investigate the functional relevance of manometric abnormalities. Patients with persistent symptoms of gastroesophageal reflux in spite of adequate treatment with proton pump inhibitors may still have weakly acidic reflux and/or bile reflux associated with their symptoms. It has been shown that non-acid or weakly acid reflux can be associated with symptoms in patients with GERD or LPR symptoms [79]. Sifrim et al. could significantly correlate a subgroup of chronic cough to weakly acidic reflux [77].

3.5.4 Esophageal manometry

Manometry is used to evaluate UES function, esophageal peristalsis and LES function. There are several motor function disturbances associated with GERD, (esophageal dysmotility and variation of either the LES or the UES sphincter tonus [80]) but no significant casual linkage have been found [81]. The UES pressure has with standard manometry shown large variability in pressure values, which is why no conclusions regarding the risk to develop LPR can be drawn [82]. Kahrilas et al. did however find a marked decrease in UES resting pressure during sleep in normal controls which may have significance in that it diminishes the barrier for nocturnal reflux [82]. Today, manometry in conjunction with pH metry is therefore mainly used to correctly position the pH probes. High-resolution manometry (HRM), may however, potentially improve on diagnostics of manometric abnormalities associated with LPR in the future.

3.5.5 Esophagogastroduodenoscopy (EGD)

Patients with symptoms of heartburn and acid regurgitation (GERD) but without visible ulcers or erosive damage to the esophageal mucosa, are referred to as non-erosive reflux disease patients (NERD). Between 50-70% of the GERD population are without visible morphologic change to the esophageal mucosa, i.e. NERD patients [20,83,84] while up to one third of the esophagitis patients lack symptoms [20].
Furthermore, Martinez found that only 45% of the NERD population have pathological 24-hour pH monitorings [85]. Tutuian et al. reported that the 24-hour pH monitorings of fifty percent of patients with symptoms of GERD and negative endoscopy was negative,

thus suggesting that in some cases symptoms are not caused by abnormal esophageal acid exposure [78]. In the LPR group approximately 10-20% of the patients have been found to have esophagitis which is similar to the prevalence of esophagitis in the general population [12,20,86]. EGD thus has a low predictive value for the diagnosis of LPR disease.

3.5.6 Other considerations

Possible future improvements in the diagnosis of LPR could be had through a pepsin assay of sputum/saliva. Pepsin is a proteolytic enzyme produced only in the stomach and is initially secreted in zymogen form as either pepsinogen I or pepsinogen II by gastric chief cells and mucous neck cells of the fundic gland mucosa [87]. The presence of pepsin in salivary or pulmonary secretions would therefore be a direct evidence of reflux of gastric contents into the oropharynx or lungs. In the presence of acid, pepsinogen would be converted to pepsin and could cause mucosal injury to the esophageal, oropharyngeal, and/or tracheal mucosa [88].

Pepsin in the larynx has been shown to result in depletion of carbonic anhydrase isoenzyme III (CAI III) and squamous epithelial stress protein (Sep70) which are laryngeal protective proteins [57,89]. This might explain that LPR symptoms and signs are seen also with weakly acidic reflux as pepsin has been found to be active up to pH 6.5 [90]. This test might have the potential of facilitating diagnosis with less discomfort for the patients.

Further recent developments of pH diagnostics are the use of reflux area index (RAI) which is calculated from the number and duration of proximal reflux events, both at pH 4 and 5 [91], and wireless upper esophageal monitoring using the Bravo system, which may allow longer registration periods with less discomfort for the patient, though the positioning in the upper esophagus instead of in the hypopharynx has been questioned [92].

3.6 Treatment of LPR-disease

Behavioural changes including dietary modification, weight loss, smoking cessation and alcohol avoidance is commonly recommended in LPR disease as well as in GERD [93,94]. Although the scientific foundation for such recommendations is limited

there are reports that could support the practise. Steward et al. found that lifestyle modification for 2 months, with or without PPI therapy, significantly improved chronic laryngitis symptoms [94]. The current treatment recommendation is BID PPI for 3-6 months for suspected LPR patients [95]. LPR is believed to require a more aggressive and prolonged therapy than GERD [96], which is why high dose, twice daily is recommended. This is in part also motivated to reduce nocturnal acid breakthrough, which is believed to be more common in LPR-patients than in GERD [39]. There are many advocates of an empirical 2-month trial PPI treatment in suspected LPR patients [97,98]. However, the practice of trial PPI-treatment has been questioned, as randomized controlled trial (RCT) studies in suspected LPR-disease have not shown a convincing treatment outcome with PPI compared to placebo in LPR-patients [41,42,94,99,100], Table 2. This practice also entails considerable economical costs both for the health system and the patients.

Table 2. RCT's comparing PPI-treatment with placebo in LPR-patients.

Study	Number	≥ 50% reduction in laryngeal symptoms		
	(PPI/Placebo)	PPI (n/%)	Placebo (n/%)	Risk Ratio *
El-Serag -01	12/10	6 (50)	1 (10)	5.00
Noordzij -01	15/15	9 (60)	6 (40)	1.50
Steward -04	21/21	8 (38)	9 (43)	0.89
Wo -05	20/19	8 (40)	8 (42)	0.95
Vaezi -06	95/51	40 (42)	23 (46)	0.93

* A risk ratio of more than 1 favours PPI compared to Placebo (adapted from Qadeer, permission to reprint granted)

Numerous observational trials of medical or surgical therapy of reflux laryngitis report a partial improvement in upper airway symptoms and to some extent laryngeal findings [39,40]. A recent Cochrane review by Hopkins et al. on acid reflux treatment for hoarseness identified 302 studies, among which 6 were RCT's [101]. The authors concluded that sufficient evidence based on randomized controlled trials is lacking and

that no reliable conclusions could be drawn due to differences in inclusion criteria, symptom registration, short assessment periods and small numbers of patients. They also stated the need for a carefully designed prospective placebo controlled study to determine whether anti-reflux treatment is effective on hoarseness.
Similarly, a recent meta-analysis showed that PPI treatment is not significantly better than placebo treatment for suspected chronic laryngitis [102]. The poor treatment outcomes may at least in part be explained by difficulties in patient selection underlined by the fact that abnormal findings of pH monitoring do not predict response to therapy [102].
This creates a problem of patient selection which in turn may explain the poor treatment outcomes [102]. Better diagnostic tools such as pepsin assays, impedance monitoring, validated questionnaires and diagnostic guidelines are therefore much needed in order to improve the selection of patients and treatment outcomes.

3.7 Patient Reported Symptoms - Outcome variables

In 2006 the Food and Drug Administration (FDA) presented a set of guidelines for the development and evaluation of patient-reported outcome (PRO) instruments used as endpoints in clinical trials [103]. A PRO is described as a measurement of any aspect of patient health status that comes directly from the patient. In clinical trials, a PRO instrument can be used to measure the impact of an intervention on one or more aspects of patients' health status, ranging from the symptomatic (e.g. heartburn) to more complex concepts such as activities of daily living, to extremely complex concepts such as health-related quality of life (HRQL) which includes physical, social and psychological components. Health-related quality of life is defined as the subjective perception of the degree of physical, psychosocial and social well-being. A HRQL instrument attempts to measure both the impact of disease and the treatment effect. PRO concepts can be general (e.g. physical function, psychological well-being) or specific (e.g. frequency and severity of specific symptoms). It can also be generic (applicable in a broad scope of diseases) or disease-specific.

To ensure the reliability of obtained data there must be evidence that the PRO instrument effectively measures the concept/s being studied, i.e. has the ability to measure the claimed treatment benefit and that it is specific and relevant to the intended

patient population as well as to the condition treated [104]. It can be argued that for concepts such as pain intensity, the patient is the only source of data with a unique perspective, which objective measurements cannot give. Patient-reported questionnaires give a more direct response than observer-reported measures, which is an interpretation of the experienced pain and therefore often is affected by inter-observer variability. It is recommended that patients should be assessed using two kinds of PROs: generic and disease specific. The generic measures, designed to measure e.g. domains of general health, overall disability and HRQL, are important for comparisons across patient populations and with a normative population. This often occurs at the expense of the responsiveness to clinically relevant change in specific diseases. Therefore, disease-specific instruments measuring e.g. attributes of symptoms and functional status relevant to a particular disease or condition have been developed and they are often more responsive to the target condition when compared to generic measures [105]. To understand and document the impact of LPR on HRQL and the effect of treatment, it is also important to measure functional health status [106,107]. Patient views are important in order to understand and document both symptoms and impact of reflux on health-related quality of life and the effect of treatment in LPR patients.

3.8 The validation process

Questionnaires have to be carefully validated to ensure their accuracy.
Four factors are of importance when evaluating the validity of a questionnaire:

1. Content validity, i.e. the instrument covers the relevant aspects of the disease.
2. The reliability/stability of the instrument.
3. The discriminative ability of the instrument, i.e. the ability to distinguish between different patient groups.
4. Sensitivity to change/the evaluative ability, i.e. adequate detection of change in relation to an intervention.

The development and validation of a patient reported symptom questionnaire includes the following principal steps [108]:

1. Face and content validity. Item generation is conceived through literature review, the experience of specialized physicians and input from patients, including cognitive interviews. This process is to ensure that all relevant symptoms are included. Also, careful attention is placed on how the questions are perceived by the patients, i.e. that they are easily understood.
2. Stability. Test-retest procedure to determine the intraclass correlation coefficient and the reliability. To ensure that the instrument is accurate when measuring the same condition on repeated occasions.
3. Construct validity refers to whether the hypothesised scales are actually measuring the underlying construct. Exploratory factor analysis is used to identify and confirm the subscale structure, i.e. to find clusters of symptoms that are logically connected. Often used is the principal component factor analysis (with Varimax rotation) to identify possible meaningful and homogenous factors. Factors and items are retained according to well-established criterias [108].
4. Internal consistency is usually measured with Cronbach's alpha, where the recommended level is 0.7 or more [109]. Cronbach's alpha measures how well a set of items measures a single unidimensional latent construct. Cronbach's alpha will generally increase when the correlations between the items increase. When data have a multidimensional structure, Cronbach's alpha will usually be low.
5. Item reduction is done based on validity and reliability assessment, and individual item performance. Items with poor statistical performance (floor or ceiling effects) and with poor subscale internal consistency reliability (scaling errors) are eligible for elimination.
6. Convergent validity is analysed with Spearman non-parametric correlation by correlating the scales in the questionnaire being analysed with the similar scales in other already validated questionnaires. Convergent validity shows that the scale is related to what it should theoretically be related to.
7. Predictive validity is the extent to which a score on a scale or of the entire instrument predicts scores on some criterion measure. Predictive validity is achieved when scales correlate adequately against other relavant external sources, e.g. a specialist diagnosis.

8. Responsiveness is tested before and after treatment and analysed e.g. with student t-test or ANOVA [108]. This is to ensure that the instrument is sensitive enough to display a significant change following intervention.

4 Aims of the thesis

The overall aim of the present thesis was to develop and refine diagnostic tools for the LPR disease.

More specifically:

- To establish normal values for pharyngeal reflux episodes and exposure time at pH 5 in healthy controls and to correlate these to the pH monitoring results from the esophagus and the hypopharynx when a cut-off limit of pH 4 was used.
- To evaluate whether acid exposure in the esophagus and pharynx increase over time in healthy subjects and to describe the relation to symptom occurrence as well as laryngeal findings.
- To evaluate whether asymptomatic pharyngeal reflux is a risk factor for the development of LPR disease.
- To translate and validate the Swedish version of a disease related HRQL questionnaire for patients with LPR disease; Laryngo Pharyngeal Reflux – Health Related Quality of Life.
- To develop and validate a disease specific patient reported questionnaire for LPR disease, the Pharyngeal Reflux Symptom Questionnaire (PRSQ).

5 Methodology

5.1 Subjects and design

5.1.1 Study I and II

The investigation originated from a cross-sectional study by Bove et al. 1993 in which 40 healthy hospital employees and their relatives and friends, volunteered to participate in a normative 24-hour pH monitoring study with the aim of creating reference boundaries [59].

In study I, 35 of the pH monitorings were retrospectively re-analysed with a new cut-off limit, i.e. pH 5. Four of the pH monitorings were not retrievable and one was excluded due to technical reasons.

In study II, 33 of the subjects included in study I were asked to participate in a prospective follow-up examination, which took place after a mean time of 14 years. Two subjects from study I were not available due to residency outside of Sweden and a further 3 subjects were excluded due to health issues (dementia, pregnancy and chronic severe illness). After commencing the study a further 4 subjects withdrew due to personal matters and 2 subjects were excluded from the analysis because of technical artifacts in the pH measurements. Thus, evaluable data was retrieved from 24 subjects who completed the follow-up study.

At baseline the symptoms were assessed with the Upper Gastrointestinal Disease Questionnaire (UGDQ) and a clinical examination. At follow-up, the subjects completed the questionnaires UGDQ, PRSQ and Short Form -36 (SF-36), were re-examined with a dual 24-hour pH monitoring (esophagus and hypopharynx) and a videolaryngoscopic examination.

Table 3. Subjects in study I, II and the study Bove et al. [59]

	Subjects	Age	Gender	Weight	BMI	Smokers
	n	Mean (range)	n male/female	Mean (range)	Mean (range)	n (%)
Study -93	40	43 (23-64)	20/20	74 (51-102)	24.2 (20.0-32.6)	7 (18)
Study I	35	44 (24-64)	16/19	74 (51-102)	24.6 (20.0-32.6)	4 (17)
Study II						
Baseline	24	44 (26-64)	9/15	75 (52-102)	25.0 (20.8-32.6)	3 (12)
Follow-up	24	57 (38-76)	9/15	78 (51-110)	26.0 (20.2-35.1)	3 (12)

n = number

5.1.2 Study III and IV

All patients who had performed a 2-level 24-hour pH-monitoring between year 2000 and 2006 at either Sahlgrenska University hospital, Göteborg or Karolinska University Hospital, Huddinge due to symptoms presumed to be caused by LPR (e.g. hoarseness, chronic cough, globus, or chronic throat clearing during ≥ 1 month) were asked to participate in the study. A letter of introduction and a battery of questionnaires including one for sociodemographic data, the LPR-HRQL, the Reflux Symptom Index (RSI) and the SF-36 were sent to 372 identified patients. In case of no reply, two reminders were mailed to the patients with an interval of 1 month.
Exclusions were made of 27 patients due to interfering illnesses that might confound or inhibit an assessment of the effect of LPR on HRQL (e.g. cancer, major psychiatric illness, previous anti-reflux surgery and/or unstable chronic illnesses).

The patients were classified according to the RSI cut-off score [110], i.e. 102 patients with a RSI score >13 were defined as abnormal; LPR+, i.e. having LPR disease and 126 patients with a score between 0-13 were defined as normal controls; LPR-.

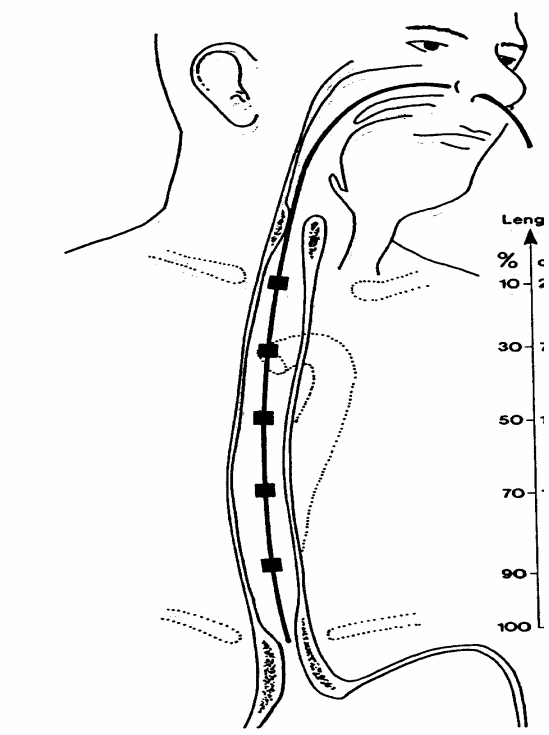
Table 4. Subjects in study III and IV

	Patients			Gender	BMI	Age
Study	Contacted n	Responses n (%)	Included n (%)	M/F n	Mean (SD) kg/m²	Mean (SD) years
III & IV	372	255 (69)	228 (61)	101/127	26.1 (5.2)	59 (13)

n = number, M = male, F = female, SD = standard deviation

5.2 24-hour pH monitoring

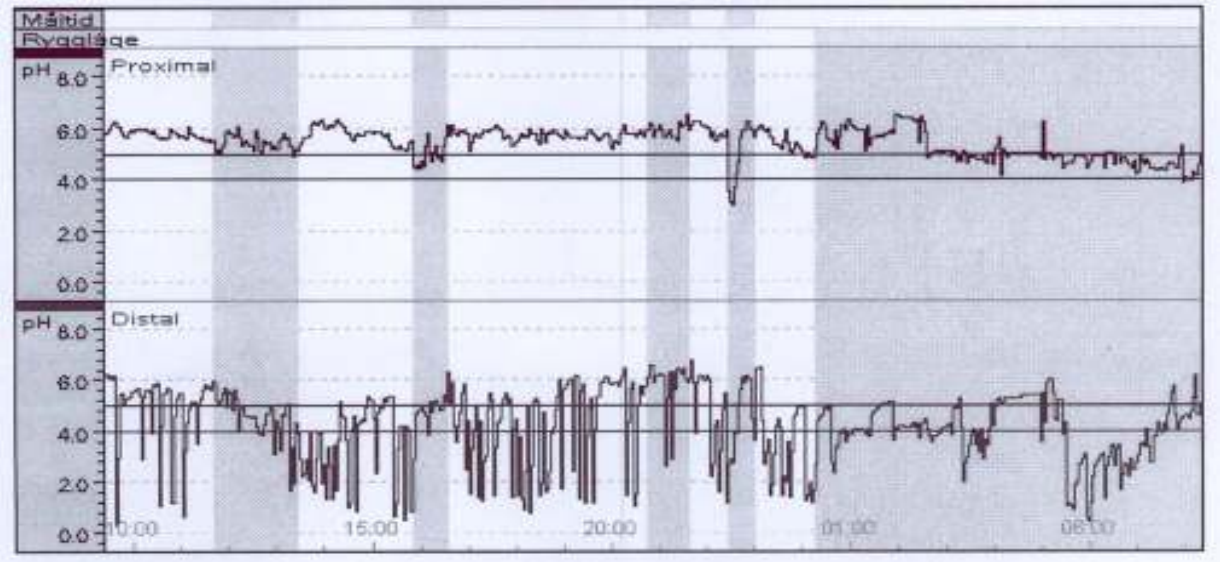
Figure 2. Manometric positioning of pH electrodes.



In all the studies (I-IV) the patients performed a stationary pull through manometry determining the pressure characteristics and the exact locations of the LES and the UES, followed by an ambulatory dual-probe 24-hour pH monitoring, depicted in Figure 2. The pH recordings were done with 2 antimony electrodes positioned 5 cm above the upper limit of LES and 2 cm above the superior limit of UES respectively. The relative position of the electrodes was secured by taping them together and the assembly was then fixed to the nose. The recordings were stored in a portable data logger (Digitrapper, Synectics, Stockholm, Sweden) and computed using a commercial software program

(Polygram, Synectics, Stockholm, Sweden). Drugs affecting gastric acidity (PPI) were not allowed the week prior to the investigation. During the sampling period the subject was asked to lead a normal life but to avoid food with a low pH, carbonized beverages and alcohol. The subjects were asked to mark symptom occurrences, meals as well as time spent in the supine position by pressing registration buttons at the Digitrapper. The event was also registered by the patient in a diary.

Figure 3. Graphic presentation of hypopharyngeal (upper curve) and esophageal (lower curve) pH measurement



The beginning of a reflux episode in the distal esophagus was defined as a decrease in pH below 4 and the end when the pH rose above pH 5. A pharyngeal reflux episode at the proximal probe with cut-off at pH 4 was considered to start when the pH fell below 4 and end with the subsequent rise above pH 5. An acid event with cut-off at pH 5 in the proximal probe was considered when pH decreased below pH 5 and end with the following rise above pH 5. All registrations were manually analyzed to exclude meal periods and technical artifacts. To qualify as a pharyngeal acid event the decrease in pH at the pharyngeal probe had to be abrupt and either simultaneous with or preceded by an esophageal reflux event within 20 seconds prior to the pharyngeal reflux event. An example of a pH measurement can be seen in Figure 3. The analyzed parameters in the hypopharynx were; the percentage of time < pH 4 and pH 5 respectively (study I and II), the number of reflux events < pH 4 and pH 5 (study I and II). These were further

subclassified as total values and according to occurrence in upright, supine position or during the postprandial 2 hour period.
Corresponding parameters were used also for the esophageal registration of reflux with a pH < 4 [73,76].

5.3 Laryngoscopic examination

In study II a videolaryngoscopic examination was performed of the subjects with a rigid endoscope (n=23, Storz 8706 CJ, 70°, Tuttlingen, Germany) or if not possible, with a flexible fiberscope (n=2, Olympus ENF-P3, 3.5 mm, Tokyo, Japan). The endoscopes were connected to a light source (Wolf 5052, Knittlingen, Germany) and to video equipment (camera: Panasonic KS152; Super-VHS video recorder: Panasonic MD 835, Tokyo, Japan; monitor: Sony CBM-1810E, Tokyo, Japan). The examinations were performed using a standardized protocol [22]

In order to analyze the results of the laryngeal examinations, all video recordings were copied in a random order to a separate super-VHS (S-VHS) tape. An S-VHS video recorder (monitor: Sony CVM-1810E) with the option to view the recordings in slow motion or frame-by-frame was used. Two experienced phoniatricians, who remained blinded to subject data, examined the video tapes using a standardized evaluation protocol, where the different sections of the glottis were evaluated separately according to previously published definitions [22]. Prior to the evaluation, a training session was organized to accustom the investigators to the definitions. A consensus procedure was used, i.e. the investigators agreed on the ratings. The investigators were asked to categorise the findings as either “larynx without mucosal abnormalities”, “posterior laryngitis (PL)”, “chronic laryngitis” or “other additional diagnosis”.

5.4 Questionnaires

Upper Gastrointestinal Disease Questionnaire (UGDQ) study II.

The UGDQ has 21 items, with several multiple-choice questions addressing esophageal symptoms and gastro-esophageal reflux. The questionnaire has an open recall period. While not formally validated, its content relevance has been shown by extensive use in clinical routine at the esophageal laboratory, Department of Otolaryngology,

Sahlgrenska University Hospital. Additionally, the UGDQ has been applied previously in two epidemiological studies [111,112].

Pharyngeal Reflux Symptom Questionnaire (PRSQ) study II and IV.

In its initial version the disease-specific, self-administered PRSQ consisted of 24 items, including both frequency and severity aspects within the following domains; Cough (9 questions), Voice/Hoarse (5 questions), Dysphagia (4 questions), Reflux (3 questions) and Chest (3 questions). The patients were asked to respond to each item on a 6-point Likert scale for frequency and severity with a 4 week recall period. The frequency ranged from 0 (never) to 5 (7 days a week) and the severity ranged from 0 (not at all/no bother) to 4 (very bothersome). Additional items regarding medical conditions and medications, used to identify factors that might impact patient symptoms, were also included. After psychometric analyses performed in study IV a slimmed psychometrically valid version was achieved. The final PRSQ version contains 17 items with the domains; Cough (6 questions), Voice/Hoarse (5 questions), Dysphagia (3 questions) and Reflux (3 questions), Appendix A

Laryngo Pharyngeal Reflux – Health Related Quality of Life (LPR-HRQL) study III and IV.

The LPR-HRQL is a 43 item disease-specific, self-administered questionnaire with a 4 week recall period addressing HRQL domains affected by the LPR disease. The LPR-HRQL is using a standard 7-point Likert scale for reporting frequency of symptoms from 0 (never) to 6 (6-7 days per week). It contains 5 domains; Voice/Hoarse (12 questions), Cough (6 questions), Clear throat (6 questions) and Swallow (5 questions). Additionally, each domain is followed by a question, addressing the way the domain affects overall HRQL. The final domain Overall Impact of Acid Reflux (OIAR) has 9 questions assessing the combined impact of acid reflux-related symptoms. The last question in each domain and the OIAR questions scores ranges from 1 (no effect on HRQL) to 10 (enormous effect on HRQL). In the original study by Carrau et al. the questionnaire has shown promising psychometrical results [17]. The LPR-HRQL questionnaire was translated into Swedish using a formal forward–backward translation

method, pre-tested on LPR patients and reviewed by clinicians and patient focus groups, Appendix B.

Reflux Symptom Index (RSI) study III and IV.

The RSI is a validated 9-item, self-administered questionnaire designed to measure the severity of laryngeal symptoms that may be secondary to LPR. The questions included are; hoarseness or voice problems, throat clearing, excess mucus or postnasal drip, difficulty swallowing, coughing after meal or lying down, breathing difficulties or choking episodes, troublesome cough, sensation of sticking or lump in throat, heartburn, chest pain or regurgitation. The RSI has a recall period of 4 weeks and each item response ranges from 0 (no problem) to 5 (severe problem), giving a maximum total score of 45 points. The psychometrical properties of the questionnaire have been found to be satisfactory. Patients with an RSI score > 13 were defined as abnormal, i.e. having LPR disease [110].

Short Form-36 version 2 (SF-36 v2) study II, III and IV.

The SF-36 is a widely used generic questionnaire for measuring HRQL with a recall period of 4 weeks [113]. The instrument contains 36 items in 8 domains: Physical Functioning (PF, 10 items), Role limitations due to Physical problems (RP, 4 items), Bodily Pain (BP, 2 items), General Health (GH, 5 items), Vitality (VT, 4 items), Social Functioning (SF, 2 items), Role limitations due to Emotional problems (RE, 3 items), Mental Health (MH, 5 items) and a question concerning perceived health during the last year. A score for each domain between 0 (worst possible HRQL) to 100 (best possible HRQL) is calculated using a standardized scoring system The Swedish version has a well documented reliability and validity [114].

5.5 Statistical methods

Study I. The results are expressed as medians and percentiles since the values of the pharyngeal pH measurements were skewed. The 95th percentiles were used as the upper limit of normality (ULN). The Mann-Whitney test was used for comparisons between groups. The Spearman correlation coefficient was used to calculate correlations between the reflux parameters.

Study II. Fisher's exact test (dichotomous variables), Mantel-Haenszel chi-square test (ordered categorical variables) and Mann-Whitney U-test (continuous variables) were used for tests between groups. For tests of changes from baseline to follow-up, the Sign test (dichotomous and non-continuous variables) and the Wilcoxon signed rank test (continuous variables) were used. Correlation between continuous variables was tested with Spearman correlation and the corresponding p-value. All tests were two-tailed and conducted at the 1% significance level due to the large number of tests. To control for multiple significance, the upper limit of the expected number of false significances was calculated. The upper limit of the expected number is denoted by =alpha (N-n [alpha]) / (1-alpha), where N= number of tests, n (alpha) = number of significances on level alpha, alpha=significance level. The calculation was done separately for the primary variable and the secondary variables to avoid mutual influence. Primary analyses were pH variables at baseline compared to symptoms, laryngeal findings and pH at follow-up respectively. All other analyses were either secondary or exploratory. The expected numbers of false significant results for the primary and secondary variables respectively, were 1.6 / 4 and 2.6 / 21. Given the population, n=24, a difference of +/- 2 reflux episodes in the hypofarynx at pH 4 between baseline and follow-up was found to give a statistical power of 89.2%.

Study III, IV. The principal steps in the psychometric evaluation of the LPR-HRQL and PRSQ were a) convergent and discriminant validity assessment; and b) stability and reliability assessment. Prior to this the PRSQ was also subjected to item reduction and domain development. Item reduction was done based on validity and reliability assessment and individual item performance. Items with poor statistical performance (floor or ceiling effects) and with poor domain internal consistency reliability (scaling

errors) were eligible for elimination. Descriptive statistics and histograms for distribution were used to assess statistical validity.

Exploratory factor analysis was used to identify and confirm the domain structure of the LPR-HRQL and the PRSQ. We used factor analysis with Varimax rotations to identify possible meaningful and homogenous factors. Factors were retained if they met Kaiser's criterion (eigenvalue >1) [108] and if the factor loadings were >|0.4| and conceptually relevant in that factor.

Confirmation of the structure of domains was achieved using multitrait scaling analysis, which was based on item domain correlation. Evidence of item convergent validity was defined as a correlation of 0.40 or greater between an item and its own domain (corrected for overlap). Item discriminant validity was based on the comparison of the correlation with its hypothesised domain compared with other domains. If the correlation between an item and its own domain was more than two standard errors below its correlation with another scale a "definite" scaling error was established. A correlation within two standard errors was regarded as a "probable" scaling error.

Convergent validity was analysed in study III by correlating the LPR-HRQL with the RSI and the SF-36 questionnaires, using the Spearman correlation coefficient. The PRSQ domains in study IV were correlated with the RSI questions, the LPR-HRQL and the SF-36 domains. Discriminant validity of the questionnaire domains, e.g. known group validity was achieved dividing the patients into groups with or without a current LPR-disease. Reliability of the domains was assessed by internal consistency (Cronbach's alpha coefficient), which measures the overall correlation between items within a domain. A level of 0.7 or higher is considered desirable.

Mean, SD and range were used for descriptive purposes. In the case of domains with missing items, non-missing items within that given domain are rescaled to generate a value comparable to subjects responding to all items. However, if more than 50% of the items within the domain are missing, the domain score will be set as missing.

Tests for comparing the two groups established through RSI scores were performed using Mann-Whitney U-test for continuous variables, Chi-square tests for nominal (categorical) variables and Fisher's exact test for binary variables. The Spearman correlation coefficient was used for correlations between corresponding domains in different questionnaires.

All tests were two-tailed and the significance level was set to 5% throughout. Prior to analysis of response patterns, assumptions of inter-relationships were made, thereby minimizing the risk of overestimation of the number of significant tests.

Ethics The studies were approved by the Ethical Committee for Human research at Sahlgrenska University Hospital and were conducted in accordance with the Declaration of Helsinki.

6 Results

6.1 Study I

Pharyngeal pH 5 reflux episodes occurred in 32/35 subjects (91%). The median number of pharyngeal reflux episodes at pH 5 was 4.0. A vast majority of these reflux episodes (92%) occurred in the upright position, especially in the postprandial period. The median time pH < 5 in pharynx was 0.1% while the upper limit of normality was 1.5% of the registered time. Pharyngeal pH 5 reflux episodes were 5 times more common than pH 4 reflux episodes. There was a significant positive correlation between hypopharyngeal and esophageal acid exposure time at both pH 4 and pH 5 ($p < 0.01$).

Table 5. 24 hour pH registration at pH 4 and pH 5 in the esophagus and the hypopharynx (n=35)

	pH < 4 hypopharynx		pH < 5 hypopharynx		pH < 4 esophagus	
	%	n	%	n	%	n
Mean	0.1	1.7	0.3	7.7	2.6	26.1
Median	0	1	0.1	4	1.1	22
ULN * 95th percentile	0.2	9	1.5	34	7.6	68

* ULN; upper limit of normality, % total time

6.2 Study II

Twenty-four subjects completed the follow-up after a mean time of 14 years. The number of subjects with pathological esophageal reflux, percentage of time per 24 hour < pH 4 exceeding 4.2%, increased from 5 (21%) at baseline to 8 (33%) at follow-up ($p=0.38$), whereas the proportion with pharyngeal acid exposure of at least 0.1% decreased from 10 (42%) to 3 (13%) ($p=0.04$).

Table 6. Distal esophageal pH monitoring results at baseline and follow-up

	Baseline (n=24)	Follow-up (n=24)
Total number of reflux episodes	26 (2-68)	21 (3-48)
- Upright	25 (2-62)	20 (1- 44)
- Supine	1 (0-12)	1 (0-22)
- Postprandial	17 (2-51)	9 (0-24)
Total % time with pH < 4	2.3 (0-7.6)	1.7 (0-14.2)
- Upright	2.8 (0.1-11.7)	2.2 (0-14.1)
- Supine	0.1 (0-7.7)	0.1 (0-14.2)
- Postprandial	3.6 (0.2- 13)	2.1 (0-16.6)

Values expressed as medians and (5th and 95th percentiles)

Table 7. Hypopharyngeal 24-hour pH monitoring at baseline and follow-up

	Baseline (n=24)		Follow-up (n=24)	
	pH 4	pH 5	pH 4	pH 5
Total number of reflux episodes	2 (0-10)	5 (0-25)	0 (0-4)	3 (0-28)
- Upright	2 (0-8)	5 (0-24)	0 (0-4)	3 (0-16)
- Supine	0 (0-1)	0 (0-2)	0 (0, 0)	0 (0-5)
- Postprandial	2 (0-6)	2 (0-13)	0 (0-2)	1 (0-10)
Total % time	0 (0-0.2)	0.1 (0-1.5)	0 (0- 0.1)	0.1 (0-1.3)
- Upright	0 (0- 0.3)	0.2 (0-2.7)	0 (0- 0.2)	0.1 (0-1.8)
- Supine	0 (0)	0 (0-0.5)	0 (0)	0 (0- 0.1)
- Postprandial	0 (0-0.4)	0.2 (0-6.3)	0 (0- 0.2)	0 (0-3.6)

Values expressed as medians and (5th and 95th percentiles)

Laryngeal pathology was found in 9 of 23 subjects (39%) at follow-up.
The presence of airway symptoms was similar among subjects with or without laryngeal findings or with or without pharyngeal reflux.

6.3 Study III

In this validation study a total of 228 patients were included and classified according to the RSI cut-off score. Patients with an RSI score > 13 were defined as abnormal; LPR+, i.e. having LPR disease (n=102) and those with a score between 0-13 as normal controls (n= 126); LPR-. The questionnaire was well accepted by the patients, compliance was satisfactory, and missing item values were low. However, the data on all scales and single items were skewed toward low values (few problems), especially in the LPR- group, but responses covered the full range of scores for most of the scales. The psychometric tests performed fulfilled the criteria for structural integrity, validity and reliability. Discriminant validity was satisfactory as the questionnaire discriminated between patients with and without LPR disease.

6.4 Study IV

The PRSQ was developed based on empirical evidence from literature review, expert input from physicians and patients and tested in a pilot study. The PRSQ was well accepted by the 228 patients. Compliance was satisfactory and missing item rates low. In its initial version the PRSQ had 24 questions in 5 domains. After item reduction, due to items not being conceptually relevant or scaling errors and/or low factor loadings, a construct was achieved with no scaling errors and high internal consistency (Cronbach's alpha 0.79-0.93). The final PRSQ version contains 17 items with the domains of; Cough (6 questions), Voice/Hoarse (5 questions), Dysphagia (3 questions) and Reflux (3 questions).
The correlations between the PRSQ and similar dimensions in the RSI and the LPR-HRQL were generally strong. Discriminant validity was satisfactory as the questionnaire discriminated between patients with and without LPR disease.

7 Discussion

There is an ongoing debate whether LPR is an entity of its own, separate from GERD or if they in fact are two steps on the same ladder. There is, however, increasingly more evidence suggesting that LPR and GERD belong together in a continuous spectra. Groome et al. found that the prevalence of LPR increases with the severity of GERD [115]. Another study which included both GERD patients and non-GERD patients with LPR symptoms showed that when treated with PPI, laryngitis symptoms and signs improved only in the GERD group [116]. Numerous studies have reported that healthy subjects and LPR patients overlap in exposure of LPR [58,60,117]. This is in accordance with the results from study 2 where laryngeal findings and upper airway symptoms were found to increase; even though correlation between pH-monitoring, airway symptoms and laryngeal findings was weak. The exact limits to where normality ends and disease begins are still unclear. These results suggest that LPR, as well as GERD, is a continuous spectrum, where progression and regression occurs [7,118]. Furthermore, the fact that healthy volunteers have LPR contradicts Kaufman's statement that one single reflux episode would be enough to create symptoms.

The current lack of consensus regarding how to confirm the diagnosis of LPR [58] and consequently how to successfully treat LPR [102], is due to the fact that neither symptom registration, pH-monitoring or laryngoscopic examination have been sensitive and specific enough to successfully select the patients who can benefit from treatment. This thesis aimed to develop tools for the diagnostics of LPR through establishing reference boundaries for pH-registration of weakly acidic reflux, i.e. at pH 5 and to potentially improve upon symptom diagnosis with validated patient-reported symptom questionnaires.

Weakly acidic reflux

Diagnosis of LPR-disease through pH-monitoring have traditionally used the classical pH cut-off limit of pH 4 which misses patients with weakly acidic reflux (pH > 4) that is potentially nocioceptive to the laryngeal tissue. Furthermore, mucosal damage in the larynx secondary to pepsin exposure up to pH 6 has been demonstrated in a porcine model by Johnston et al. [57]. Weakly acidic reflux with a cut-off at pH 5 was in study I found to be 5 times more common than with the traditional cut-off at pH 4. The

upper limit of normality for exposure was 34 episodes, or 1.5% of the registered time. This cut-off level enables a higher sensitivity for capturing potentially nocioceptive reflux. In fact, intervention studies with PPI have shown weak results in the treatment of LPR disease [42,94,102,119]. In these studies pH 4 has been used as cut-off to identify the LPR patients. The inclusion of weakly acidic reflux could in future studies improve the selection of patients and thus the treatment results.

Study 1 is the first study that sets reference limits for pharyngeal reflux at pH 5. The generalizability of the study may, however, be hampered by the limited cohort size of 35 subjects, although in comparison with other existing studies on the subject, the number of study patients is not small.

Problems with pH monitoring

There are several evident problems with 24-hour pH monitoring. The sensitivity of standard pharyngeal pH monitoring has been questioned and is found to be as low as around 50% [11,120]. This can be contrasted to the higher distal esophageal sensitivity of at least 70%. In part this has to do with the limited reliability of the hypopharyngeal pH probe.

The pharynx is a wide cavity and the probe may lose contact with the mucosa causing it to become dry, especially during sleep when swallowing is less frequent. This results in false pH declines i.e. pseudoreflux events. As a consequence, manual analysis of pharyngeal pH measurements is important. A total of 49% of the pH-drops in study I were, in fact, manually detected pseudoreflux, which is similar to what other authors have found [9,60]. Further problems with standard pH probe-monitoring are failure to identify gaseous and non acid reflux events. This may be of even more importance in LPR patients as gases are more diffusible and can reach higher. It is expected that the diagnostic sensitivity and specificity may be improved by the recent introduction of combined pH-metry and multichannel intraluminal impedance monitoring. This technique enables monitoring of gastroesophageal reflux and the relation to typical and atypical symptoms independent of the acidity of the refluxate. The technique thus allows the recognition of acidic (pH < 4), weakly acidic (pH 4-6.5), weakly alkaline (pH > 6.5), as well as gas, liquid and mixed reflux events [51,77,78]. However, impedance testing as well as traditional pH monitoring suffers from lack of established norms, pseudoreflux

events and artefacts [58]. Furthermore, the double probe pH-monitoring (study 1 and 2), in which the retrograde direction of the reflux can be manually visualized; give the same information regarding weakly acidic or weakly alkaline reflux as impedance monitoring. The impedance monitoring can however, in addition, also differentiate between liquid, mixed and gaseous refluxes. This can be of importance since there have been reports of acid gaseous reflux provoking symptoms [51,78].

The exact positioning of the proximal probe has also been debated. A placement 1-2 cm above UES is judged to give more accurate and consistent information, differentiating normal subjects from patients with LPR disease, than probe-locations in the proximal esophagus [13]. A higher placement reduces contact of the probe with the mucosa with drying and false-positive readings, whereas reflux at or below the sphincter correlate less well with LPR symptoms. Furthermore, acid exposure percentage was found to be more reliable than the number of reflux events [13].

Hypopharyngeal reflux in healthy volunteers

Twenty-four of the subjects from study I were re-examined after a mean time of 14 years which makes study II the first study to describe the natural history of the esophageal and hypopharyngeal reflux in healthy subjects. It also reports that the presence of asymptomatic hypopharyngeal reflux (silent reflux) do not constitute a risk factor for future development of LPR disease. Airway symptoms were found to increase over time and laryngeal pathological findings developed in 39% of the subjects. The increase in symptoms and laryngeal abnormalities were however not related to a significant increase in acid exposure. An analogy can be made to non-erosive GERD (NERD) patients. Fass et al. discovered that 50% of the patients with NERD had normal pH-monitoring despite a typical symptomatology [84]. In the case of esophageal reflux two explanations to this phenomenon have been suggested; the first is a hypersensitive esophagus (functional heartburn) which Martinez et al found 40% of the NERD population to have [85]. These patients partially respond to PPI treatment and it is believed that hypersensitive esophagus is caused by weakly acidic or weakly alkaline reflux, [85]. Secondly, the causing factor in the remaining group is considered to be not reflux related.

Laryngeal findings

The unspecificity of laryngeal findings has been demonstrated in several studies [22,60,64] as they can be caused by many other conditions such as allergies, sinusitis, voice abuse, smoking etc. This is in accordance with the results in study 2. There are however, attempts to find specific mucosal lesions that might be more patognomonic, such as pseudosulcus, granuloma and interarytenoid thickening [9,65]. Another problem is the weak inter- and intra-rating scoring seen when experienced laryngologists examine the larynx and compare the results [64]. A route to circumvent this is through standardized evaluation protocols with training sessions and consensus agreement to achieve consistency and reproducibility [64]. To properly evaluate the value of different laryngeal findings in LPR diagnostics, large prospective placebo-controlled double-blinded treatment studies are needed.

Symptom questionnaires

Diagnosis of LPR disease through symptom registration has suffered the lack of properly developed and evaluated symptom questionnaires valid for use in the intended patient population [17,110,121]. The PRO in an intervention study should be a primary efficacy variable. A recent review by Hopkins et al. highlights the lack of reliable data in randomized controlled trials (RCT) studies in the PPI treatment of hoarseness, and only 6 RCT's among 302 studies were identified. The authors concluded that sufficient evidence based on randomised controlled trials is lacking and no reliable conclusions could be drawn. Inclusion and diagnostic criteria varied which rendered subsequent meta-analyses deficient [101]. Their conclusion was that there is a need for high-quality randomized controlled trials to evaluate the efficacy of antireflux therapy. The fact that RCT-studies have not shown conclusive results with PPI-treatment may partly be due to the lack of use of such questionnaires in these studies.

Apart from the Reflux Symptom Index (RSI) designed to measure only the severity of laryngeal symptoms [110], there is a shortage of validated symptom questionnaires. Only recently; the Supraesophageal Reflux Questionnaire (SERQ) [121], a disease specific self-administered questionnaire, and the Laryngopharyngeal Reflux-Health Related Quality of Life questionnaire (LPR-HRQL) [17,122], a questionnaire that addresses specific HRQL domains affected by the disorder, were presented.

Shortcomings such as limited psychometric evaluations or excessive questionnaire length may limit the success in previously developed instruments [106,110,121]. It is desirable that a patient-reported instrument should have a defined recall period, be short enough to facilitate compliance and detailed enough to be sufficiently sensitive and specific. Although the mentioned questionnaires in general have demonstrated satisfactory psychometric properties, the RSI lacks aspects concerning frequency and duration of symptoms and the SERQ have not presented data on internal consistency. In fact, there is presently no available disease specific validated questionnaire for LPR symptoms that includes both frequency and severity dimensions, which could improve the sensitivity of the instruments.

In study III the LPR-HRQL was successfully translated, adaptated and found to have good psychometrical validity, confirming the results found by Carrau et al. in the original LPR-HRQL version [17]. Even though all responses covered the full range of scores for most of the scales, suggesting that the response categories to some extent were sensible, the data on all scales and single items were skewed toward low values (few problems). This finding was in accordance with the findings in the original study by Carrau et al. An item reduction could possibly be undertaken in a future prospective study to limit this tendency. However, this is to date the only disease-specific LPR questionnaire to include the HRQL aspect of the disease and might be considered a valuable tool in future studies as it includes HRQL aspects of the LPR disease. Possibly in a revised version with fewer items due to the tendency towards a floor effect in the response profiles.

In study IV we reported the development and validation of a comprehensive, LPR disease specific PRO, the Pharyngeal Reflux Symptom Questionnaire (PRSQ) that includes both frequency and severity dimensions. The PRSQ was well accepted by the patients, compliance was satisfactory and number of missing items low. After analysis with item reduction and scale development, it was found to be psychometrically valid with good convergent and discriminant validity. This is the first formally validated disease specific instrument that includes both frequency and severity aspects for the LPR disease. The instrument has the potential of facilitating the standardization of PRO's in studies to come. Drawbacks are the lack of test-retest reliability and responsiveness to intervention, aspects that will be addressed in a future prospective study.

Also important in the process of validating a PRO instrument is the interpretability. How will the instrument be used in a clinical setting and which is the smallest difference that is considered clinically important [104]. A possible future strategy to achieve a higher interpretability of the PRSQ could be through creating a composite PRSQ score. In order to find a clinically useful cut-off score the standard deviation or the upper 95% confidence interval limit of the mean total product PRSQ score in the LPR- group might be used. The total mean product score (frequency x severity) and standard deviation (SD) was 100.7 (65.2) and 23.9 (30.4) in the LPR+ and LPR- groups respectively. The upper 95% confidence interval limit of the LPR- group was 83.5, hence a total mean product score (frequency x severity) ≥ 84 might be interpreted as having LPR disease. This has however to be further investigated in a prospective study before actual implementation. There are many unanswered questions as to how to best identify the LPR patients.

The three legs of the diagnosis of the LPR disease; pH-monitoring, symptom evaluation and larynx examination have in previous studies reported a low predictive value. At the same time, large prospective studies such as the ProGerd study has shown a high odds ratio for airway disorders in GERD patients [7] thus indicating that a clinically significant relationship does exist. The dilemma is how to best identify these patients. To do this we need large prospective intervention RCT's with validated symptom questionnaires, standardized evaluation protocols of laryngeal findings, with consensus agreement between trained laryngologists and also reference intervals for pH-monitoring, including weakly acidic reflux.

8 Conclusion

Weakly acidic reflux with a cut-off limit at pH 5 in the pharynx is 5 times more common than at pH 4. This cut-off level might enable a higher sensitivity for capturing potentially nocioceptive reflux.

A significant correlation was observed between the hypopharyngeal and the esophageal reflux exposure time at both pH 4 and pH 5.

Healthy individuals do not exhibit increased LPR or esophageal reflux, according to pH-monitoring, over time. The presence of asymptomatic hypopharyngeal reflux, i.e. silent reflux does not constitute a risk factor for future development of LPR.

However, upper airway symptoms and pathological findings upon laryngeal examination increase. Alternative explanations to why this occurs have to be sought.

Psychometrically tested, stable patient reported symptom questionnaires such as PRSQ and LPR-HRQL may contribute to clearer criteria for diagnosing LPR. Hopefully this can contribute to improved patient selection and thus treatment results.

9 Future research and goals

I. A prospective intervention study of patients seeking medical assistance for upper-airway symptoms is ongoing. The aim is to investigate the test-retest reliability of the LPR-HRQL and PRSQ questionnaires as well as their responsiveness to treatment.

II. To evaluate the occurrence of salivary/sputum pepsin in healthy volunteers and patients with reflux symptoms and laryngitis. To relate the pepsin contents to laryngeal acid exposure and to evaluate the effect of PPI treatment on the acid/pepsin relationship. The study will also include impedance monitoring of pharyngeal reflux.

10 Acknowledgments

I wish to express my sincere gratitude to the people who have supported me in the completion of this work at the department of Otolaryngology, Sahlgrenska University Hospital and in particular:

Caterina Finizia; Associate Professor, supervisor and co-author, for your tremendous work capacity and fabulous general knowledge in research, your continuous encouraging and swift support, and enthusiasm.

Magnus Ruth; Associate Professor, assistant supervisor and co-author, for your scientific knowledge in the field of reflux, friendly encouragements and swift and fantastic support.

Riitta Ylitalo; Associate Professor, assistant supervisor and co-author, for your scientific knowledge in the field of LPR, invaluable help and encouraging support.

Anna Rydén; co-author, for proof-reading and sharing of expert assistance in the field of questionnaire validation .

Magnus Bove; co-author, for friendly encouragement.

Gösta Granström; Professor at the department of Otolaryngology at Sahlgrenska, for interest and support.

Hasse Ejnell; head of the department of Otolaryngology at Sahlgrenska, for interest and support.

Ann-Christine Mjörnheim; for skilful technical assistance and practical, caring and friendly support.

Aldina Pivodic, Gunnar Ekeroth and Nils-Gunnar Persson at Statistiska Konsultgruppen AB; for skilful help with statistics and friendly and swift responses.

Per-Åke Lindestad, Department of Otolaryngology, Karolinska University Hospital Huddinge; for evaluation of laryngeal video recordings.

Henrik Bergquist; for sharing everyday life at the ”esofagus laboratory” with a friendly smile and a listening ear.

Stefan Skrtic; room partner, for sharing mutual space and friendly acceptance.

Anders Ebenfelt; for testing me at the running course and for numerous humoristic and friendly comments.

Ingrid Parada; My wife, without whom all of this would have been impossible.

The studies were supported by grants from the Göteborgs Läkarsällskap, Acta Oto-Laryngologica, Nachmanssons fond, Assar Gabrielssons fond and Astra Zeneca, The Research and Development Council (FoU), Västra Götaland County and the Medical Faculty of Göteborg University

Göteborg 091005
Olle Andersson

11 Summary in Swedish

Laryngofaryngeal reflux (LPR), dvs. regurgitation av maginnehåll till svalget, anses kunna ge upphov till respektive försämra sjukdomar inom de övre och nedre luftvägarna. Symptom från struphuvudområdet som associeras med LPR är heshet, harkling, ökad slembildning, ont i halsen, klumpkänsla och hosta. Undersökningsfynden omfattar bl.a. rodnad, ödem och förtjockning av slemhinnan på de äkta, falska stämbanden och på arybrosken. Tydliga kriterier för hur LPR skall diagnostiseras saknas emellertid. Konsensus saknas bl.a. avseende vilket gränsvärde som skall gälla för normal syraexponering i farynx och vilka larynxfynd och symptom som är av betydelse, där bristen på psykometriskt testade symptomfrågeformulär förstärkt problematiken. Denna avhandling inkluderar 4 delarbeten med mål att utforska diagnostiska gränser för pH-registrering och beskriva naturalförloppet för sjukdomen samt validera ett nyskapat (PRSQ) och ett översatt (LPR-HRQL) symptomfrågeformulär.
I arbete I re-analyserades pH-registreringar från 35 friska frivilliga med pH 5 som cut-off värde istället för det klassiska pH 4. Den övre normalgränsen befanns vara 1.5% < pH 5 av dygnsregistreringen och 34 refluxepisoder. I arbete II följdes 24 av de friska frivilliga försökspersonerna longitudinellt dvs. 14 år senare med förnyad pH mätning, symptomregistrering och larynx bedömning. Populationen hade vid uppföljningen utvecklat övre luftvägssymptom i 42 % och patologiska larynxfynd i 39 % medan fraktionen med patologisk syraexponering i hypofarynx gick ner från 42 % till 13 %. I arbete III och IV genomfördes psykometrisk testning av två symtomfrågeformulär, den svenska översättningen av LPR-HRQL (III) och det nyskapade frågeformuläret PRSQ (IV) i en population av 228 patienter med övre luftvägs symptom. Exploratorisk och konfirmatorisk faktoranalys av den svenska versionen av frågeformuläret LPR-HRQL visade acceptabla psykometriska egenskaper och resultat jämförbara med den amerikanska originalversionen. PRSQ var lätt att fylla i och var väl accepterad av patienterna. Genomförd faktoranalys av PRSQ resulterade i att 7 av formulärets frågor togs bort och gav en slutlig PRSQ version (2) med 4 subskalor. PRSQ 2 visade goda psykometriska egenskaper med bl.a. signifikant förmåga att diskriminera på gruppnivå.
Avhandlingen visar att övre luftvägssymptom och patologiska larynxfynd i ett friskt normalmaterial är vanliga och ökar över tid, samt att några signifikanta samband mellan symptom, larynxfynd och pH-registreringar inte kunde säkerställas. Vidare, att ett cut-off värde på pH 5 kan fånga svagt sur reflux och förbättra diagnostiken vid LPR sjukdom och att validerade diagnosspecifika symptomfrågeformulär bör användas i framtida studier för att förbättra diagnostiken och därmed patientselektionen.

12 References

1. Castell DO, Murray JA, Tutuian R, Orlando RC, Arnold R. Review article: the pathophysiology of gastro-oesophageal reflux disease - oesophageal manifestations. Aliment Pharmacol Ther 2004;20 Suppl 9:14-25
2. Jaspersen D, Kulig M, Labenz J, et al. Prevalence of extra-oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the ProGERD Study. Aliment Pharmacol Ther 2003;17:1515-1520
3. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991;101:1-78
4. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2005;54:710-717
5. Andersson O, Moller RY, Finizia C, Ruth M. A more than 10-year prospective, follow-up study of esophageal and pharyngeal acid exposure, symptoms and laryngeal findings in healthy, asymptomatic volunteers. Scand J Gastroenterol 2009;44:23-31
6. Connor NP, Churas KL, Cohen SB, Leverson GE, Bless DM. Symptoms of Extraesophageal Reflux in a Community-Dwelling Sample. J Voice 2006
7. Labenz J, Nocon M, Lind T, et al. Prospective follow-up data from the ProGERD study suggest that GERD is not a categorial disease. Am J Gastroenterol 2006;101:2457-2462
8. Pace F, Bollani S, Molteni P, Bianchi Porro G. Natural history of gastro-oesophageal reflux disease without oesophagitis (NERD)--a reappraisal 10 years on. Dig Liver Dis 2004;36:111-115
9. Ylitalo R, Lindestad PA, Ramel S. Symptoms, laryngeal findings, and 24-hour pH monitoring in patients with suspected gastroesophago-pharyngeal reflux. Laryngoscope 2001;111:1735-1741
10. Vakil N. The frontiers of reflux disease. Dig Dis Sci 2006;51:1887-1895
11. Ahmed TF, Khandwala F, Abelson TI, et al. Chronic laryngitis associated with gastroesophageal reflux: prospective assessment of differences in practice patterns between gastroenterologists and ENT physicians. Am J Gastroenterol 2006;101:470-478
12. Vaezi MF. Laryngitis and gastroesophageal reflux disease: increasing prevalence or poor diagnostic tests? Am J Gastroenterol 2004;99:786-788

13. Merati AL, Lim HJ, Ulualp SO, Toohill RJ. Meta-analysis of upper probe measurements in normal subjects and patients with laryngopharyngeal reflux. Ann Otol Rhinol Laryngol 2005;114:177-182
14. Johnston N, Bulmer D, Gill GA, et al. Cell biology of laryngeal epithelial defenses in health and disease: further studies. Ann Otol Rhinol Laryngol 2003;112:481-491
15. Adhami T, Goldblum JR, Richter JE, Vaezi MF. The role of gastric and duodenal agents in laryngeal injury: an experimental canine model. Am J Gastroenterol 2004;99:2098-2106
16. Vaezi MF. Sensitivity and specificity of reflux-attributed laryngeal lesions: experimental and clinical evidence. Am J Med 2003;115 Suppl 3A:97S-104S
17. Carrau RL, Khidr A, Gold KF, et al. Validation of a quality-of-life instrument for laryngopharyngeal reflux. Arch Otolaryngol Head Neck Surg 2005;131:315-320
18. Berstad A, Hatlebakk JG. The predictive value of symptoms in gastro-oesophageal reflux disease. Scand J Gastroenterol Suppl 1995;211:1-4
19. An evidence-based appraisal of reflux disease management--the Genval Workshop Report. Gut 1999;44 Suppl 2:S1-16
20. Ronkainen J, Aro P, Storskrubb T, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. Scand J Gastroenterol 2005;40:275-285
21. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900-1920; quiz 1943
22. Ylitalo R, Lindestad P, Hertegard S. Pharyngeal and laryngeal symptoms and signs related to extraesophageal reflux in patients with heartburn in gastroenterology practice: a prospective study. Clin Otolaryngol 2005;30:347-352
23. Harding SM. Recent clinical investigations examining the association of asthma and gastroesophageal reflux. Am J Med 2003;115 Suppl 3A:39S-44S
24. Sontag SJ. Why do the published data fail to clarify the relationship between gastroesophageal reflux and asthma? Am J Med 2000;108 Suppl 4a:159S-169S
25. Jack CI, Calverley PM, Donnelly RJ, et al. Simultaneous tracheal and oesophageal pH measurements in asthmatic patients with gastro-oesophageal reflux. Thorax 1995;50:201-204
26. Tuchman DN, Boyle JT, Pack AI, et al. Comparison of airway responses following tracheal or esophageal acidification in the cat. Gastroenterology 1984;87:872-881

27. Ruigomez A, Rodriguez LA, Wallander MA, et al. Gastroesophageal reflux disease and asthma: a longitudinal study in UK general practice. Chest 2005;128:85-93
28. Ing AJ, Ngu MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med 1994;149:160-167
29. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest 2006;129:1S-23S
30. Pratter MR. Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome): ACCP evidence-based clinical practice guidelines. Chest 2006;129:63S-71S
31. Kiljander TO, Salomaa ER, Hietanen EK, Terho EO. Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with omeprazole. Eur Respir J 2000;16:633-638
32. Ours TM, Kavuru MS, Schilz RJ, Richter JE. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. Am J Gastroenterol 1999;94:3131-3138
33. Jailwala JA, Shaker R. Oral and pharyngeal complications of gastroesophageal reflux disease: globus, dental erosions, and chronic sinusitis. J Clin Gastroenterol 2000;30:S35-38
34. Munoz JV, Herreros B, Sanchiz V, et al. Dental and periodontal lesions in patients with gastro-oesophageal reflux disease. Dig Liver Dis 2003;35:461-467
35. Hicks DM, Ours TM, Abelson TI, Vaezi MF, Richter JE. The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. J Voice 2002;16:564-579
36. Ulualp SO, Toohill RJ, Hoffmann R, Shaker R. Pharyngeal pH monitoring in patients with posterior laryngitis. Otolaryngol Head Neck Surg 1999;120:672-677
37. Woo P, Noordzij P, Ross JA. Association of esophageal reflux and globus symptom: comparison of laryngoscopy and 24-hour pH manometry. Otolaryngol Head Neck Surg 1996;115:502-507
38. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope 2001;111:1313-1317
39. Kamel PL, Hanson D, Kahrilas PJ. Omeprazole for the treatment of posterior laryngitis. Am J Med 1994;96:321-326

40. So JB, Zeitels SM, Rattner DW. Outcomes of atypical symptoms attributed to gastroesophageal reflux treated by laparoscopic fundoplication. Surgery 1998;124:28-32
41. El-Serag HB, Lee P, Buchner A, et al. Lansoprazole treatment of patients with chronic idiopathic laryngitis: a placebo-controlled trial. Am J Gastroenterol 2001;96:979-983
42. Noordzij JP, Khidr A, Evans BA, et al. Evaluation of omeprazole in the treatment of reflux laryngitis: a prospective, placebo-controlled, randomized, double-blind study. Laryngoscope 2001;111:2147-2151
43. Groen JN, Smout AJ. Supra-oesophageal manifestations of gastro-oesophageal reflux disease. Eur J Gastroenterol Hepatol 2003;15:1339-1350
44. Weaver EM. Association between gastroesophageal reflux and sinusitis, otitis media, and laryngeal malignancy: a systematic review of the evidence. Am J Med 2003;115 Suppl 3A:81S-89S
45. el-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. Gastroenterology 1997;113:755-760
46. Holloway RH, Penagini R, Ireland AC. Criteria for objective definition of transient lower esophageal sphincter relaxation. Am J Physiol 1995;268:G128-133
47. Pandolfino JE, Zhang QG, Ghosh SK, et al. Transient lower esophageal sphincter relaxations and reflux: mechanistic analysis using concurrent fluoroscopy and high-resolution manometry. Gastroenterology 2006;131:1725-1733
48. Eubanks TR, Omelanczuk PE, Maronian N, et al. Pharyngeal pH monitoring in 222 patients with suspected laryngeal reflux. J Gastrointest Surg 2001;5:183-190; discussion 190-181
49. Sifrim D. Acid, weakly acidic and non-acid gastro-oesophageal reflux: differences, prevalence and clinical relevance. Eur J Gastroenterol Hepatol 2004;16:823-830
50. Koufman JA. Laryngopharyngeal reflux is different from classic gastroesophageal reflux disease. Ear Nose Throat J 2002;81:7-9
51. Kawamura O, Aslam M, Rittmann T, Hofmann C, Shaker R. Physical and pH properties of gastroesophagopharyngeal refluxate: a 24-hour simultaneous ambulatory impedance and pH monitoring study. Am J Gastroenterol 2004;99:1000-1010
52. Galli J, Cammarota G, De Corso E, et al. Biliary laryngopharyngeal reflux: a new pathological entity. Curr Opin Otolaryngol Head Neck Surg 2006;14:128-132
53. Sasaki CT, Marotta J, Hundal J, Chow J, Eisen RN. Bile-induced laryngitis: is there a basis in evidence? Ann Otol Rhinol Laryngol 2005;114:192-197

54. Gill GA, Johnston N, Buda A, et al. Laryngeal epithelial defenses against laryngopharyngeal reflux: investigations of E-cadherin, carbonic anhydrase isoenzyme III, and pepsin. Ann Otol Rhinol Laryngol 2005;114:913-921
55. Field SK, Evans JA, Price LM. The effects of acid perfusion of the esophagus on ventilation and respiratory sensation. Am J Respir Crit Care Med 1998;157:1058-1062
56. Burton LK, Jr., Murray JA, Thompson DM. Ear, nose, and throat manifestations of gastroesophageal reflux disease. Complaints can be telltale signs. Postgrad Med 2005;117:39-45
57. Johnston N, Knight J, Dettmar PW, Lively MO, Koufman J. Pepsin and carbonic anhydrase isoenzyme III as diagnostic markers for laryngopharyngeal reflux disease. Laryngoscope 2004;114:2129-2134
58. Joniau S, Bradshaw A, Esterman A, Carney AS. Reflux and laryngitis: a systematic review. Otolaryngol Head Neck Surg 2007;136:686-692
59. Bove M, Ruth M, Cange L, Mansson I. 24-H pharyngeal pH monitoring in healthy volunteers: a normative study. Scand J Gastroenterol 2000;35:234-241
60. Noordzij JP, Khidr A, Desper E, et al. Correlation of pH probe-measured laryngopharyngeal reflux with symptoms and signs of reflux laryngitis. Laryngoscope 2002;112:2192-2195
61. Shaker R, Bardan E, Gu C, et al. Intrapharyngeal distribution of gastric acid refluxate. Laryngoscope 2003;113:1182-1191
62. Ylitalo R, Ramel S. Gastroesophagopharyngeal reflux in patients with contact granuloma: a prospective controlled study. Ann Otol Rhinol Laryngol 2002;111:178-183
63. Maronian NC, Azadeh H, Waugh P, Hillel A. Association of laryngopharyngeal reflux disease and subglottic stenosis. Ann Otol Rhinol Laryngol 2001;110:606-612
64. Branski RC, Bhattacharyya N, Shapiro J. The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. Laryngoscope 2002;112:1019-1024
65. Belafsky PC, Postma GN, Koufman JA. The association between laryngeal pseudosulcus and laryngopharyngeal reflux. Otolaryngol Head Neck Surg 2002;126:649-652
66. Ylitalo R, Lindestad PA, Hertegard S. Is pseudosulcus alone a reliable sign of gastroesophago-pharyngeal reflux? Clin Otolaryngol Allied Sci 2004;29:47-50
67. Oelschlager BK, Eubanks TR, Maronian N, et al. Laryngoscopy and pharyngeal pH are complementary in the diagnosis of gastroesophageal-laryngeal reflux. J Gastrointest Surg 2002;6:189-194

68. Calabrese C, Fabbri A, Bortolotti M, et al. Dilated intercellular spaces as a marker of oesophageal damage: comparative results in gastro-oesophageal reflux disease with or without bile reflux. Aliment Pharmacol Ther 2003;18:525-532
69. Franchi A, Brogelli B, Massi D, et al. Dilation of intercellular spaces is associated with laryngo-pharyngeal reflux: an ultrastructural morphometric analysis of laryngeal epithelium. Eur Arch Otorhinolaryngol 2007;264:907-911
70. Shaker R, Milbrath M, Ren J, et al. Esophagopharyngeal distribution of refluxed gastric acid in patients with reflux laryngitis. Gastroenterology 1995;109:1575-1582
71. Euler AR, Byrne WJ. Twenty-four-hour esophageal intraluminal pH probe testing: a comparative analysis. Gastroenterology 1981;80:957-961
72. Fuchs KH, DeMeester TR, Albertucci M. Specificity and sensitivity of objective diagnosis of gastroesophageal reflux disease. Surgery 1987;102:575-580
73. Johnson LF, Demeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol 1974;62:325-332
74. Rosen SN, Pope CE, 2nd. Extended esophageal pH monitoring. An analysis of the literature and assessment of its role in the diagnosis and management of gastroesophageal reflux. J Clin Gastroenterol 1989;11:260-270
75. Stanciu C, Hoare RC, Bennett JR. Correlation between manometric and pH tests for gastro-oesophageal reflux. Gut 1977;18:536-540
76. Wiener GJ, Morgan TM, Copper JB, et al. Ambulatory 24-hour esophageal pH monitoring. Reproducibility and variability of pH parameters. Dig Dis Sci 1988;33:1127-1133
77. Sifrim D, Dupont L, Blondeau K, et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. Gut 2005;54:449-454
78. Tutuian R, Castell DO. Review article: complete gastro-oesophageal reflux monitoring - combined pH and impedance. Aliment Pharmacol Ther 2006;24 Suppl 2:27-37
79. Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut 2004;53:1024-1031
80. Demeester TR, Johnson LF, Joseph GJ, et al. Patterns of gastroesophageal reflux in health and disease. Ann Surg 1976;184:459-470

81. Kahrilas PJ, Clouse RE, Hogan WJ. American Gastroenterological Association technical review on the clinical use of esophageal manometry. Gastroenterology 1994;107:1865-1884
82. Kahrilas PJ, Dodds WJ, Dent J, et al. Effect of sleep, spontaneous gastroesophageal reflux, and a meal on upper esophageal sphincter pressure in normal human volunteers. Gastroenterology 1987;92:466-471
83. El-Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. Clin Gastroenterol Hepatol 2007;5:17-26
84. Fass R. Erosive esophagitis and nonerosive reflux disease (NERD): comparison of epidemiologic, physiologic, and therapeutic characteristics. J Clin Gastroenterol 2007;41:131-137
85. Martinez SD, Malagon IB, Garewal HS, Cui H, Fass R. Non-erosive reflux disease (NERD)--acid reflux and symptom patterns. Aliment Pharmacol Ther 2003;17:537-545
86. Koufman JA, Belafsky PC, Bach KK, Daniel E, Postma GN. Prevalence of esophagitis in patients with pH-documented laryngopharyngeal reflux. Laryngoscope 2002;112:1606-1609
87. Tobey NA, Hosseini SS, Caymaz-Bor C, et al. The role of pepsin in acid injury to esophageal epithelium. Am J Gastroenterol 2001;96:3062-3070
88. DeRosa J, Marcinkiewicz M, Sarosiek J, Edmunds M, McCallum RW. Modulatory impact of acid and pepsin on esophageal hydrophobicity in humans. Am J Gastroenterol 1995;90:2020-2024
89. Johnston N, Dettmar PW, Lively MO, et al. Effect of pepsin on laryngeal stress protein (Sep70, Sep53, and Hsp70) response: role in laryngopharyngeal reflux disease. Ann Otol Rhinol Laryngol 2006;115:47-58
90. Johnston N, Dettmar PW, Bishwokarma B, Lively MO, Koufman JA. Activity/stability of human pepsin: implications for reflux attributed laryngeal disease. Laryngoscope 2007;117:1036-1039
91. Reichel O, Issing WJ. Impact of different pH thresholds for 24-hour dual probe pH monitoring in patients with suspected laryngopharyngeal reflux. J Laryngol Otol 2008;122:485-489
92. Friedman M, Schalch P, Vidyasagar R, et al. Wireless upper esophageal monitoring for laryngopharyngeal reflux (LPR). Otolaryngol Head Neck Surg 2007;137:471-476
93. Ford CN. Evaluation and management of laryngopharyngeal reflux. Jama 2005;294:1534-1540

94. Steward DL, Wilson KM, Kelly DH, et al. Proton pump inhibitor therapy for chronic laryngo-pharyngitis: a randomized placebo-control trial. Otolaryngol Head Neck Surg 2004;131:342-350
95. Vaezi MF. Therapy Insight: gastroesophageal reflux disease and laryngopharyngeal reflux. Nat Clin Pract Gastroenterol Hepatol 2005;2:595-603
96. Park W, Hicks DM, Khandwala F, et al. Laryngopharyngeal reflux: prospective cohort study evaluating optimal dose of proton-pump inhibitor therapy and pretherapy predictors of response. Laryngoscope 2005;115:1230-1238
97. Fass R. Empirical trials in treatment of gastroesophageal reflux disease. Dig Dis 2000;18:20-26
98. Williams RB, Szczesniak MM, Maclean JC, et al. Predictors of outcome in an open label, therapeutic trial of high-dose omeprazole in laryngitis. Am J Gastroenterol 2004;99:777-785
99. Vaezi MF, Richter JE, Stasney CR, et al. Treatment of chronic posterior laryngitis with esomeprazole. Laryngoscope 2006;116:254-260
100. Wo JM, Koopman J, Harrell SP, et al. Double-blind, placebo-controlled trial with single-dose pantoprazole for laryngopharyngeal reflux. Am J Gastroenterol 2006;101:1972-1978; quiz 2169
101. Hopkins C, Yousaf U, Pedersen M. Acid reflux treatment for hoarseness. Cochrane Database Syst Rev 2006:CD005054
102. Qadeer MA, Phillips CO, Lopez AR, et al. Proton pump inhibitor therapy for suspected GERD-related chronic laryngitis: a meta-analysis of randomized controlled trials. Am J Gastroenterol 2006;101:2646-2654
103. Administration. FD. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. . http://wwwfdagov/cder/guidance/5460dftpdf
104. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes 2006;4:79
105. Patrick DL, Chiang YP. Measurement of health outcomes in treatment effectiveness evaluations: conceptual and methodological challenges. Med Care 2000;38:II14-25
106. Carrau RL, Khidr A, Crawley JA, et al. The impact of laryngopharyngeal reflux on patient-reported quality of life. Laryngoscope 2004;114:670-674

107. Lenderking WR, Hillson E, Crawley JA, et al. The clinical characteristics and impact of laryngopharyngeal reflux disease on health-related quality of life. Value Health 2003;6:560-565
108. Nunally J, Bernstein I. Psychometric theory. New York: McGraw Hill; 1994
109. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika 1951;16:297-334
110. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice 2002;16:274-277
111. Ruth M, Finizia C, Lundell L. Occurrence and future history of oesophageal symptoms in an urban Swedish population: results of a questionnaire-based, ten-year follow-up study. Scand J Gastroenterol 2005;40:629-635
112. Ruth M, Mansson I, Sandberg N. The prevalence of symptoms suggestive of esophageal disorders. Scand J Gastroenterol 1991;26:73-81
113. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol 1998;51:903-912
114. Taft C, Karlsson J, Sullivan M. Performance of the Swedish SF-36 version 2.0. Qual Life Res 2004;13:251-256
115. Groome M, Cotton JP, Borland M, et al. Prevalence of laryngopharyngeal reflux in a population with gastroesophageal reflux. Laryngoscope 2007;117:1424-1428
116. Qua CS, Wong CH, Gopala K, Goh KL. Gastro-oesophageal reflux disease in chronic laryngitis: prevalence and response to acid-suppressive therapy. Aliment Pharmacol Ther 2007;25:287-295
117. Tauber S, Gross M, Issing WJ. Association of laryngopharyngeal symptoms with gastroesophageal reflux disease. Laryngoscope 2002;112:879-886
118. Fullard M, Kang JY, Neild P, Poullis A, Maxwell JD. Systematic review: does gastro-oesophageal reflux disease progress? Aliment Pharmacol Ther 2006;24:33-45
119. Eherer AJ, Habermann W, Hammer HF, et al. Effect of pantoprazole on the course of reflux-associated laryngitis: a placebo-controlled double-blind crossover study. Scand J Gastroenterol 2003;38:462-467
120. Vaezi MF. Review article: the role of pH monitoring in extraoesophageal gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2006;23 Suppl 1:40-49
121. Dauer E, Thompson D, Zinsmeister AR, et al. Supraesophageal reflux: validation of a symptom questionnaire. Otolaryngol Head Neck Surg 2006;134:73-80

122. Andersson O, Rydén A, Ruth M, Ylitalo R, Finizia C. Validation of the Swedish translation of LPR-HRQL. Manuscript 2009

I

II

III

IV

Appendix A

PRSQ

Hur ofta har Du under den *senaste månaden*:		Hur besvärad har du varit vid varje tillfälle?
1) hostat dagtid	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
2) hostat nattetid	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
3) upplevt att Din röst förändrats, låtit sämre	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
4) haft svårt att svälja	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
5) haft astmaattacker	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket

Hur ofta har Du under den *senaste månaden*:		Hur besvärad har du varit vid varje tillfälle?
6) känt att det sticker, kliar i halsen	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
7) känt att det ”bränner” i halsen	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
8) hostat efter måltider	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
9) harklat Dig	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
10) haft sura uppstötningar	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket

Hur ofta har Du under den *senaste månaden*:		Hur besvärad har du varit vid varje tillfälle?
11) haft bröstsmärtor	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
12) haft ont i halsen	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
13) varit hes	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
14) haft slem i halsen	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
15) haft baksnuva (rinner bakom näsan)	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket

Hur ofta har Du under den *senaste månaden*:		Hur besvärad har du varit vid varje tillfälle?
16) haft smärtor när Du sväljer	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
17) haft halsbränna	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
18) haft en ansträngd röst	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
19) fått ont i halsen när du pratat	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
20) hostat i liggande läge	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket

Hur ofta har Du under den *senaste månaden*:		Hur besvärad har du varit vid varje tillfälle?
21) hostat i upprätt läge	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
22) fått andnödsattacker	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
23) känt rösttrötthet, att det varit jobbigt att prata	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket
24) haft en klump i halsen	☐ Aldrig ☐ Mindre än 1 dag i veckan ☐ 1-2 dagar i veckan ☐ 3-4 dagar i veckan ☐ 5-6 dagar i veckan ☐ 7 dagar i veckan	☐ Inte aktuellt ☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket

Appendix B

LPR-HRQL

Ange hur ofta under de senaste 4 veckorna…

		Aldrig	1 dag/ månad	2-3 dag./ månad	1 dag/ vecka	2-3 dag./ vecka	4-5 dag./ vecka	6-7 dag./ vecka
1.	Mina röstproblem gör det svårt för mig att arbeta	☐	☐	☐	☐	☐	☐	☐
2.	Jag är nöjd med hur min röst låter	☐	☐	☐	☐	☐	☐	☐
3.	Att vara hes (ha en raspig röst) gör det svårt för mig att visa fram vem jag verkligen är	☐	☐	☐	☐	☐	☐	☐
4.	På grund av min röst känner sig andra obekväma av att lyssna på mig	☐	☐	☐	☐	☐	☐	☐
5.	På grund av min röst kan jag inte sjunga så mycket jag vill	☐	☐	☐	☐	☐	☐	☐
6.	Det är svårt att träffa nya människor för jag undrar vad dom tänker om mig när dom hör min röst	☐	☐	☐	☐	☐	☐	☐
7.	Min röst får andra att tro att jag är arg eller upprörd trots att jag inte är det	☐	☐	☐	☐	☐	☐	☐
8.	Att anstränga sig att tala är uttröttande	☐	☐	☐	☐	☐	☐	☐
9.	Jag är generad över hur min röst låter	☐	☐	☐	☐	☐	☐	☐
10.	Jag undviker att prata eftersom det är så ansträngande	☐	☐	☐	☐	☐	☐	☐
11.	På grund av mina röstproblem har jag svårt att sköta mitt jobb	☐	☐	☐	☐	☐	☐	☐
12.	Jag är rädd för att tappa rösten för alltid	☐	☐	☐	☐	☐	☐	☐

 Svensk version 1.2, Ruth, Finizia, Ylitalo, Rydén 2006

+ +

Under de senaste 4 veckorna…

13. Var vänlig ange hur mycket Din totala livskvalitet har påverkats av Dina problem med att prata, sjunga och med din röst. *(ringa in en siffra)*

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

Ange hur ofta under de senaste 4 veckorna…

	Aldrig	**1 dag/ månad**	**2-3 dag./ månad**	**1 dag/ vecka**	**2-3 dag./ vecka**	**4-5 dag./ vecka**	**6-7 dag./ vecka**
14. Min hosta gör mig generad	☐	☐	☐	☐	☐	☐	☐
15. Jag undviker sociala tillställningar. t ex att gå på konserter och bio, eftersom min hosta kan störa omgivningen	☐	☐	☐	☐	☐	☐	☐
16. Jag måste lämna rummet på grund av min hosta	☐	☐	☐	☐	☐	☐	☐
17. Folk tror att jag är sjuk eftersom jag hostar	☐	☐	☐	☐	☐	☐	☐
18. Mina medarbetare hör mig komma i korridoren på grund av min hosta	☐	☐	☐	☐	☐	☐	☐
19. Jag oroar mig för att få en hostattack vid ett olämpligt tillfälle	☐	☐	☐	☐	☐	☐	☐

Under de senaste 4 veckorna…

20. Var snäll ange mellan 1 och 10 hur mycket Din totala livskvalitet påverkats av Dina problem med hosta. *(ringa in en siffra)*

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

+ +

Ange hur ofta under de senaste 4 veckorna…

		Aldrig	1 dag/ månad	2-3 dag./ månad	1 dag/ vecka	2-3 dag./ vecka	4-5 dag./ vecka	6-7 dag./ vecka
21.	Folk lägger märke till hur ofta jag måste harkla mig	☐	☐	☐	☐	☐	☐	☐
22.	Mitt sexliv påverkas negativt av att jag måste harkla mig	☐	☐	☐	☐	☐	☐	☐
23.	Relationen till mina vänner påverkas negativt av att jag måste harkla mig	☐	☐	☐	☐	☐	☐	☐
24.	Behovet att harkla mig gör det svårt att prata	☐	☐	☐	☐	☐	☐	☐
25.	Jag blir frustrerad av att behöva harkla mig så ofta som jag gör	☐	☐	☐	☐	☐	☐	☐
26.	Jag undviker sociala tillställningar. t ex att gå på konserter och bio, eftersom jag behöver harkla mig	☐	☐	☐	☐	☐	☐	☐

Under de senaste 4 veckorna…

27. Var snäll ange mellan 1 och 10 hur mycket Din totala livskvalitet påverkats av Dina problem med harkling. *(ringa in en siffra)*

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

+ +

Ange hur ofta under de senaste 4 veckorna…

		Aldrig	1 dag/ månad	2-3 dag./ månad	1 dag/ vecka	2-3 dag./ vecka	4-5 dag./ vecka	6-7 dag./ vecka
28.	Jag känner en klump i halsen som gör det svårt att svälja	☐	☐	☐	☐	☐	☐	☐
29.	Jag drar mig för att äta offentligt, t ex på restauranger eller fester, eftersom jag har svårt att svälja	☐	☐	☐	☐	☐	☐	☐
30.	Jag är rädd för att kvävas i sömnen	☐	☐	☐	☐	☐	☐	☐
31.	Jag besväras av en brännande känsla i halsen	☐	☐	☐	☐	☐	☐	☐
32.	Jag vaknar av att jag kippar efter luft	☐	☐	☐	☐	☐	☐	☐

Under de senaste 4 veckorna…

33. Var snäll ange mellan 1 och 10 hur mycket Din totala livskvalitet påverkats av Dina halsproblem. *(ringa in en siffra)*

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

Under de 4 senaste veckorna, hur mycket har de tidigare beskrivna symtomen med röst, hosta, harkling, sväljning/hals påverkat … *(ringa in en siffra)*

34. Din energi i allmänhet

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

35. Din arbetskapacitet

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

+ +

36. Dina sociala relationer

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

37. Dina äktenskapliga/intima relationer

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

38. Dina sexuella relationer

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

39. Din sömn

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

40. Din möjlighet att ligga bekvämt i en säng

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

41. Din uppfattning om Dig själv

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

42. Din livsstil (t ex, rökning, alkoholintag, motion, matvanor)

1	2	3	4	5	6	7	8	9	10
Ingen påverkan									En enorm påverkan

43. Hur mycket har de tidigare beskrivna symtomen begränsat Din förmåga att göra sådant du tycker om? *(ringa in en siffra)*

1	2	3	4	5	6	7	8	9	10
Inte alls begränsad									Mycket begränsad – oförmögen att göra