RHEUMATOID ARTHRITIS IN THE LARYNX

a clinical and methodological study

by

Åke Geterud

Göteborg 1991

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som för avläggande av doktorsexamen i medicinsk vetenskap med vederbörligt tillstånd av medicinska fakulteten, kommer att offentligen försvaras i föreläsningssal F3, Sahlgrenska sjukhuset, Göteborg, fredagen den 15 mars, kl 13.00

av

Åke Geterud
leg. läkare

Avhandlingen baseras på följande arbeten:

I. Laryngeal involvement in rheumatoid arhtritis.
Å Geterud, B Bake, B Berthelsen, A Bjelle and H Ejnell. Submitted for publication.

II. Swallowing problems in rheumatoid arhtritis.
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ABSTRACT

Åke Geterud: Rheumatoid arthritis in the larynx.
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Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology that predominantly affects joints. Beside joint involvement, systemic manifestations of the disease are known.

The small cricoarytenoid joints in the larynx may be involved in the arthritic process. In order to assess the prevalence of laryngeal involvement in patients with RA and the occurrence of extrathoracic airway obstruction, 29 female patients with definite or classical RA and 30 controls were studied. Physical examination including direct fiberoptic laryngoscopy, respiratory function tests and low voltage radiography were used. The physical examination revealed laryngeal involvement in 17 RA patients (59%), extrathoracic airway obstruction was indicated by spirometry in 4 patients (14%) and radiography revealed obvious pathological findings in 3 patients (10%). In the control group no subject had any finding indicating laryngeal involvement.

The same group of RA patients were also studied regarding symptoms and signs of oral and swallowing disorders by means of a questionnaire, physical examination, stimulated saliva secretion and esophageal manometry. Subjective symptoms related to swallowing and dry mouth were reported four times more often by the RA patients than the controls. Xerostomia was associated with decreased stimulated saliva secretion. The amplitude of the peristaltic pressure complex in the proximal part of the esophagus was significantly decreased in the RA group.

In order to find a noninvasive method of assessing a laryngeal obstruction, the narrowest area of a short constriction of a plastic tube was calculated by means of computed tomography. The obtained area was compared with the airflow resistance, assessed by flow-pressure measurements. The same methods were applied to 12 patients with laryngeal obstructions of varying origin. High correlations (model, $r=1.0$; patients, $r=0.85$) were found in both cases.

Long-term results of a simple laterofixation procedure introduced in the late 1970s in Göteborg were evaluated in 11 consecutive patients with bilateral vocal cord paralysis. The improvement of breathing obtained with the operation in most cases was shown to be longlasting. At the follow-up assessment, 9 patients were improved and 2 deteriorated compared to the preoperative situation. The voice quality did not change during the years after operation and most of the voices were judged socially acceptable by listening panels. No aspiration problems were evoked by the operation.

A modified laterofixation procedure, applied to RA patients with laryngeal ankylosis, was presented and documented. The procedure included mobilization of the arytenoid cartilages followed by laterofixation of one vocal cord. Five out of 6 operated patients were improved. Four of 5 patients with tracheostomas preoperatively were decannulated within 14 days postoperatively. The 5 patients without cannulas had acceptable voices postoperatively. No patient developed aspiration problems.

Key words: rheumatoid arthritis, larynx, cricoarytenoid joint, ankylosis, laterofixation, vocal cord paralysis, upper airway resistance, spirometry, radiography, computed tomography, esophageal manometry, dysphagia.

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ABBREVIATIONS

Frequently used abbreviations.

CT	Computed tomography
D_{CO}	Lung diffusing capacity for carbon monoxide
FEV_1	Forced expiratory volume in one second
FIV_1	Forced inspiratory volume in one second
FOV	Field of view
G	Conductance
HU	Hounsfield Units
Ig	Immunoglobulin
kPa	Kilopascal
ΔN_2	The slope of the alveolar plateau with the nitrogen test
PEF	Peak expiratory flow
PIF	Peak inspiratory flow
RA	Rheumatoid arthritis
ROI	Region of interest
R_{ol}	Resistance of the orolaryngeal airway
R_{rs}	Resistance of the respiratory system
SAVS	Stand alone viewing system
SEM	Standard error of mean
VC	Vital capacity

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INTRODUCTION

A few patients with rheumatoid arthritis (RA) presented at our emergency unit with severe breathing difficulties. Further investigation revealed that the dyspnea was due to arthritis of the cricoarytenoid joints leading to laryngeal ankylosis. These cases evoked our interest in the problems concerning laryngeal involvement in RA and prompted further studies.

In the clinical setting, many RA patients reported problems associated with the upper aero-digestive tract, e.g. voice problems, dysphagia and dry mouth. A pilot study was carried out in order to evaluate the frequency of problems related to the larynx and the oral cavity (1). The study revealed that many RA patients had symptoms and signs related to breathing, voice and swallowing.

An airway obstruction due to laryngeal disease may be serious and even life-threatening. It is important to analyse objectively any method proposed for treatment of laryngeal obstructions. However, objective documentation has often been lacking. This may depend on the difficulties connected with quantification of upper airway obstructions. In this thesis, an invasive method for assessing the orolaryngeal resistance (R_{ol}) is used as a reference method. The method is applied to evaluate the long-term results of a simple surgical treatment of bilateral vocal cord paralysis. It is also applied to document a new mobilization and laterofixation procedure for cricoarytenoid ankylosis in RA. However, there is a potential hazard inherent in tracheal punctures. We therefore continuously seek and evaluate noninvasive methods, e.g. assessment of the horizontal area of an obstruction by computed tomography (CT).

Rheumatoid arthritis

Etiology

The etiology of RA is not known despite substantial research efforts (2). A multifactorial etiology has been proposed with activation of the immune system by an external unknown factor, e.g. a Yersinia infection, which, in predisposed individuals, would start a chronic rheumatic inflammation (3).

Prevalence

The prevalence of RA is approximately 1% (4). The prevalence has earlier been thought to be 2 to 4% (4, 5) and it has been proposed that it may be decreasing (4). Methodological differences make the interpretation of different epidemiological studies difficult. Women are affected three times more frequently than men (5, 6) and the mean age of onset is 40 years (6).

Signs and symptoms

Since the etiology is not known, the diagnosis of RA is based on criteria, where a defined number of clinical signs must be present. Those criteria presented by the American Rheumatism Association (ARA) in 1958 (Table 1) are the most frequently used (7). The diagnosis of definite RA requires 5 of the 11 criteria, while the diagnosis of classical RA requires 7 of the criteria. The criteria were revised in 1987, the total number of criteria being reduced to 7, e.g. all histological criteria were withdrawn. Rheumatoid arthritis is defined by the presence of 4 or more criteria, and no further qualifications (classical or definite) (8, 9).

RA usually starts quietly with peripheral and symmetrical polyarthritis. Most patients are positive for rheumatoid factor and have radiographic changes like usures in their joints with deformity. Although the joint manifestations are dominating, a large number of extra-articular changes have also been reported. The rheumatic nodules are probably

best known but, for example pulmonary, ocular, cardiac, spleenic, neurological, muscle and skin involvement have been described (10, 11).

Table 1. *Criteria for the diagnosis of rheumatoid arthritis presented by the American Rheumatism Association in 1958.*

1. Morning stiffness.
2. Pain on motion or tenderness in at least one joint.
3. Swelling in at least one joint.
4. Swelling of at least one other joint.
5. Symmetrical joint swelling with simultaneous involvement of the same joint on both sides of the body. Terminal phalangeal joint involvement will not satisfy this criterion.
6. Subcutaneous nodules over bony prominences, on extensor surfaces or in juxta-articular regions.
7. X-ray changes typical of rheumatoid arthritis.
8. Positive agglutination test - demonstration of the "rheumatoid factor" by any method which, in two laboratories, has been positive in not more than 5% of normal controls - or positive streptococcal agglutination test.
9. Poor mucin precipitate from synovial fluid.
10. Characteristic histological changes in synovial membrane with three or more of the following: marked villous hypertrophy; proliferation of superficial synovial cells often with palisading; marked infiltration of chronic inflammatory cells with tendency to form "lymphoid nodules"; deposition of compact fibrin, either on the surface or interstitially; foci of cell necrosis.
11. Characteristic histological changes in nodules showing granulomatous foci with central zones of cell necrosis, surrounded by proliferation fixed cells, and peripheral fibrosis and chronic inflammatory cell infiltration, predominantly perivascular.

Laryngeal involvement

Historical perspective

Laryngeal involvement in RA was described as early as in 1880 by Mackenzie (12) but it was not until the 1950s, when Montgomery started his research in this field, that our knowledge increased more substantially. Montgomery has in several reports described the condition of cricoarytenoid arthritis (13-16). Several case reports have been published and many of them have emphasised the emergency aspect (17-25). Fatal outcomes have been reported (26-28). In a recent study, 4 out of 13 classical female RA patients had sleep apnea (29), which could be due to upper airway obstruction.

A few systematically performed studies have been presented with prevalence figures of laryngeal involvement ranging from 13% to 75% depending on the definition of laryngeal involvement, material and methods (30-37). The frequency of RA involvement of the cricoarytenoid joint has in postmortem studies varied between 45 and 88% (30, 32, 38). A few reports concern children affected with cricoarytenoid arthritis, the youngest being only two years of age (39-41). Besides RA, several other diseases have been associated with cricoarytenoid arthritis, e.g. infections, gout, systemic lupus erythematosus and ankylosing spondylitis (42-45).

Pathology

The cricoarytenoid joint is a diarthrodial modified ball and socket joint with complicated patterns of movement including rocking, gliding and rotatory movements of the arytenoid cartilage on the cricoid cartilage (46, 47). The joint is histologically comparable with bigger joints with cartilagenous articular surfaces held in position by a ligamentous capsule lined by a synovial layer. The inflammatory changes start with synovitis leading to synovial proliferation, effusions with fibrin deposits, the formation of pannus on the joint surfaces, erosion of joint cartilage and end with obliteration and ankylosis of the joint, by fibrous or occasionally bony tissue (6, 14, 26, 27, 30, 32, 38). Other causes of impaired vocal cord mobility have been reported. Polymyositis of laryngeal muscles and degenerative changes of the peripheral nerves due to polyarteritis

of the vasa nervorum resulting in secondary muscular atrophy were also found besides cricoarytenoid arthritis in patients with RA (48, 49).

Signs and symptoms

In the acute phase, laryngoscopy reveals bright red swelling over the arytenoid regions (15, 39, 50, 51). The first symptom in the acute phase is said to be fullness in the throat or a feeling of tension (15). Other reported symptoms are: hoarseness, odynophagia, dysphagia, stridor, referred otalgia and pain when speaking or coughing (15, 27, 48-52).

In the chronic stage, a roughness and thickening of the mucosa over the arytenoids can be seen and fixation of the arytenoid cartilages may occur, resulting in a reduced glottic rima (15). During the chronic stage, the patients may have a slight hoarseness but more important is the symptom of dyspnea. Inspiratory stridor may be present during sleep, exertion and airway infections (6, 15).

Discrepancy between symptoms and signs has been reported (30, 31, 33, 53). During recent years low voltage radiography (35, 54) and computed tomography (36, 55) have been added to the diagnostic arsenal. Both these methods have revealed a high prevalence of laryngeal involvement in RA patients, but also demonstrated the asymptomatic course in many cases.

Treatment

An acute exacerbation of RA with engagement of the cricoarytenoid joints should be treated with antiinflammatory drugs (15, 30, 32, 38, 56, 57). Local application of steroids by means of injection (58, 59) or aerosol (60-62) has been proposed to be of value. The arthritic changes in the joints are probably reversible at this stage (38). Laryngeal ankylosis at the chronic stage has to be treated surgically. If the patient presents with severe airway obstruction, tracheotomy has to be performed in the acute phase. Patients with severe RA usually have finger deformities rendering the handling of a cannula difficult or even impossible. Few procedures specifically intended for treating cricoarytenoid ankylosis have been presented (15, 63). Montgomery described a method in which one arytenoid cartilage was removed and the vocal cord lateralized with a steel suture. The operation was performed via laryngofissure, preceded by tracheotomy. Unfortunately, the effects of these procedures on breathing were not documented. A new method of laterofixation, preceded by mobilization of the arytenoid cartilages, has been found to relieve most patients of their breathing difficulties (paper V)(64).

AIMS OF THE STUDY

The specific purpose of this study was:

- to study laryngeal involvement in RA and the occurrence of extrathoracic airway obstruction (I),
- to assess oral symptoms and swallowing difficulties in patients with RA (II),
- to investigate whether the degree of a laryngeal obstruction could be determined by measuring the glottic area noninvasively by computed tomography (III),
- to study the long-term effects on breathing, voice quality and aspiration of a new method for surgical treatment of bilateral vocal cord paralysis (IV), and
- to evaluate a modified version of the laterofixation procedure presented in paper IV in patients with laryngeal ankylosis due to RA (V).

MATERIAL

Patients and controls (I, II)

Twenty-nine rheumatoid-factor-positive female outpatients with definite or classical RA took part in these two studies. They were randomly selected from a register of 139 women receiving parenteral gold treatment during 1985 at the Department of Rheumatology, Sahlgrenska sjukhuset. Thirty healthy, age-matched women served as controls.

Model (III)

A model made of a semi-rigid plastic tube (internal diameter 1.9 cm, length 53 cm) simulating the human upper airway was used. A triangular constriction, modelling the vocal cords, was made 19 cm from the oral end (i.e. the approximate distance from the lips to the vocal cords in man) by external compression. The triangle was varied from that simulating normal conditions to severe laryngeal obstruction.

Patients (III)

Twelve consecutive patients with laryngeal obstructions were included in this study (Table 2). Eight patients had bilateral vocal cord paralysis and 4 patients laryngeal ankylosis.

Patients (IV)

Eleven patients were included in this follow-up study. They were all operated upon with a laterofixation procedure according to Ejnell et al because of bilateral vocal cord paralysis. The investigation was made 5 to 9 years postoperatively.

Patients (V)

Six patients with laryngeal ankylosis due to RA were operated upon using a mobilization and laterofixation technique. One of them was a 25-year-old man with juvenile, seronegative RA. The others, 5 female patients with severe handicaps and a long disease duration (mean 36 years), had seropositive, classical RA. Three of the women were confined to wheelchairs.

Table 2. *General data, glottic area and orolaryngeal resistance in 12 patients with laryngeal obstructions.*

Patient number	Sex	Age (years)	Diagnosis	Glottic area (cm^2) individual halfway value	Glottic area (cm^2) fixed halfway value	Orolaryngeal airway resistance (kPa/[l/s])
1.	M	75	Vocal cord paralysis	0.5	0.6	0.1
2.	M	65	-"-	0.3	0.3	0.4
3.	F	59	-"-	0.5	0.5	0.2
4.	F	42	-"-	0.3	0.3	0.4
5.	F	64	Ankylosis of the cricoarytenoid joints (Rheumatoid arthritis)	0.4	0.4	0.3
6.	M	50	-"-	0.4	0.4	0.3
7.	F	68	-"-	0.1	0.3	1.0
8.	M	76	Vocal cord paralysis	0.4	0.4	0.4
9.	M	73	-"-	0.2	0.3	1.2
10.	M	72	Ankylosis of the crico-arytenoid joints (Mb Bechterew)	0.2	0.3	1.2
11.	M	73	Vocal cord paralysis	0.3	0.3	0.5
12.	F	61	-"-	0.3	0.3	0.7

METHODS

Physical examination (I, II)

The subjects' voices were judged to determine whether they were noticeably weak or if phonatory air leakage was present during normal speech in a quiet room. The larynx was externally inspected and palpated. Tenderness during pressure on the thyroid cartilage was noted. Inspection of the mucous membranes of the oral cavity and the pharynx for signs of dryness like absence of a normal mucus layer was performed. Mouth ulcers were looked for. Secretion stagnation in the hypopharynx was noted. The hypopharynx and larynx were studied indirectly using a mirror and directly using a fiberoptic laryngoscope (Fujinor). The mucous membranes and the mobility of the vocal cords were inspected. Deviation of the larynx from the midline was noted (65). The examinations were performed by the same investigator (ÅG), who had no knowledge of any other test results at the time of the examinations.

At the physical examination, laryngeal involvement was defined as a localised erythema and/or thickening of the mucosa over the arytenoids and/or impaired abduction of a vocal cord.

Respiratory function (I, III, IV, V)

Spirometry (I, IV, V)

A volume-displacement, water-sealed spirometer (Bernstein) was used to determine vital capacity (VC) and forced expiratory and inspiratory volume in one second (FEV_1, FIV_1). At least three acceptable spirograms were obtained for each variable and the best was used in the subsequent analysis. Predicted normal VC and FEV_1 values were obtained from Berglund et al (66).

Flow-volume curves (I)

Peak expiratory and inspiratory flow (PEF, PIF) were determined from flow-volume loops obtained with a volume-displacement, rolling, sealed spirometer (Electro Med. 70) connected to a plotter (Hewlett-Packard 7090). The procedure was repeated until acceptable and reproducible recordings were obtained.

Forced oscillation technique (I)

The resistance of the respiratory system (R_{rs}) (i.e. the airways, lungs and thorax) was assessed using the forced oscillation technique (67). The set-up was similar to that described by Aronsson et al (68). Briefly described, the mouthpiece was connected to a loudspeaker generating a sinusoidal oscillating pressure (frequency 4 Hz). The mouth pressure was measured by a transducer (Validyne model DP 45-16) and the flow by a pneumotachograph (Fleisch no 2). From the relationship between the pressure and the flow oscillations, the resistance could be calculated. The set-up was calibrated with mechanical resistance before each measurement.

The average R_{rs} in healthy women is 0.3-0.4 kPa/(l/s) (69).

Nitrogen test (I)

The slope of phase III, i.e. of the alveolar plateau (ΔN_2), was measured using the single-breath nitrogen method (70). This test has been claimed to be sensitive when it comes to detecting structural and functional changes in the small peripheral airways or lung parenchyma. Reference values were predicted according to Sixt et al (71).

Lung diffusing capacity (I)

The lung diffusing capacity for carbon monoxide (D_{CO}) was determined using the single-breath technique (Jaeger Transferscreen II) and reference values were obtained according to Salorinne (72).

Orolaryngeal airway resistance (III, IV, V)

The orolaryngeal airway resistance (R_{Ol}) was calculated from flow-pressure curves obtained with a set-up illustrated in Fig. 1. It was similar to that described earlier by other authors (73-78). Subglottic pressure was obtained by means of a catheter (Venflon 1.4 mm outer diameter and 1.2 mm inner diameter) introduced into the trachea about 2 cm below the cricoid cartilage, and the pressure at the mouth opening was measured with an identical catheter at the mouthpiece. Flow was recorded with a pneumotachograph (Fleisch No 2). The differential pressure manometers for pressure and flow were identical (Elema-Schönander EMT 32).

Flow and differential pressure signals were recorded in x-y mode on a storage oscilloscope (Tektronix) and photographed. Measurements were made on tracings of several consecutive reproducible breaths. At least two such tracings were obtained each time. Pressure and flow signals were calibrated at each investigation.

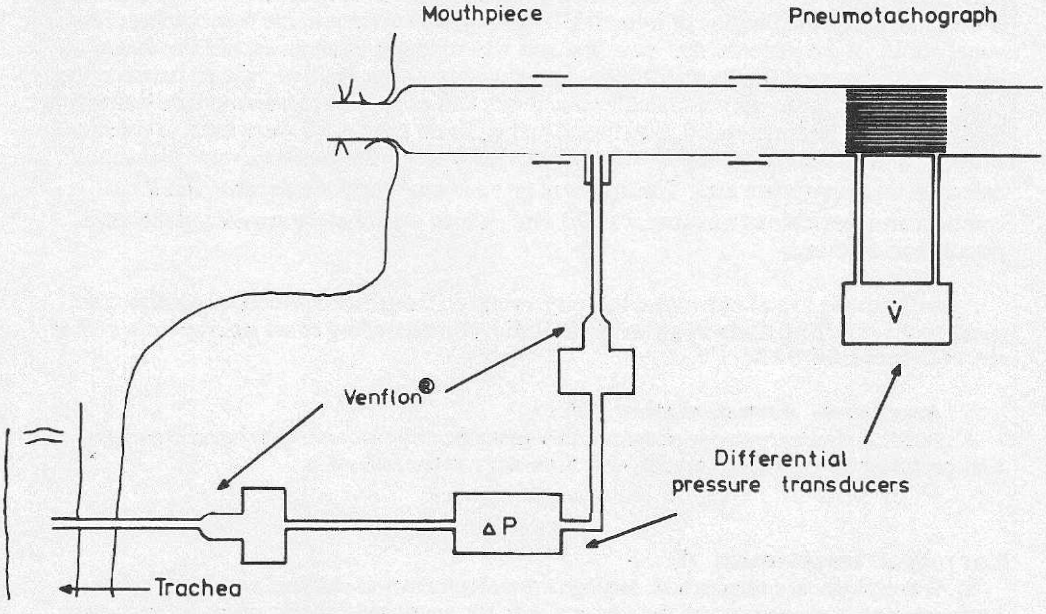

Fig. 1. *Schematic illustration of the set-up.*

Extrathoracic obstruction (I, III, IV, V)

In line with previous reports, FIV_1 and PIF were adopted as the most suitable variables for detecting extrathoracic obstructions (78, 79). For quantification of extrathoracic obstructions R_{oI} was used.

Radiography (I, III, IV)

Low-voltage technique (I)

The radiography of the larynx was performed on a Siemens Orbix using a low-voltage technique (54). A high resolution film-screen combination (Kodak MR1 film and MinR screen) was used. The films were taken while the patients held their breath. Remnants of one or both arytenoid cartilages as a sign of cartilage destruction were regarded as laryngeal involvement (35).

Computed tomography (III)

The investigation was performed on a Philips Tomoscan 310 with 3 mm, 1.5 mm overlapping slices through and in the same plane as the "vocal cords" of the model and the vocal cords of the patients. The slices were obtained with 120 kV, 200 mA, scan time 9.6 s, FOV 90 (field of view) and convolution filter 6 (edge-enhancing filter).

To obtain slices in the same plane as the vocal cords, the patient was placed supine with his or her neck extended. From a lateral scanogram of the neck, the appropriate angulation of the gantry was chosen. The patient was instructed to breathe calmly.

The measurements were performed on a separate display unit (SAVS=Stand alone viewing system). The constricted area in the model and the glottic area in the patients were measured according to the findings reported by Baxter and Sorensen (80). The attenuation value of air is by definition -1000 HU (Hounsfield Units). The mean attenuation value of the "vocal cords" of the model and the vocal cords of the patients was obtained from a small region of interest (ROI) outlined adjacent to the free border of the vocal cords. In the patients, this measurement was repeated three times and the mean value was calculated. Thereafter, the mean attenuation value (halfway value) between that of the vocal cords and air was calculated and this halfway value represented the boundary (81, 82). Software functions (Level detect and ROI) on the SAVS were used to enhance the picture elements (pixels) with attenuation values below the halfway value and to calculate the appropriate area. The area was given in cm^2 with one decimal and the smallest area possible to measure was 0.1 cm^2, which was also the smallest difference possible to measure.

Apart from the use of individual halfway values in the patients, we also calculated the glottic area at a fixed halfway value of -500 HU, corresponding to an attenuation value of the vocal cords of 0 HU.

Aspiration documentation (IV)

A routine hypopharynx-esophageous radiographic examination with barium contrast was performed. This investigation was done only at the follow-up.

Laryngeal involvement (I)

a) At the physical examination, laryngeal involvement was defined as a localised erythema and/or thickening of the mucosa over the arytenoids and/or impaired abduction of a vocal cord.

b) FIV_1<2.0 l and PIF<2.5 l/s were adopted as signs of impairment of the extrathoracic airways and as indirect signs of laryngeal involvement. The level was chosen in such a way that the specificity was above 80% (79).

c) Regarding radiography, remnants of one or both arytenoid cartilages as a sign of cartilage destruction were regarded as laryngeal involvement (35).

Questionnaire (I, II)

Patients and controls completed a comprehensive questionnaire. Most questions related to symptoms, signs and consequences of their rheumatic disease.

Laryngeal involvement (I)

Those questions possibly associated with rheumatic laryngeal involvement are listed in Table 5 (page 22). Questions 1-4 relate to voice problems, 5-9 to breathing problems and 10-13 to fullnes and pain in the throat.

Swallowing difficulties (II)

Questions related to esophageal symptoms, xerostomia, xerophthalmia and parotid gland disease are listed in Table 7 (page 24). The sections of the questionnaire relating to xerostomia, xerophthalmia and parotid gland disease (Table 7) were scored positive if the patient answered affirmatively to more than half of the questions according to Moutsopoulos et al (83).

Stimulated saliva secretion (II)

Quantitative evaluation of secretion of stimulated whole saliva was performed. Briefly, the subject was asked to chew paraffin and after the paraffin was softened the subject was asked to spit into a funnel connected to a graduated glass. The collection of saliva lasted for 5 min. A stimulated secretion rate of 0.7 ml/min or less was considered pathological (84-86).

Histopathology of minor salivary glands (II)

Labial salivary gland biopsy was performed through normal-appearing mucosa in the lower lip between the midline and the commisure (87, 88). After local anaesthesia, a single horizontal 1.5-2 cm incision was made through the lip mucosa. After blunt dissection, about five separate glands were removed and fixed in 4 % formaldehyde.

Salivary gland specimens were embedded in paraffin, cut and stained with hematoxylin and eosin and examined microscopically. The area of salivary gland tissue was determined by means of a graticule. The degree of inflammation was determined by focus scoring, a method which provides a semiquantitative assessment of the inflammation (87). One standardized score is the number of focal inflammatory cell aggregates, containing 50 or more mononuclear cells, in each 4 mm^2 area of salivary gland tissue. A focus score of at least 2/4 mm^2, fullfilling proposed criteria for secondary Sjögren's syndrome, was required for a diagnosis of focal sialoadenitis (89).

Esophageal manometry (II)

Pressures of the esophagus were transmitted by a nasally inserted, water-filled, continuously perfused catheter assembly to external pressure transducers (Triplus). These transducers were connected to a computer (via Synectics PC Polygraf). A writer was connected to the computer.

The catheter bundle was passed naso-gastrically and the subject then assumed the supine position. The patient was asked to swallow 5 ml of water at room temperature

intermittently with an interval of approximately 25 s between swallows. The registration apparatus was calibrated to atmospheric pressure and to standardized hydrostatic pressures before and after every examination.

All calculations were based on the results obtained from paper tracings. Amplitudes and durations of the peristaltic pressure complexes were analysed in the proximal (approximately 5 cm below the upper esophageal sphincter) and distal (approximately 5 cm above the lower esophageal sphincter) part of the esophagus. The amplitude was the difference between the peak of the contraction and the precontraction baseline. The contraction duration was the time between the sharp upstroke of the contraction from the baseline and the return to the precontraction baseline. The mean values of two representative contractions are given.

Repeated dry swallowing test (II)

The patients were instructed to swallow 11 times as fast as possible and no fluids were given. Pressure was recorded continuously during the test. The swallowing test time was defined as the time between the first and last pharyngeal pressure peaks (90).

Laboratory data (I, II)

The erythrocyte sedimentation rate was determined and immunoglobulin class-specific rheumatoid factors were analysed using a diffusion-in-gel, enzyme-linked, immunosorbent assay technique (91, 92).

Operation (IV, V)

Bilateral vocal cord paralysis (IV)

The operation was performed under general anaesthesia. Two surgeons operated at the same time: one externally on the neck and the other via a laryngoscope using a microscope. The external surgeon made an incision in the skin and exposed one lamina of the thyroid cartilage. Two needles were inserted through the cartilage (Fig. 2), one above and the other below the vocal cord (Fig. 3). A nylon thread was passed through the lower needle and then brought out again through the upper needle, thus forming a loop around the vocal cord. The needles were withdrawn and the loop was tightened until the vocal cord was sufficiently lateralized.

Laryngeal ankylosis (V)

The method of laterofixation was the same as described for vocal cord paralysis (IV). The laterofixation was, however, preceded by a mobilization procedure by means of semirigid esophageal dilators passed through the glottal rima between the vocal processes of the arytenoid cartilages. The vocal cords thus became temporarily mobile.

Voice quality (IV)

Tape recordings were made on a Revox tape-recorder in a soundproof room while the patients read aloud from a standard text. Voice samples of one minute's duration were edited to make one tape. Two panels listened to the recordings. One panel consisted of 10 people who had no previous experience of speech therapy, the amateur panel, and the other panel consisted of 6 speech therapists. Each member of the panel was instructed to evaluate each voice sample and to score it from 0 to 4 regarding timbre, tempo and inspiratory stridor. Each voice sample was also judged by the panels as to whether it was socially acceptable or not. A recorded voice was to be judged socially acceptable if the patient was considered to be able to perform normal daily activities like shopping, making telephone calls and keeping a job.

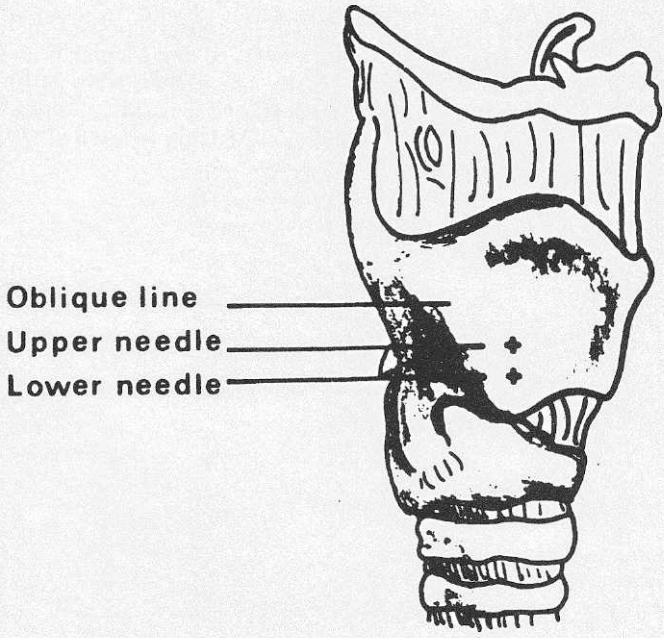

Fig. 2. *Insertion points of the needles in the thyroid cartilage.*

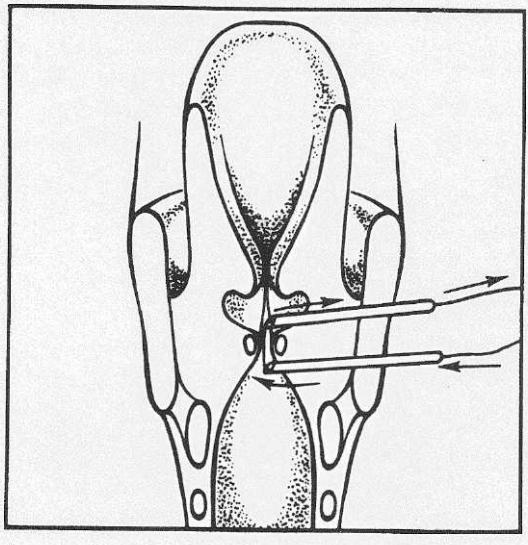

Fig. 3. *Frontal projection of the larynx with the needles and the thread around the vocal cord.*

Statistics (I, II, III, IV)

Student's *t* test for unpaired (I,II) and paired (III, IV) observations, Chi-Square test with continuity correction (I, II), Fisher's exact test (I, II) and Mantel-Haenszel's chi-square test (I) were used. Sensitivity and specificity calculations were performed (I). The correlation coefficient (*r*) was determined in paper III and the critical values for statistical significance were taken from Pearson and Hartley (93). Only two-tailed tests were used.

RESULTS AND DISCUSSION

Physical examination (I, II)

No patient or control subject was judged to have a noticeably weak or hoarse voice or to have inspiratory stridor during tidal breathing or when speaking.

Tenderness during pressure on the thyroid cartilage was reported by 6 patients (21%), compared with none in the control group ($p<0.05$). A slightly deviated larynx was found in one patient but in no control subject.

On inspection, 26 of the 29 RA patients were judged to have normal mucous membranes in the oral cavity and the pharynx and no secretion stagnation in the hypopharynx. Two RA patients had dry mucous membranes in the mouth and pharynx. Both of them had decreased stimulated saliva secretion while only one reported xerostomia. One of them was treated with antidepressant and antihistamine drugs. A third patient showed secretion stagnation in the hypopharynx. No patient had ulcerations in the mucous membranes. No abnormal findings were found on examination of the control subjects.

A localised erythema and/or thickening of the mucosa over the arytenoids was found in 16 of the RA patients (55%) but in none of the control group ($p<0.001$). Impaired abduction of the vocal cords was observed in 5 RA patients. Two of them showed bilateral limitation of abduction and the remaining 3 displayed unilateral limitation. No subject in the control group had impaired abduction of the vocal cords. No case of severely impaired abduction or complete midline fixation of the vocal cords was observed. A vocal cord nodule was observed in one RA patient.

On indirect mirror and direct fiberoptic laryngoscopy, the mean maximum transverse distance of the glottal rima was visually judged to be 10.3 ± 0.3 mm (SEM) in the RA group and 11.8 ± 0.2 mm in the control group ($p<0.001$). The maximum transverse distance of the glottal rima for the 5 RA patients with impaired abduction was shorter, 8.2 ± 0.6 mm, compared with 10.8 ± 0.3 mm for the remaining 24 patients ($p<0.01$).

The overall prevalence of laryngeal abnormality in the RA group, found with indirect mirror and/or direct fiberoptic laryngoscopy, was 59% (17/29), compared with zero in the control subjects ($p<0.001$).

Routine indirect mirror laryngoscopy usually gives a good view of the arytenoid region and the vocal cords. Advantages of mirror investigation are the good overview and the clear sight with an undisturbed colour impression. However, some patients have enhanced swallowing reflexes or a covering epiglottis making conventional mirror investigation difficult or impossible. In addition, RA patients may have stiff necks and a reduced ability to open the mouth due to involvement of the temporomandibular joints. However, in this series no RA patient had any difficulties open her mouth at the mirror investigation. With a fiberoptic laryngoscope, it has been possible to investigate all patients and controls. In particular, it is a superior tool when the vocal cord motions are investigated.

The physical examination revealed rheumatic laryngeal involvement in 59% of the RA patients in this series, which is in accordance with Lawry et al, who reported a laryngeal abnormality prevalence of 52% in their RA material (36). When a broader definition of laryngeal involvement was used, including minor disturbances of the vocal cord motions, a prevalence of 75% was reported (37). In postmortem studies, even higher figures have been reported (32).

All patients with tenderness during pressure on the thyroid cartilage, one of them also with a deviated larynx, belonged to the group of RA patients with laryngeal involvement.

Respiratory function (I)

The results of the spirometric tests reflecting the extrathoracic airways are presented in Table 3. A significant reduction of the forced inspiratory volume in one second and the peak inspiratory flow was observed in the RA group. Three patients had FIV_1<2.0 l and 2 patients PIF<2.5 l/s. One patient had decreased values in both tests. Thus, 4 patients had FIV_1<2.0 l and/or PIF<2.5 l/s. No controls had FIV_1<2.0 l or PIF<2.5 l/s.

Table 3. *Spirometric results with special reference to the extrathoracic airways in 29 RA patients and 30 controls (mean ± SEM).*

Test	RA	Controls
FIV_1 (l)	2.8 ±0.1*	3.3 ±0.1
FIV_1/VC (%)	85 ±2*	90 ±1
FEV_1/FIV_1	0.9 ±0.04	0.9 ±0.02
PIF (l/s)	4.0 ±0.2*	5.0 ±0.3
PEF/PIF	1.5 ±0.1	1.5 ±0.1

** denotes p<0.05.*

Generally, the RA group showed impaired spirometric values compared with the control group (Table 4). The resistance of the respiratory system was significantly elevated in the RA group. A reduction in the gas transfer ability, indicated by significantly reduced D_{CO}, could also be observed.

Table 4. *Lung function test results in 29 RA patients and 30 controls (mean ± SEM).*

Test	RA	Controls
VC (% pred)	102 ±3	108 ±3
FEV_1 (% pred)	101 ±4	109 ±3
FEV_1/VC (% pred)	98 ±2	100 ±2
ΔN_2 (% pred)	278 ±60	172 ±27
D_{CO} (% pred)	84 ±3*#	98 ±3†
PEF (l/s)	5.9 ±0.2*	7.0 ±0.3
R_{rs}exp (kPa/[l/s])	0.59 ±0.04*	0.42 ±0.03†
R_{rs}insp (kPa/[l/s])	0.40 ±0.03*	0.30 ±0.02†

** denotes p<0.05, # denotes n=28, † denotes n=29.*

Breathing difficulties in patients with RA could be due to laryngeal involvement. However, several pulmonary manifestations of RA have been described, including pleurisy with or without effusion and interstitial fibrosis, also resulting in dyspnea (94-97). Although many papers dealing with RA and pulmonary function have been published, to our knowledge no investigation has been focused on the extrathoracic airways. In the present study, 4 of the RA patients (14%) had spirometric signs of

obstruction of the extrathoracic airways, i.e. presumable laryngeal obstruction (78). These 4 patients had normal vital capacity, forced expiratory volume and diffusing capacity.

Low-voltage radiography (I)

Small remnants of one or both arytenoid cartilages were found in 3 patients. No similar changes were found in the control group. One or both arytenoid cartilages were invisible in 8 RA patients and in 7 control subjects. One patient and one control subject were excluded from the investigation due to massive motion artefacts.

The low-voltage radiography technique produced a wide variation in the degree of calcification and visibility of the laryngeal cartilages in both groups. The invisibility of one or both arytenoid cartilages in 8 RA patients could be due to total destruction. It is also possible that the cartilages were not calcified. A third explanation might be purely methodological. The cartilages were not demonstrable in 7 of the control subjects. The high proportion of investigations which could not be evaluated using the present procedure made the examination less useful.

The results of the low-voltage radiography, with only 10% pathology and a relatively high number of investigations which could not be evaluated, differed markedly from previous reports (35, 36, 55). The reason could be partly technical. Only Jurik et al (35) used the low-voltage technique and, in their material, 9 of the 17 female RA patients showed erosions of the arytenoid cartilages when compared with a normal material of 16 females; all of them had symmetrically calcified arytenoid cartilages with visible articular facets (54). It was noteworthy that only 2 of their female controls were aged below 50. As we used an orbix instead of mammography equipment, discrete erosions and faint calcifications may have been missed. Bienenstock et al (32) found RA changes in the cricoarytenoid joints in 7 of 8 patients with RA in postmortem studies. However, only one of them had a clear erosion of an arytenoid cartilage.

Laryngeal involvement (I)

Four patients (group A) fulfilled the criteria for laryngeal involvement in two of the three investigations (physical examination, spirometry and radiography). Sixteen patients (group B) fulfilled the criteria in one investigation. No patient fulfilled the criteria for laryngeal involvement in all three investigations. Thus, at least one sign of laryngeal involvement was found in 20 patients (69%). Nine RA patients (group C) and all the controls were negative. No difference in the prevalence of laryngeal involvement was noted among the patients who were smokers or ex-smokers compared with those who were non-smokers.

Questionnaire (I, II)

Laryngeal involvement (I)

Table 5 shows the positive answers to 13 questions on laryngeal involvement. Patients with signs of laryngeal involvement (groups A and B) had more symptoms than patients without such signs (group C)(n.s.) and controls ($p<0.001$). Three or more of the 13 questions in Table 5 were answered affirmatively by 3 out of 4 subjects (75%) in group A, 7 out of 16 (44%) in group B, 1 out of 9 (11%) in group C and 1 out of 30 (3%) in the control group. However, no single question was answered in the affirmative significantly more often by patients with laryngeal involvement than by patients without laryngeal involvement.

Questions 1-4 related to voice problems. Eight of 20 patients with laryngeal involvement (groups A and B) answered one or more of these questions positively (sensitivity=40%), compared with none in group C (n.s.)(specificity=100%).

Questions 5-9 related to breathing problems. Fifteen of the patients with laryngeal involvement answered one or more of these questions positively (sensitivity=75%), compared with 5 in group C (n.s.)(specificity=44%).

Questions 10-13 related to fullness and pain in the throat. Eleven of the patients with laryngeal involvement answered one or more of these questions positively (sensitivity=55%), compared with 2 in group C (n.s.)(specificity=78%).

Table 5. *Thirteen questions possibly associated with rheumatic laryngeal involvement and the numbers of RA patients and controls giving positive answers to these questions. Groups A, B and C represent patients with two, one or no signs of laryngeal involvement of the RA.*

	A *n=4*	B *n=16*	C *n=9*	Controls *n=30*
1. Do you have a hoarse voice?	2	3	0	1
2. Do you have an unusually weak voice?	0	1	0	2
3. Have you had one or more periods of hoarseness during the last year without having a cold?	2	3	0	0
4. Does your throat sometimes hurt when speaking?	1	3	0	1
5. Have you experienced difficulties breathing in at any time during the last year?	2	3	3	1
6. Do you easily get short of breath in connection with moderate physical exercise?	3	10	3	3
7. Do you experience breathing difficulties when you have a cold?	0	5	2	2
8. Can a strange or wheezing sound be heard when you breathe?	0	3	0	0
9. Can a strange or wheezing sound be heard when you speak?	1	1	0	0
10. Does your throat sometimes hurt when you cough or clear your throat?	1	2	1	0
11. Do you sometimes have earache without having a cold?	2	5	1	2
12. Do you often have a feeling of fullness in your throat?	2	4	1	1
13. Does it sometimes hurt when you swallow?	3	3	1	0
Positive answers/n	**4.8**	**2.9**	**1.3**	**0.4**

The mean age of the patients in the three RA subgroups did not differ significantly (Table 6). A longer disease duration, though not significantly, was found in patients with laryngeal involvement compared with patients without laryngeal involvement (Table 6). The functional class of the patients according to the American Rheumatism Association can be seen in the same table. A tendency towards more severe RA disease was observed among patients with laryngeal involvement compared with those without laryngeal involvement (n.s.).

Questions relating to breathing difficulties had relatively high sensitivity in this study when it came to laryngeal involvement in an RA population but their specificity was low. Questions relating to the voice had high specificity but low sensitivity.

Our findings are in accordance with Lawry et al, who reported that inspiratory difficulties had predictive value (36). Other authors found hoarseness (32, 37) or the sensation of a foreign body (31) to be the most common symptoms.

Table 6. *Mean age (years), disease duration (years) and functional class (% of n) of RA patients with two (group A), one (group B) or no (group C) signs of laryngeal involvement (mean ± SEM).*

		A *n=4*	B *n=16*	C *n=9*
Age		63±1.6	53±2.4	55±1.5
Disease duration		15±1.8	17±2.3	11±2.2
Functional class	I	0	6	33
	II	50	50	44
	III	50	44	22

It should be noted that patients with laryngeal involvement could be asymptomatic. On the other hand, some patients without laryngeal involvement reported symptoms.

The questionnaire was not able accurately to distinguish all the RA patients with laryngeal involvement from patients without laryngeal involvement. However, by questioning the patient, suspicion of laryngeal involvement could arise and the patient could then be referred for further investigation.

There was a tendency towards more severe disease in patients with laryngeal involvement which is in accordance with a previous report (37). However, in another study, no correlation was found between disease severity and laryngeal involvement (33).

Swallowing difficulties (II)

Subjective symptoms related to the esophagus (except the question regarding heartburn or acid reflux) and xerostomia (Table 7) were reported by 83% of the RA patients (controls 20%, $p<0.001$).

The answers to the questions relating to esophageal symptoms revealed that dysphagia (question no 1), odynophagia (question no 2) and troublesome heartburn or acid reflux (question no 4) were experienced significantly more frequent among the RA patients than among the control subjects (Fig. 4).

The answers to the questions relating to xerostomia and xerophthalmia are presented in Fig. 4. Six patients in the RA group had ≥5 positive answers in the group of questions relating to xerostomia. Xerophthalmia was reported by 5 patients. In addition, 2 patients had a history of parotid gland disease. None of the controls had xerostomia, xerophthalmia or parotid gland disease according to the questionnaire.

Of the 6 patients with xerostomia, 4 had decreased stimulated saliva secretion (≤0.7 ml/min), compared with 2 of the remaining 23 patients ($p<0.05$). One patient with xerostomia reported both dysphagia and odynophagia and another patient odynophagia. The remaining 4 patients reported no swallowing dysfunction symptoms.

Patients with xerostomia did not differ significantly from patients without xerostomia in terms of age or disease duration.

One of the 6 patients with xerostomia used drugs that could decrease saliva secretion; she took both antidepressant and antihistamine drugs. Another RA patient was taking an antidepressant drug. No control subject took drugs known to cause xerostomia.

Table 7. *Questionnaire for the assessment of some esophageal symptoms, xerostomia, xerophthalmia and parotid gland disease.*

Esophageal symptoms
1. Do you sometimes have difficulties swallowing solid food?
2. Does it sometimes hurt when you swallow?
3. Do you often have a feeling of a lump in your throat?
4. Are you troubled by heartburn or acid reflux?
Xerostomia
1. Do you drink lots of fluids with your meals?
2. Does food stick in your mouth or throat?
3. Can you eat a dry cracker without water?*
4. Has your sense of taste changed?
5. Do you keep a glass of water at your bedside at night?
6. Do you wake up at night because you have a dry mouth?
7. Do you carry a bottle of water with you?
8. Does your mouth feel dry?
9. Do you have excessive dental cavities?
Xerophthalmia
1. Do you often feel a "sandy" sensation in your eyes?
2. Are your eyes frequently red?
3. Are your eyes often irritated in another way?
4. Do you have excessive matter in your eyes in the morning?
5. Do your eyelids stick together in the morning?
6. Have you noticed a decreased amount of tears when you cry?
7. Are your eyes dry?
8. Do you have frequent eye infections?
9. Do you use artificial tears?
Parotid gland disease
1. Have you had mumps as an adult?
2. Have you had mumps more than once?
3. Have you had intermittent swelling of your parotid glands (in front of the ears)?

* *A "no" answer is considered positive.*

Eleven RA patients belonged to functional class III. Their mean disease duration was 16 ± 2.5 years. Seven of them had or had previously had rheumatic nodules on their elbows. None of them took antidepressant or antihistamine drugs. These 11 patients were compared with the remaining 18 RA patients in functional class I or II (mean disease duration 14 ± 1.9 years) regarding dysphagia, odynophagia, feelings of a lump in the throat, heartburn and xerostomia. Only regarding dysphagia was a significant difference found. Six patients (55%) in functional class III reported dysphagia, compared with 2 of the patients (11%) in lower functional classes ($p<0.05$).

Our finding of dysphagia in 28% of patients could be compared with a study by Doig et al (98). They reported dysphagia in 10% of RA patients without signs of Sjögren's syndrome and in 32% of RA patients with Sjögren's syndrome. Severity of the RA disease was associated with dysphagia in the present study, whereas decreased stimulated saliva secretion was not. Patients with dysphagia did not differ significantly from patients without dysphagia in terms of age or disease duration.

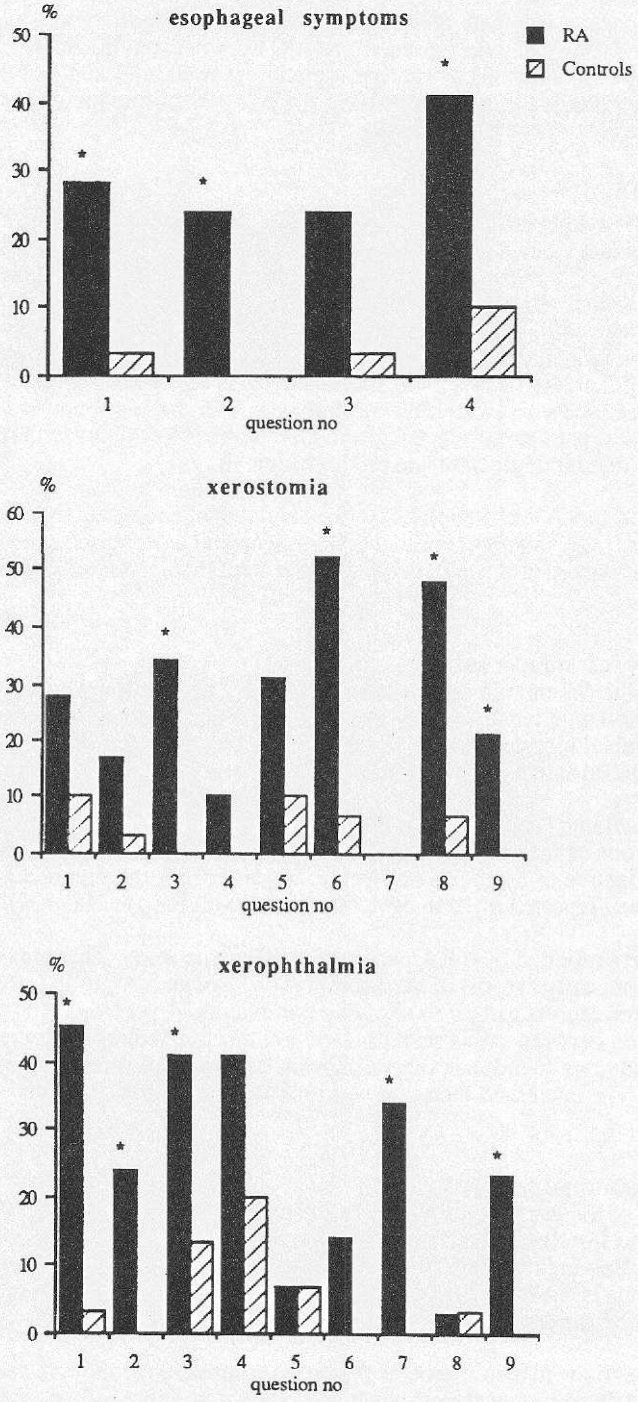

Fig. 4. *Positive answers in per cent to questions relating to esophageal symptoms, xerostomia and xerophthalmia among 29 patients with rheumatoid arthritis and 30 healthy controls. The numbers refer to the questions in Table 7 (* denotes $p<0.05$).*

Five RA patients (17%) and one of the controls (3%) had complete dentures. Three of the patients had dentures in both the upper and lower jaw. Only one of the patients with dentures had dysphagia. One patient with complete dentures reported both xerostomia and odynophagia. None had a decreased stimulated saliva secretion. However, 5 of 6 patients with excessive dental cavities had xerostomia ($p<0.001$) and 4 of them also decreased stimulated saliva secretion ($p<0.05$); the comparisons relate to the remaining 23 patients without excessive dental cavities.

Stimulated saliva secretion (II)

The mean stimulated saliva secretion in the RA group was 1.5 ± 0.1 (SEM) ml/min, compared with 1.7 ± 0.1 ml/min in the control group (n.s.). In the RA group, 6 subjects had a stimulated secretion rate of 0.7 ml/min or less, compared with 2 of the controls. Four of the 6 patients with decreased saliva secretion reported xerostomia, compared with 2 of the remaining 23 patients ($p<0.05$). The 6 patients with decreased saliva secretion had no significant increase in swallowing dysfunction symptoms. One of the 2 control subjects with decreased saliva secretion was one year after the test found to have a chronic inflammation of her left parotid gland. One of the RA patients with reduced saliva secretion was taking antidepressant and antihistamine drugs.

More patients with RA had complete dentures and dental cavities than the controls. Both the difficulty in maintaining optimal oral hygiene and a decreased salivary flow make a rheumatic patient prone to develop oral and in particular dental problems (99).

Histopathology of minor salivary glands (II)

The subjects with 0.7 ml/min or less stimulated saliva production were invited to a further examination with labial salivary gland biopsy. Four out of 6 RA patients agreed to performance of labial biopsies and focal sialoadenitis was recorded in all. The 2 control subjects with reduced saliva secretion did not want to extend the examination.

Three of our patients (10%) reported both xerostomia and xerophthalmia and 8 (28%) reported at least one of these symptoms. All 4 patients who underwent labial biopsy had focus scores indicative of Sjögren's syndrome. In earlier reports, secondary Sjögren's syndrome has been reported in 10 to 30% of patients with RA (6, 100-102).

Xerostomia was reported by 6 RA patients (21%) in this study. This prevalence is in accordance with an earlier report of xerostomia in 17% of an RA group (102). Four of 6 patients with xerostomia had no swallowing complaints. A previous report has shown that the correlation between saliva secretion and a subjective feeling of dry mouth is weak (102). In this study, we found that xerostomia was associated with decreased stimulated saliva secretion. The decreased secretion was probably due to sialoadenitis.

Esophageal manometry (II)

Twenty-eight of the RA patients agreed to participate in this investigation.The tracing of one patient was lost due to a technical error but both her manometric recording and the repeated dry swallowing test were normal as judged on the screen at the investigation. Seventeen subjects in the control group were invited to perform the esophageal manometry and the repeated dry swallowing test, and they all accepted.

The results of the motility measurements regarding contraction amplitude and duration in the proximal and distal part of the esophagus are shown in Table 8. The amplitude of the peristaltic pressure complex in the proximal part of the esophagus was significantly decreased in the RA group compared with normal controls. No significant difference was found in the distal part of the esophagus. The 2 patients taking antidepressant drugs (one

of them also an antihistamine) had amplitudes in the proximal part of the esophagus above the mean value of the RA group (33 and 35 mmHg, respectively).

Table 8. *Amplitude and duration of peristaltic contractions in the proximal and distal part of the esophagus in 27 RA patients and 17 control subjects (mean ± SEM).*

Motility	RA	Controls
Amplitude proximal part (mm Hg)	32 ±2*	45 ±7
Duration proximal part (s)	2.1 ±0.1	2.5 ±0.2
Amplitude distal part (mm Hg)	53 ±4	61 ±6
Duration distal part (s)	3.6 ±0.1	3.4 ±0.3

* *denotes $p<0.05$*

Coordination between the pharynx and the upper esophageal sphincter and peristaltic muscular activity in the whole esophagus were found in 27 RA patients and in all control subjects. Unspecific changes with some segmental contractions alternating with normal muscular activity were found in one RA patient. This patient was the one with secretion stagnation in the hypopharynx. However, she had no subjective swallowing problems.

Esophageal manometry revealed that the amplitude of the peristaltic pressure complex in the proximal part of the esophagus in RA patients was significantly reduced compared with the controls, indicating dysfunction of the striated muscles. This finding is in accordance with two previous reports (103, 104). In one of these a few cases with distal esophageal dysfunction were also reported (103). No controls were used in these two studies. Other investigators have failed to find esophageal dysfunction in RA patients (105, 106). However, in one of the studies only the distal smooth muscle part of the esophagus was examined and the other study was purely radiographic.

A slight reduction of the contraction amplitude was also seen in the lower part of the esophagus in this study, although this was not statistically significant. However, no signs of specific changes in the lower part of the esophagus, like those seen in sclerodermia, were found. Tsianos et al found one out of 25 RA patients with lower esophageal hypomotility (107). The RA patients in the present study with low contraction amplitudes (≤25 mm Hg, n=9) in the upper esophagus showed no significant increase in symptoms of dysphagia, odynophagia, a feeling of a lump in the throat or xerostomia. Only one of the patients with low amplitude had subnormal stimulated saliva secretion. Myopathy and/or neuropathy due to the RA disease and/or a side-effect of drugs might be a mechanism explaining the impaired esophageal muscular function found in this study (11, 108-111). The reduction of the contraction amplitudes seemed not to be of such magnitude that it evoked esophageal symptoms.

In patients with primary Sjögren's syndrome and systemic lupus erythematosus, absent or low contractions in the upper third of the esophagus have been reported (112, 113). In another study of patients with primary and secondary Sjögren's syndrome, however, no evidence of esophageal motility disturbance as a cause of dysphagia was found; instead, the authors favoured the opinion that dysphagia was secondary to xerostomia (114). The same opinion was stated by the authors of a paper reporting mucosal atrophy in the esophagus in patients with primary and secondary Sjögren's syndrome (115). In our study of RA patients no significant association between xerostomia or decreased stimulated saliva secretion and dysphagia was found.

Repeated dry swallowing test (II)

Twenty-seven patients and 17 controls performed this test accurately. The mean swallowing test time for the RA group was 50 ± 4 s (range 20-93 s), compared with 55 ± 5 s (range 22-92 s) in the control group (n.s.).

At this test no RA patient was found to have a prolonged swallowing test time compared to normal controls, suggesting that necessary saliva and normal receptor function were present (90, 116).

Arthritis of the temporomandibular joints has been reported in one-third to two-thirds of RA patients (99, 117, 118). Reported symptoms related to the chewing ability. Pharyngeal dysfunction registered cineradiographically has been reported to be more common in RA patients with decreased ramal height of the mandible compared with patients with a normal mandible (119). In the same study, pharyngeal dysfunction was shown to be more common in RA patients with vertical dislocation of the cervical spine compared with patients with a normal cervical spine. However, the authors found about the same degree of pharyngeal abnormalities during cineradiography in non-dysphagial patients as in dysphagial patients. This illustrates the complexity of dysphagia regarding correlation of objective findings and symptoms.

We conclude that xerostomia and dysphagia are common among RA patients. Xerostomia was, as expected, associated with low stimulated saliva secretion, presumably due to sialoadenitis. Dysphagia in RA patients may be due to several mechanisms such as rheumatic cervical involvement, arthritis of the temporomandibular joints, decreased amounts of saliva, teeth problems, pharyngeal dysfunction, laryngeal involvement and esophageal muscular dysfunction. In this study dysphagia could be significantly correlated only to the severity of the RA disease.

Laboratory data (I, II)

The values of erythrocyte sedimentation rate and of all class-specific rheumatoid factors were significantly higher ($p<0.001$) in the RA group (Table 9) than in the controls.

The 11 RA patients belonging to functional class III were compared with the remaining 18 RA patients in functional class I or II regarding erythrocyte sedimentation rate and class-specific rheumatoid factors. A statistically significant difference ($p<0.05$) was found only regarding IgG. The mean value for the 11 patients in functional class III was 8.6 ± 1.0 mm, compared with 4.7 ± 1.1 mm for the patients in lower functional classes.

No significant differences in erythrocyte sedimentation rate and class-specific rheumatoid factors were found between RA patients with and without laryngeal involvement.

Table 9. *Erythrocyte sedimentation rate (ESR) and class-specific rheumatoid factors (RF) (mean ± SEM) in the RA group (n=29) and the control group (n=30).*

	RA	Controls
ESR (mm)	34±4.5*	11±2.0
IgG RF (mm)	6.3±0.8*	1.3±0.5
IgA RF (mm)	8.0±0.9*	0.5±0.3
IgM RF (mm)	9.9±0.5*	3.7±0.6

* *denotes p<0.001.*

Patients with dysphagia and xerostomia respectively were compared with patients without dysphagia or xerostomia regarding erythrocyte sedimentation rate and class-specific rheumatoid factors. No significant differences were found in these comparisons.

Orolaryngeal airway resistance and computed tomography (III)

The calculated areas and the airflow resistances in the model are presented in Table 10 and illustrated in Fig. 5. The relationship is consistent with a curvilinear relationship.

Table 10. *Area and airflow resistance of the model.*

Area (cm^2)	R (kPa/(l/s))
0.2	0.56
0.3	0.39
0.3	0.32
0.4	0.11
0.5	0.09
0.9	0.02

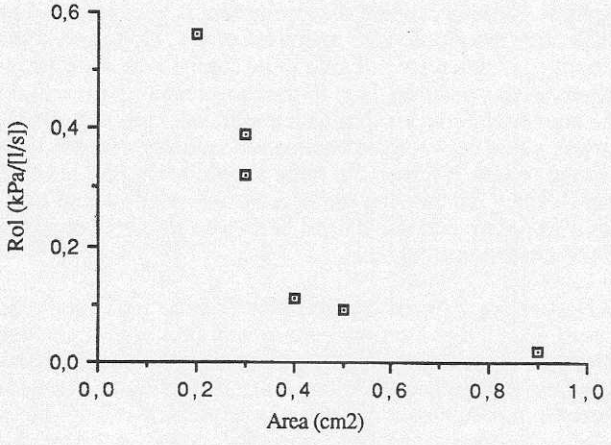

Fig. 5. *Correlation between the airflow resistance and the area in the model.*

The glottic areas in the patients are calculated both from their individual halfway values and from a fixed halfway value (-500 HU)(Table 2, page 11). The relationship between R_{ol} and the CT-determined area measured with individual halfway values is shown in Fig. 6. In this diagram, too, the relationship is consistent with a curvilinear relationship. The R_{ol} values among the patients vary from 0.1 to 1.2 kPa/(l/s), i. e. from that of a normal larynx to a severe laryngeal obstruction (78).

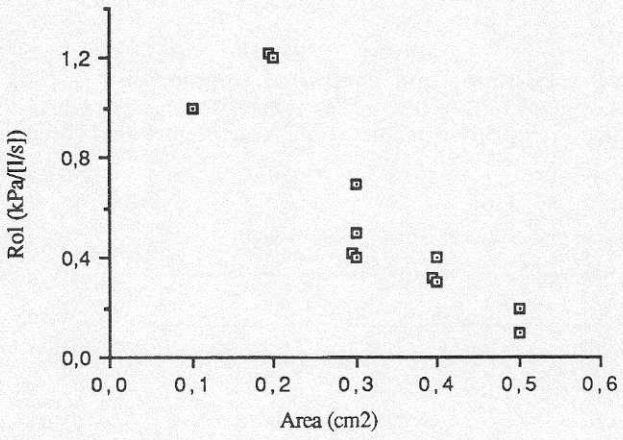

Fig. 6. *Correlation between the orolaryngeal airway resistance and the glottic area.*

Determinations of R_{ol} in patients have shown good agreement with clinical findings and repeated determinations of Rol on different occasions have given similar results (120). We consider R_{ol} to be the best available method for quantifying a laryngeal obstruction. However, determination of R_{ol} is an invasive method, which limits its usefulness. This method is not suitable for patients with bleeding disorders and small children.

Computed tomography is noninvasive and the equipment is widespread. In this study, it seemed possible to calculate the glottic area by means of CT. However, some difficulties arose, e.g. some patients were not able to lie supine with their neck extended or had breathing problems in this position. Due to the long scanning time (9.6 s) motion artefacts occurred. The boundary between an object and its background is best represented by the halfway value between the attenuation value of the object and the background (80-82). In the model, it turned out to be simple to decide this halfway value, but in man it was rather difficult, despite the use of a narrow window and an edge-enhancing filter. It was also possible to use a fixed halfway value between that of soft tissue and air, which facilitates the calculations.

Air passing a human larynx is subjected to a complex flow pattern. Jaeger & Matthys found, in a thorough study (121), that the flow pattern was similar to that existing in a Venturimeter. Thus, during very low flow rates the flow pattern is laminar and during very high flow rates the flow pattern has the character of orifice flow. In a wide interval between these flow patterns, the flow pattern cannot be expressed in a simple algebraic equation. When calculating Reynolds' number in the patients and in the model, it was found to be within the interval of 3 500 and 11 000. According to Jaeger's & Matthys' findings, the conductance (G=1/R) should then most likely be proportional to the second power of the area. Applied to the model, we found a very high coefficient of correlation ($r=1.00$) between G and the second power of the area. It thus seemed possible to assess an obstruction with CT under ideal circumstances. The corresponding coefficient of correlation among the patients was slightly lower ($r=0.85$). Measuring the area with fixed halfway values gave only a somewhat lower coefficient of correlation. The correlation coefficients regarding both the model and the patients were statistically significant ($p<0.001$).

An attempt to measure the length of the obstruction was made. Since all patients had diseases of the vocal cords, the obstructions were short, but still difficult to measure. Adding length to the calculations did not enhance the correlation coefficient.

The results of this study indicate that it is possible to measure the narrowest area of a short constriction by CT. Patients with Rol values over 0.2 kPa/(l/s) usually have symptoms of upper airway obstruction, while patients with Rol values below 0.2 kPa/(l/s) do not (120). In the present study all patients with glottal areas of 0.4 cm^2 or less had a Rol value of 0.3 kPa/(l/s) or higher. The results of this limited series indicate that it is possible to detect a laryngeal obstruction by CT and that it is possible to some extent to quantify the obstruction. Difficulties were, however, encountered, especially when measuring the narrowest obstructed areas.

Long-term results of laterofixation (IV)

Breathing

The patients were investigated preoperatively and postoperatively for the first time after a mean of 1.4 months (range 0-4). The follow-up measurements were performed on average 7.3 years (range 5-9) postoperatively. R_{ol} could be determined in all patients (Table 11).

Table 11. *Individual data and upper airway resistance (R_{ol}) for 11 patients with bilateral vocal cord paralysis operated upon with the laterofixation procedure.*

		Follow-up age	Rol (kPa/(l/s))		
No	Sex	(years)	Pre-op	Post-op	Follow-up
1	M	46	0.7	0.6	0.4
2	M	60	0.6	0.1	0.1
3	F	63	0.9	0.8	0.7
4	F	63	0.8	0.4	0.6
5	F	64	0.4	0.4	0.6
6	F	65	0.9	0.4	0.2
7	M	67	0.7	0.7	0.3
8	F	68	0.4	0.4	0.5
9	F	71	0.6	0.2	0.3
10	M	71	0.4	0.5	0.2
11	F	73	1.1	0.6	0.4

Preoperatively, the mean orolaryngeal resistance was 0.66 ± 0.07 kPa/(l/s)(SEM). Postoperatively it decreased to 0.45 ± 0.06 kPa/(l/s) and at the follow-up assessment it was 0.39 ± 0.06 kPa/(l/s) (Fig. 7). The decrease between the postoperative and the follow-up value was not significant. The improved breathing capacity was unchanged during the postoperative follow-up period. The decrease of Rol between preoperative and early postoperative values was significant ($p<0.05$). The decrease of Rol was significant also when comparing preoperative values with the follow-up results ($p<0.01$). Seven patients had improved Rol at the postoperative assessment, 3 were unchanged and one deteriorated. At the follow-up assessment, 9 patients were improved and 2 deteriorated compared to the preoperative situation.

R_{ol} is approximately 0.1 kPa/(l/s) in normal humans (78). Our patients varied from moderate to severe laryngeal obstruction. Two patients had not improved at the follow-up. These 2 patients had only a slightly increased R_{ol} (0.4 kPa/[l/s]) preoperatively.

They had only moderate stridor during exertion both pre and postoperatively and they were not severely disabled. Their symptoms were not considered severe enough to indicate a more complicated operation. In our experience, a patient with a R_{ol} of less than 0.5 kPa/(l/s) is not usually a candidate for the laterofixation procedure. Thus, in our opinion, determination of R_{ol} is useful because the degree of laryngeal obstruction can be objectively assessed, which allows improved selection of patients for the operation and contributes to the evaluation of the results.

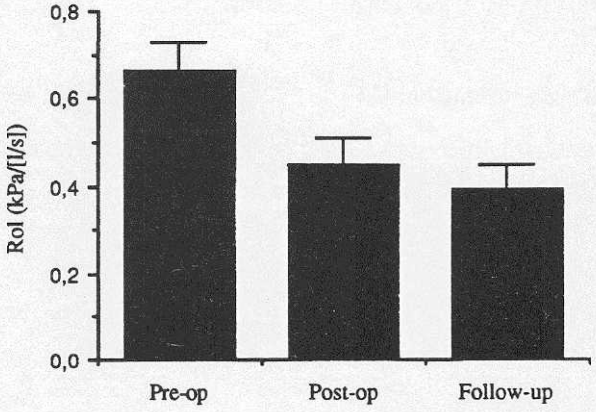

Fig. 7. *Mean orolaryngeal resistance (R_{ol}) in 11 patients operated on using the laterofixation procedure.*

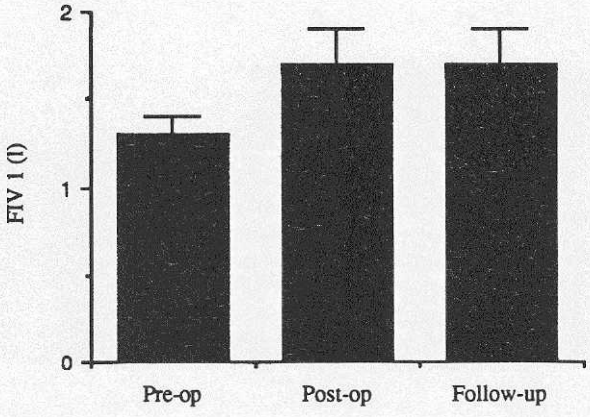

Fig. 8. *Mean FIV_1 in 7 patients with bilateral vocal cord paralysis operated on using the laterofixation procedure.*

The spirometry was evaluated in only 7 patients. No statistically significant differences were found. FIV_1 was preoperatively found to be 1.3 ± 0.1 l (SEM) and at both postoperative measurements FIV_1 was 1.7 ± 0.2 l (Fig. 8). Only minor changes were noticed regarding FEV_1 and the FEV_1/FIV_1 quotient. Four patients were not evaluated regarding spirometry. Two patients could not perform satisfactory spirometry tests on all three occasions due to high age and/or neurological disorders. An early postoperative spirometry was missing in one patient. Finally, a partial pulmonectomy, due to a neoplasm, was performed in one patient nine years postoperatively just but before the follow-up examination.

Voice quality

No significant differences of the voice regarding timbre, tempo or inspiratory stridor could be found between the first postoperative and the follow-up tape recordings. 94% of the first postoperative voice samples and 95% of the follow-up voice samples were socially acceptable according to the amateur panel. The corresponding figures for the speech therapist panel were 72% and 65%.

Voice function has to be influenced by moving a vocal cord from a median or paramedian to a lateral position. An earlier report has shown that the laterofixation influences the voice quality negatively by increasing the phonatory leakage (122). However, the disturbances from the inspiratory stridor are reduced (122). The present study indicates that the voice quality does not change during the years after operation.

Aspiration

At the hypopharynx-esophagus radiographic examination with barium contrast, all investigated patients had normal function except one patient with a tendency to aspirate. This patient had a known stricture of the upper esophageal sphincter and in 1969, 10 years before the laterofixation, aspiration was documented radiologically. According to this study, no patient has developed a tendency to aspirate after the operation.

To our knowledge, these are the only documented long-term results after bilateral vocal cord surgery. Objective documentation has often been lacking. Breathing and voice quality have only been subjectively evaluated, or only commented on by a note as to whether the patients could be decannulated or not, and aspiration has in most cases not been discussed (123-132). Flow-volume loops and airway resistance assessed with a body-plethysmograph have in some studies been used but not R_{ol} assessments (133-135).

The mobilization and laterofixation operation (V)

No preoperative or postoperative complications occurred. Four of the 5 patients with tracheostomas preoperatively were decannulated within 14 days postoperatively. One patient failed to improve. The effects of the operation on respiration are summarized in Table 12. In 5 of 6 patients, inspiratory R_{ol} decreased from an average of 1.1 kPa/(l/s) to an average of 0.4 kPa/(l/s). No patient developed any problems with aspiration.

Four of the 5 female patients had earlier been tracheotomized under more or less emergency circumstances. Three of these patients had been admitted as emergency cases with inspiratory stridor, which in 2 of them was induced by an upper airway infection. The fourth patient could not be extubated after an operation on her cervical column and had to be tracheotomized.

All 5 patients with tracheostomas needed hospital care before the operation. Patient no 2 had a very severe airway obstruction (Table 12). She was the only one not decannulated postoperatively. Two patients were able to return to their homes and another two were discharged to nursing homes postoperatively. The male patient with juvenile RA (no 1) continued working full time after the operation.

Table 12. *Effects of the mobilization and laterofixation operation on respiration.*

Patient no	Upper airway resistance (kPa/[l/s])		Tracheostomy	
	Preop.	Postop.	Preop.	Postop.
1	0.8	0.2	No	No
2	10.0	-	Yes	Yes
3	1.9	0.5	Yes	No
4	0.7	0.3	Yes	No
5	0.7	0.3	Yes	No
6	1.5	0.8	Yes	No

The effects of the operation on the voice were difficult to document objectively because 5 of the patients were tracheotomized preoperatively. The voice of the patient that was not tracheotomized was judged to be unchanged by the patient himself and by a speech therapist when listening to pre and postoperative tape recordings. All the decannulated patients had acceptable voices postoperatively, judged by themselves.

Simple laterofixation of one vocal cord (122) was not sufficient to reduce the laryngeal obstruction. However, if the arytenoid cartilages were mobilized before laterofixation, the operation was feasible. The dilation did not cause any visible laryngeal edema or bleeding.

Few procedures specifically intended for treating cricoarytenoid ankylosis have been presented. Montgomery described a method in which one arytenoid cartilage was removed and the vocal cord lateralized with a steel suture (15). The operation was performed via laryngofissure, preceded by tracheotomy. The effects of these procedures on breathing were not documented. With the present technique, no tissue is damaged, which allows any other second operation if necessary. The vocal cord laterofixation by our technique can be modified. If, for example, the voice has become aphonic, due to a to wide glottal rima, the loop can be released. On the other hand, the operation can also be repeated if the breathing has not improved sufficiently.

In patients with severe RA, involvement of the cervical column is common. The neck must therefore be bent cautiously. In this series, a special vacuum pillow (Camp Scandinavia AB), which prevented bending of the neck, was used in 2 patients with subluxations between the first and second cervical vertebrae. Although an operation microscope or chest support for the laryngoscope was impossible to use in 4 patients, the operation could be performed with only minor added difficulties. Other endolaryngeal procedures for bilateral vocal cord paralysis would be difficult to perform without chest support and a microscope.

MAIN OBSERVATIONS AND CONCLUSIONS

- Signs of laryngeal involvement were found in about two-thirds of the RA patients.
- Voice problems were reported by 40% of patients with laryngeal involvement compared to none of the patients without laryngeal involvement.
- Patients afflicted with RA had symptoms related to the esophagus and dry mouth four times more often than healthy controls.
- Esophageal manometry revealed that the amplitude of the peristaltic pressure complex in the proximal part of the esophagus was significantly decreased in the RA group.
- It seemed possible to detect a laryngeal obstruction and to some extent quantify the obstruction by CT.
- The favourable postoperative results after vocal cord laterofixation according to Ejnell et al in patients with bilateral vocal cord paralysis were longlasting regarding breathing capacity and voice quality and no aspiration was evoked.
- It was possible to operate upon RA patients with cricoarytenoid joint ankylosis with a new vocal cord mobilization and laterofixation procedure with good results.

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REFERENCES

1. Geterud Å, Ejnell H, Sandberg N, Bjelle A, Bake B. Rheumatoid arthritis in the larynx. Scand J Rheumatol Suppl 59 1986;59:77.
2. Hedfors E. Reuma-immunologi - aktuellt läge i forskningen. Kliniska konsekvenser idag och i en nära framtid. Läkartidningen 1987;84:4340-2.
3. Konttinen YT, Bergroth V, Nordström D, Saari H, Santavirta S. Vad vet vi om uppkomsten av reumatoid och reaktiv artrit? Nordisk Medicin 1987;102:301-4, 327.
4. Svensson B. Prevalensen av reumatoid artrit lägre än man tidigare känt till. Läkartidningen 1989;86:45-6.
5. Mikkelsen WM, Dodge HJ, Duff IF, Kato H. Estimates of the prevalence of rheumatic diseases in the population of the Tecumseh, Michigan, 1959-60. J Cron Dis 1967;20:351-69.
6. Brooker DS. Rheumatoid arthritis. Clin Otolaryngol 1988;13:239-46.
7. Ropes MW, Bennet GA, Cobb S, al e. Diagnostic criteria for rheumatoid arthritis; 1958 revision. Bull Rheumatol Dis 1958;9:175-6.
8. Arnett FC, Edworthy SM, Bloch DA, al e. The 1987 revised American Rheumatism Association criteria for classification of rheumatoid arthritis. Arthritis Rheumatol 1988;31:315-24.
9. Jacobsson L, Manthorpe R. Nya kriterier för reumatoid artrit. Läkartidningen 1988;85:3257-9.
10. Hollingsworth JW, Saykaly RJ. Systemic complications of rheumatoid arthritis. Med Clin North Am 1977;61:217-28.
11. Hurd ER. Extraarticular manifestations of rheumatoid arthritis. Sem Arthritis Rheumatol 1979;8:151-76.
12. Mackenzie M. Diseases of the pharynx, larynx and the trachea. William Wood & Co, New York 1880:347.
13. Montgomery WM, Perone PM, Schall LA. Arthritis of the cricoarytenoid joint. Ann Otol Rhinol Laryngol 1955;64:1025-33.
14. Montgomery WW. Pathology of cricoarytenoid arthritis. New England J Med 1959;260:66-9.
15. Montgomery WW. Cricoarytenoid arthritis. Laryngoscope 1963;73:801-36.
16. Montgomery WW, Goodman ML. Rheumatoid cricoarytenoid arthritis complicated by upper esophageal ulcerations. Ann Otol 1980;89:6-8.
17. Smith RF. Rheumatoid arthritis of the cricoarytenoid joint with ankylosis. Ann Int Med 1964;60:473-5.
18. Phelps JA. Laryngeal obstruction due to cricoarytenoid arthritis. Anesthesiology 1966;27:518-22.
19. Vassallo CL. Rheumatoid arthritis of the cricoarytenoid joints. Arch Intern Med 1966;117:273-5.
20. Pinals RS. Rheumatoid arthritis presenting with laryngeal obstruction. Brit Med J 1966;1:842.
21. Funk D, Raymon F. Rheumatoid arthritis of the cricoarytenoid joints: an airway hazard. Anesthesia Analgesia 1975;54:742-5.
22. Chalmers A, Traynor JA. Cricoarytenoid arthritis as a cause of upper airway obstruction. J Rheumatol 1979;6:541-2.
23. Kandora FK, Gilmore IM, Sorber JA, Rose FB, Matta II. Cricoarytenoid arthritis presenting as cardiopulmonary arrest. Ann Emerg Med 1985;14:700-2.
24. Jurik AG. Rheumatoid arthritis of the cricoarytenoid joints: a case of laryngeal obstruction due to acute and chronic joint changes. Laryngoscope 1985;95:846-8.
25. Ten Holter JBM, van Buchem FL, van Beusekom HJ. Cricoarytenoid arthritis may be a case of emergency. Clin Rheumatol 1988;7:288-90.
26. Gresham GA, Kellaway TD. Rheumatoid disease in the larynx and lung. Ann Rheumatol Dis 1958;17:286-92.
27. Polisar IA, Burbank B, Levitt LM, Katz HM, Morrione TG. Bilateral midline fixation of cricoarytenoid joints as a serious medical emergency. JAMA 1960;172:901-6.

28. Beckman M, Wallén E. Rheumatoid arthritis of the larynx. Acta Anesth Scand 1964;8:107-14.
29. Lavie P, Nahir M, Lorber M, Sharf Y. Clinical improvement in rheumatic arthritis patients by NSAID medication is not associated with improvement in sleep. 10th Congress of the European Sleep Research Society 1990;Abstracts book:317.
30. Grossman A, Martin JR, Root HS. Rheumatoid arthritis of the crico-arytenoid joint. Laryngoscope 1961;71:530-44.
31. Lofgren RH, Montgomery WW. Incidence of laryngeal involvement in rheumatoid arthritis. N Engl J Med 1962;267:193-5.
32. Bienenstock H, Ehrlich GE, Freyberg RH. Rheumatoid arthritis of the cricoarytenoid joint: a clinicopathologic study. Arthritis Rheumatol 1963;6:48-62.
33. Harris ER, Grossman A, Martin JR. Crico-arytenoid joint involvement in rheumatoid arthritis: its detection and manifestations. Arthritis Rheumatol (abstract) 1973;16:553.
34. Ferdynus-Chromy J. Clinical and morphology pictures of the cricoarytenoid articulations on the course of the rheumatoid arthritis. Otolaryngol Polska 1978;32:81-2.
35. Jurik AG, Pedersen U. Rheumatoid arthritis of the crico-arytenoid and crico-thyroid joints: a radiological and clinical study. Clin Radiol 1984;35:233-6.
36. Lawry GV, Finerman ML, Hanafee WN, Mancuso AA, Fan PT, Bluestone R. Laryngeal involvement in rheumatoid arthritis. Arthritis Rheumatol 1984;27:873-82.
37. Charlin B, Brazeau-Lamontagne L, Levesque R-Y. Cricoarytenoiditis in rheumatoid arthritis: comparison of fibrolaryngoscopic and high resolution computerized tomographic findings. J Otolaryngol 1985;14:381-6.
38. Bridger MWM, Jahn AF, van Nostrand AWP. Laryngeal rheumatoid arthritis. Laryngoscope 1980;90:296-303.
39. Jacobs JC, Hui RM. Cricoarytenoid arthritis and airway obstruction in juvenile rheumatoid arthritis. Pediatrics 1977;59:292-4.
40. Goldhagen JF. Cricoarytenoiditis as a cause of acute airway obstruction in children. Ann Emerg Med 1988;17:532-3.
41. Malleson P, Riding K, Petty R. Stridor due to cricoarytenoid arthritis in pauciarticular onset juvenile rheumatoid arthritis. J Rheumatol 1986;13:952-3.
42. Leicht MJ, Harrington TM, Davis DE. Cricoarytenoid arthritis: a cause of laryngeal obstruction. Ann Emerg Med 1987;16:885-8.
43. Bienenstock H. Cricoarytenoid arthritis in a patient with ankylosing spondylitis. Arch Otolaryngol 1977;103:738-9.
44. Libby DM, Schley WS, Smith JP. Cricoarytenoid arthritis in ankylosing spondylitis. Chest 1981;80:641-3.
45. Smith GA, Ward PH, Berci G. Laryngeal involvement by systemic lupus erythematosus. Tr Am Acad Ophth & Otol 1976;84:124-8.
46. Sellars I, Sellars S. Cricoarytenoid joint structure and function. J Laryngol Otol 1983;97:1027-34.
47. Leden H, Moore P. The mechanics of the cricoarytenoid joint. Arch Otolaryngol 1961;73:541-55.
48. Wolman L, Darke CS, Young A. The larynx in rheumatoid arthritis. J Laryngol Otol 1965;79:403-34.
49. Darke CS, Wolman L, Young A. Laryngeal stridor in rheumatoid arthritis. Br Med J 1958;5082:1279-84.
50. Copeman WSC. Rheumatoid arthritis of the crico-arytenoid joints. Br Med J 1957;1:1398-9.
51. Baker OA, Bywaters EGL. Laryngeal stridor in rheumatoid arthritis due to crico-arytenoid joint involvement. Br Med J 1957;1:1400.
52. Pearson JEG. Rheumatoid arthritis of the larynx. Br Med J 1957;1:1047.
53. Jurik AG. Asymptomatisk crico-arythenoidea-arthrit. Ugeskr Laeger 1984;146: 975-6.
54. Jurik AG. Visualisation of the intralaryngeal joints: a low voltage radiological study. Clin Radiol 1982;33:687-90.
55. Brazeau-Lamontagne L, Charlin B, Levesque R-Y, Lussier A. Cricoarytenoiditis: CT assessment in rheumatoid arthritis. Radiology 1986;158:463-6.

56. Woldorf NM, Pastore PN, Terz JT. Rheumatoid arthritis of the cricoarytenoid joint. Arch Otolaryngol 1971;93:623-7.
57. Weiner SR. Emergencies in rheumatoid arthritis. Am Fam Physician 1984;29: 127-31.
58. Habib MA. Intra-articular steroid injection in acute rheumatoid arthritis of the larynx. J Laryngol Otol 1977;91:909-10.
59. Simpson GT, Javaheri A, Janfaza P. Acute cricoarytenoid arthritis: local periarticular steroid injection. Ann Otol 1980;89:558-62.
60. Sladek GD, Vasey FB, Saraceno C, Davis BJ, Germain BF, Espinoza LR. Beclomethasone dipropionate in the treatment of the rheumatoid larynx. J Rheumatol 1983;10:518-9.
61. Goldberg J, Kovarsky J. Beclomethasone diproprionate inhalation treatment for chronic hoarseness in rheumatic disease. Arthritis Rheumatol 1983;26:1412.
62. Copeman WSC. Rheumatoid arthritis and the crico-arytenoid joints. Br J Clin Pract 1968;22:421-2.
63. Rontal M, Rontal E. Endoscopic laryngeal surgery for bilateral midline vocal cord obstruction. Ann Otol Rhinol Laryngol 1990;99:605-10.
64. Geterud Å, Ejnell H, Månsson I, Sandberg N, Bake B, Bjelle A. Severe airway obstruction caused by laryngeal rheumatoid arthritis. J Rheumatol 1986;13:948-51.
65. Keenan MA, Stiles CM, Kaufman RL. Acquired laryngeal deviation associated with cervical spine disease in erosive polyarticular arthritis. Anesthesiology 1983;58:441-9.
66. Berglund E, Birath G, Bjure J, et al. Spirometric studies in normal subjects. Acta Med Scand 1963;173:185-92.
67. DuBois A, Brody AW, Lewis DB, Burgess Jr BF. Oscillation mechanics of lung and chest in man. J Appl Physiol 1956;8:587-94.
68. Aronsson H, Solymar L, Dempsey I, Bjure T, Olson T, Bake B. A modified forced oscillation technique for measurements of respiratory resistance. J Appl Physiol 1977;42:650-5.
69. Peslin R, Hannhart B, Pino J. Impédance mécanique thoracopulmonaire chez des sujets fumeurs et non-fumeurs. Bull Europ Physiopath Resp 1981;17:93-105.
70. Oxhöj H, Bake B. Measurement of closing volume with the single breath nitrogen method. Scand J Resp Dis 1974;55:320-31.
71. Sixt R, Bake B, Oxhöj H. The single-breath N_2-test and spirometry in healthy non-smoking males. Eur J Respir Dis 1984;65:296-304.
72. Salorinne Y. Single-breath pulmonary diffusing capacity. Scand J Resp Dis 1976;suppl 96:1-84.
73. Blide RW, Kerr HD, Spicer Jr WS. Measurements of upper and lower airway resistance and conductance in man. J Appl Physiol 1964;19:1059-69.
74. Ferris Jr BG, Mead J, Opie LH. Partitioning of respiratory flow resistance in man. J Appl Physiol 1964;19:653-8.
75. Hoorn B, Ingelstedt S. A method for objective analysis of stenosis of larynx. Acta Otolaryngol 1960;Suppl 158:10.
76. Hyatt RE, Wilcox RE. Extrathoracic airway resistance in man. J Appl Physiol 1961;16:326-30.
77. Schiratzki H. Upper airway resistance in normal man during mouth breathing. Acta Otolaryngol 1964;58:535-54.
78. Ejnell H, Bake B, Månsson I. Spirometric indices in the assessment of laryngeal obstruction. Eur J Res Dis 1984;65:600-10.
79. Höijer U, Ejnell H, Bake B. The ability of noninvasive methods to detect and quantify laryngeal obstruction. Eur J Resp Dis; in press.
80. Baxter BS, Sorensen JA. Factors affecting the measurements of size and CT number in computed tomography. Invest Radiol 1981;16:337-41.
81. Koehler PR, Anderson RE, Baxter BS. The effect of computed tomography viewer controls on anatomical measurements. Radiology 1979;130:189-94.
82. Magnusson A. Object size determination at computed tomography. Upsala J Med Sci 1987;92:277-86.

83. Moutsopoulos HM, Klippel JH, Pavlidis N, et al. Correlative histologic and serologic findings of sicca syndrome in patients with systemic lupus erythematosus. Arthritis Rheumatol 1980;23:36-40.
84. Ericson T. Secretion of salivary glycoproteins. In: Emmelin N, Zotterman Y, eds. Oral Physiology, Oxford: Pergamon Press 1972:75-81.
85. Heintze U, Birkhed D, Hilding B. Secretion rate and buffer effect of resting and stimulated whole saliva as a function of age and sex. Swed Dent J 1983;7:227-38.
86. Parvinen T. Stimulated salivary flow rate in relation to size and sex. Proc Finn Dent Soc 1984;80:127-30.
87. Daniels T. Labial salivary gland biopsy in Sjögren's syndrome. Arthritis Rheumatol 1984;27:147-56.
88. Cleary RC, Batsakis JG. Biopsy of the lip and Sjögren's syndrome. Ann Otol Rhinol Laryngol 1990;99:323-5.
89. Fox RI, Robinson CA, Curd JG, Kozin F, Howell FV. Sjögren's syndrome. Arthritis Rheumatol 1986;29:577-85.
90. Månsson I, Sandberg N. Salivary stimulus and swallowing reflex in man. Acta Otolaryngol (Stockh) 1975;79:445-50.
91. Elwing H, Nygren H. Diffusion-in-gel enzyme-linked immunosorbent assay (DIG-ELISA): a simple method for quantitation of class-specific antibodies. J Immunol Meth 1979;31:101-7.
92. Tarkowski A, Bjursten LM, Nilsson L-Å, Nygren H. False positive results in class-specific rheumatoid factor (RF) assays due to interaction between RF and the Fc fragments of anti-immunoglobulin indicator reagents. J Immunol Meth 1983;58:171-82.
93. Pearson ES, Hartley HO. Biometrika tables for statisticians. Cambridge University Press 1966.
94. Hunninghake GW, Fauci AS. Pulmonary involvement in the collagen vascular disease. Am Rev Respir Dis 1979;119:471-503.
95. Krane SM, Simon LS. Rheumatoid arthritis: clinical features and pathogenetic mechanisms. Med Clin North Am 1986;70:263-84.
96. MacFarlane JD, Dieppe PA, Rigden BG, Clark TJH. Pulmonary and pleural lesions in rheumatoid arthritis. Br J Dis Chest 1978;72:288-300.
97. Shiel WC, Prete PE. Pleuropulmonary manifestations of rheumatoid arthritis. Semin Arthritis Rheumatol 1984;13:235-43.
98. Doig JA, Whaley K, Dick WC, Nuki G, Williamsson J, Buchanan WW. Otolaryngological aspects of Sjögren's syndrome. Br Med J 1971;4:460-3.
99. Tegelberg Å, Kopp S. Subjective symptoms from the stomatognathic system in individuals with rheumatoid arthritis and osteoarthrosis. Swed Dent J 1987;11:11-22.
100. Bloch KJ, Buchanan WW, Wohl MJ, Bunim JJ. Sjögren's syndrome. Medicine 1965;44:187-231.
101. Ben-Aryeh H, Nahir M, Scharf Y, Gutman D, Laufer D, Szargel R. Sialochemistry of patients with rheumatoid arthritis. Oral Surg 1978;45:63-70.
102. Ericson S, Sundmark E. Studies on the sicca syndrome in patients with rheumatoid arthritis. Acta Rheumatol Scand 1970;16:60-80.
103. Ramirez-Peredo J, Pena Ancira F, Ramirez-Mata M, Moctezuma M, Alarcon-Segovia D. Esophageal motor dysfunction in rheumatoid arthritis. J Rheumatol 1974;1:80.
104. Turner R, Lipshutz W, Miller W, Rittenberg G, Schumacher HR, Cohen S. Esophageal dysfunction in collagen disease. Am J Med Sci 1973;265:191-9.
105. Stevens MB, Hookman P, Siegel CI, Esterly JR, Shulman LE, Hendrix TR. Aperistalsis of the esophagus in patients with connective-tissue disorders and Raynaud's phenomenon. N Engl J Med 1964;270:1218-22.
106. Tatelman M, Keech M. Esophageal motility in systemic lupus erythematosus, rheumatoid arthritis, and scleroderma. Radiology 1966;86:1041-6.
107. Tsianos EB, Drosos AA, Chiras CD, Moutsopolos HM, Kitridou RC. Esophageal manometric findings in autoimmune rheumatic diseases: is scleroderma esophagus a specific entity? Rheumatol Int 1987;7:23-7.
108. Tozman E, Gottlieb N. Adverse reactions with oral and parenteral gold preparations. Med Toxicol 1987;2:177-89.

109. Chamberlain M, Bruckner F. Rheumatoid neuropathy. Ann Rheumatol Dis 1970;29:609-16.
110. Danneskiold-Samsöe B. Muscle function in women with rheumatoid athritis - the influence of glucocorticosteroids. Dan Med Bull 1988;35:48-64.
111. Sokoloff L, Wilens SL, Bunim JJ. Arteritis of striated muscle in rheumatoid arthritis. Am J Pathol 1951;27:157-73.
112. Ramirez-Mata M, Pena-Ancira F, Alarcon-Segovia D. Abnormal esophageal motility in primary Sjögren's syndrome. J Rheumatol 1976;3:63-9.
113. Ramirez-Mata M, Reyes PA, Alarcon-Segovia D, Garza R. Esophageal motility in systemic lupus erythematosus. Amer J Digest Dis 1974;19:132-6.
114. Kjellén G, Fransson SG, Lindström F, Sökjer H, Tibbling L. Esophageal function, radiography, and dysphagia in Sjögren's syndrome. Dig Dis Sci 1986;31: 225-9.
115. Hradsky M, Hybasek I, Cernoch V, Sazmova V, Juran J. Oesophageal abnormalities in Sjögren's syndrome. Scand J Gastroenterol 1967;2:200-3.
116. Månsson I, Sandberg N. Oro-pharyngeal sensitivity and elicitation of swallowing in man. Acta Otolaryngol (Stockh) 1975;79:140-5.
117. Tegelberg Å, Kopp S. Clinical findings in the stomatognathic system for individuals with rheumatoid athritis and osteoarthrosis. Acta Odontol Scand 1987;45: 65-75.
118. Ogus H. Rheumatoid arthritis of the temporomandibular joint. Br J Oral Surg 1975;12:275-84.
119. Ekberg O, Redlund-Johnell I, Sjöblom KG. Pharyngeal function in patients with rheumatoid arthritis of the cervical spine and temporomandibular joints. Acta Radiol 1987;28:35-9.
120. Ejnell H. Assessment and treatment of vocal cord paralysis. Thesis, University of Göteborg, Sweden 1984:1-34.
121. Jaeger MJ, Matthys H. The pattern of flow in upper human airways. Respir Physiol 1968;6:113-27.
122. Ejnell H, Månsson I, Hallén O, Bake B, Stenborg R, Lindström J. A simple operation for bilateral vocal cord paralysis. Laryngoscope 1984;94:954-8.
123. Kleinsasser O. Microlaryngoscopy and endolaryngeal microsurgery. Philadelphia: WB Saunders 1968:120-1.
124. Helmus C. Microsurgical thyrotomy and arytenoidectomy for bilateral recurrent nerve paralysis. Laryngoscope 1972;82:491-503.
125. Banfai P. Die operative Lösung der laryngo-trachealen Stenosen. HNO 1976;24:371-82.
126. Singer MI, Hamarker RC, Miller SM. Restoration of the airway following bilateral recurrent laryngeal nerve paralysis. Laryngoscope 1985;95:1204-7.
127. Ossoff RH, Sisson GA, Duncavage JA, Moselle HI, Andrews PE, McMillan WG. Endoscopic laser arytenoidectomy for the treatment of bilateral vocal cord paralysis. Laryngoscope 1984;94:1293-7.
128. Prasad U. CO2 surgical laser in the management of bilateral vocal cord paralysis. J Laryngol Otol 1985;99:891-4.
129. Lim RY. Laser arytenoidectomy. Arch Otolaryngol 1985;111:262-3.
130. Clerf LH. The surgical treatment of bilateral posticus paralysis of the larynx. Laryngoscope 1950;60:142-51.
131. Schobel H. Glottiserweiterung bei beidseitiger Stimmlippenlähmung. HNO 1986;34:485-95.
132. Lichtenberger G. Laryngomikrochirurgische Laterofixation gelämhter Stimmlippen mit Hilfe eines neuen Nahtinstrument. Laryngol Rhinol Otol 1989;68:678-82.
133. Dennis DP, Kashima H. Carbon dioxide laser posterior cordectomy for treatment of bilateral vocal cord paralysis. Ann Otol Rhinol Laryngol 1989;98:930-4.
134. Amedee RG, Mann WJM. A functional approach to lateral fixation in bilateral abductor cord paralysis. Otolaryngol Head Neck Surg 1989;100:542-5.
135. Abramson AL, Endolaryngeal carbon dioxide laser arytenoidectomy: evaluation using the flow-volume loop. Bull N Y Acad Med 1984; 60:825-45.

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