

A randomized prospective controlled study of acoustical measures of reflux with symptoms in the larynx

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Abstract

We have made a randomized prospective controlled study in order to evaluate whether acoustical measures are of interest in gastro-esophageal reflux patients with complaints in the larynx: laryngo-pharyngeal reflux (GERD/LPR).

The set-up was made with Multi-Dimensional Voice Program (MDVP) by the firm Laryngograph Ltd. compared with high speed films from Wolf Ltd. with 4000 frames pr second.

The subjective complaints and their reduction corresponded to the reduction of oedema in the arytenoid regions.

The acoustical tests did show significant but weak reduced variation of frequency %, intensity % during reading of a standard text and the electroglottographic signal variation (EGG%).

There

might be other results of the highest notes of singers, if focused upon. Reduction of oedema of the arytenoid region is a better prognostic factor of treatment effect of laryngopharyngeal reflux than acoustical analysis.

Key words: Laryngopharyngeal reflux, oedema of the arytenoids, acoustical
<http://www.mpedersen.org> measures, MDVP, randomized controlled trials.

Introduction

The literature on acoustical analysis of voice related to reflux is interesting in its diversity. The definition of the gastro-oesophageal reflux disease (GERD) has been made [1]. In our Cochrane review on laryngeal reflux and hoarseness, studies seem to be insufficient to document specific connections to the larynx [2]. **The point is probably that there is one disorder, GERD, which in some cases has laryngeal symptoms [3, 4].** Still mucosal irritation up to the larynx of GERD does reduce quality of life even if the concepts are not sufficiently elucidated [5, 6, 7]. The problem is the lack of evidence in randomized controlled trials between hoarseness and GERD even if the theoretical association is there [8, 9, 10].

Introduction

We have earlier tried to define differences between normal and abnormal voices with the Multi-Dimensional Voice Program (MDVP) by Laryngograph Ltd. Some differences have been found [11].

But an overall meta-analysis does not give validated conclusions [12]. Maybe phrases and sentences have to be used instead of sustained tones [13,14].

In this study the MDVP program by Laryngograph Ltd. has been used for the acoustical measurements of the voices in patients with laryngo-pharyngeal reflux (LPR/GERD), often used program is the Multi-Dimensional Voice Program, (MDVP) by Kay Elemetrics.

With MDVP by Kay Elemetrics only sustained tones are usually used. The Praat programme is mainly used in phonetics [15]. Comparison can be questioned in pathology.

Introduction

With the Laryngograph Ltd. MDVP setup sustained tones and reading of a standard text are used. Analyses of fundamental frequency (Fo), jitter and shimmer are made for sustained tones, but also frequency and intensity variation measures during reading of a standard text.

Routine measures of electroglottographic online signals (EGG) are used for evaluating exact curves of the vocal cords in time and calculations made of variation of the sinus tone deviations in % and also irregularity measures the percentage of laryngeal cycles which have bigger cycle-to-cycle changes than a threshold. (Fx 3% threshold, Qx 6% threshold).

Introduction

High speed films and exact online evaluation of the vocal cords is used in our clinical practise [16]. With **high speed films** it has been possible to document treatment effect of reflux with laryngeal symptoms including oedema of the arytenoid region.

The statistical difference was significant in an earlier study comparing **subjective complains related to oedema of the arytenoids regions** after two weeks treatment [17].

Introduction

The aim of this prospective randomized study was to make an acoustical analysis with MDVP by Laryngograph Ltd. on sustained tones as well as reading of a text for documenting treatment effect of voice related reflux.

Laryngo-pharyngeal reflux (LPR/GERD) might not influence the speaking voice, related to the fundamental frequency. Further studies should be made on the singing voice.

Material

All participating patients signed a written consent, which was scanned and stored in the database.

Patients were randomized into three groups of treatment with Laryngo-Pharyngeal Reflux/ Gastro Esophageal Reflux Disorder (LPR/GERD) treatment:

1. LPR/ GERD related lifestyle guidance (avoid the following acid provoking habits and food: smoking, fatty and smoked food, coffee, chocolate, spices, strong alcohol (alcohols containing a lot of tannins), acidic fruits and juices. No food 2-3 hours before sleep, avoid over eating, sleep with your head high. Singers should avoid eating just before a concert).

2. LPR/GERD related life style correction + acid pump inhibitors (esomeprazol) 1 tablet daily 40 mg and a group

3. with supplementary alginate 1 tablet after the evening meal.

All the included patients were aged 18 or over.

Material

The required symptom duration for inclusion was at least 2-4 weeks. Each participating patient had, as minimum, three subjective complaints of GERD with laryngeal symptoms. The presence of inter-arytenoid oedema, documented with high speed films, was also required for the inclusion to the study.

The LPR/ GERD complaints in the larynx were:

- Hoarseness or a problem with your voice
- Clearing your throat/excess throat mucus or postnasal drip
- Difficulty swallowing food, liquids, or pills (dysphagia)
- Coughing after you ate or after lying down, troublesome or annoying cough
- Breathing difficulties or choking episodes (larynx spasms and hick up)
- Sensational of something sticking in your throat or lump in your throat (globules)
- Heartburn, chest pain, indigestion or stomach acid coming up, pain or burning feeling in the throat.

Material

Reasons for exclusion were: Under 18 years of age, less than three subjective complaints, and lack of oedema of the inter-arytenoid region on high speed films.

Other reasons were malignancies, pregnancies, and lack of cooperation.

The data collection in the database of patients was made during a period of 2½ years. The design and upper airway test parameters were routine examinations at ear-, nose-, throat clinics for laryngological patients with benign disorders.

The first examination

included diagnosis, planning of examinations, registration of complaints and related treatment.

The second examination

after two weeks was used for evaluation of results of examination including results of blood tests, and treatment evaluation, and

The third examination

after two to three months was for a follow up.

Method

The Multi-Dimensional Voice Program (MDVP by Laryngograph Ltd.) was used together with subjective complaints and high speed films (Wolf Ltd. 4000 pictures/sec. for 2 sec.), and all parameters were stored in the software program based FileMaker.

The Multi-Dimensional Voice Program, MDVP, was used for **sustained tones and reading of a standard text** including frequency (Fo), intensity (dB) and electroglottograms with percent variation, and irregularity measures of the percentage of laryngeal cycles which had bigger cycle-to-cycle changes than a threshold. (Fx 3% threshold, QX 6 % threshold).

Method

The sustained tones were “ah” in the patient’s spontaneous speech area and the standard reading text: “the North wind and the Sun”.

The measurements were made in the ear- nose- throat clinic with background noise between 50-60 dB.

Storage of sound was made in the MDVP software program and analyses filed together with the analyses of all other parameters online, made at the clinical consultation.

Method

Sample size consideration for the prospective randomized controlled study:

A total of 49 patients were needed in the group of lifestyle correction, lifestyle correction + proton pump inhibitor and the third group with supplementary alginate, to obtain a power of 90% in a two-group, one-sided, *t*-test to detect a difference of 20% under the assumption that the true difference was 5% and that the standard deviation was 25%.

Based on this general consideration and taking into account, possible drop out and evaluation of multiple endpoints, a total **of 237 patients were randomized in the study.**

Statistical analysis

Each numerical week 2, endpoint was evaluated in an analysis of covariance including baseline value as covariate and treatment group as fixed effect. This included acoustical analysis with MDVP by Laryngograph Ltd, subjective complains, inter arytenoids oedema scores on high speed films.

For each endpoint the hypotheses were tested:

An effect of treatment based on acoustical analysis, subjective complaints and high speed films.

Statistical analysis

A difference between treatment group of lifestyle guidance and lifestyle guidance and added treatment with the acid pump inhibitor esomeprazole 40 mg, one tablet at night against the two sided alternative that there is a difference.

A difference between treatment group of lifestyle guidance and lifestyle guidance combined with esomeprazole 40 mg **and alginate**, 1-2 chewing tablets after the evening meal against the two sided alternative that there is a difference.

Missing values were analysed as such and no imputation was made, which means that missing data were not included in the analysis.

Statistical analysis

The subjective complaints had descriptive statistics for each complaint.

Formal statistical analysis was conducted on the derived endpoint: Total number of complaints.

The total number of complaints was calculated as the sum of the individual evaluations of each of the complaints.

Only patients who had both baseline and week 2 visits were included in the analysis. Missing data for symptoms were imputed to be absent.

The total number of complaints was analysed as for the numerical endpoints.

Statistical analysis

The study comprised a baseline visit with **complaints as the inclusion criteria and a visual inter arytenoid oedema score on high speed films with 4000 frames per second.**

The investigator was blinded as to the allocation of the patients in the groups, prior to inclusion where the lowest randomization number was given.

At the second examination, the follow up was planned after a period of two to three months, both with the same analysis.

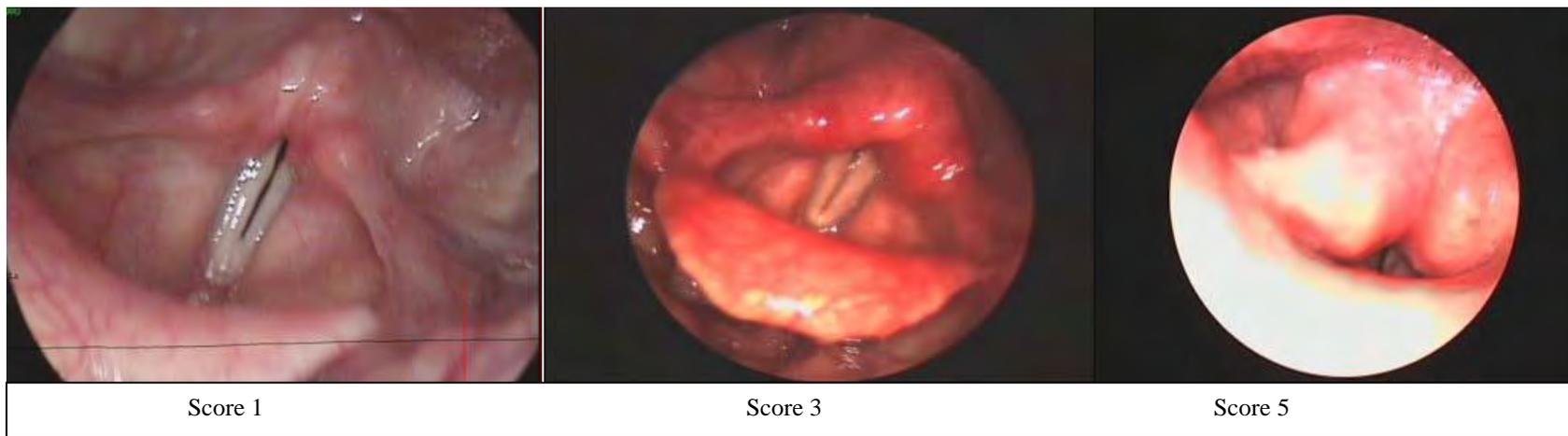
Statistical analysis

The **symptom evaluation** was dichotomized in the way that each symptom was considered maximally present or absent. As for the objective findings, a scaling for **acoustical analysis**, and **the inter arytenoid oedema of one (normal) to five** was made [Figure 1].

The significant correlation between inter arytenoid oedema score and the subjective complaints was earlier evaluated in a scatter plot where total number of symptoms was plotted against the inter arytenoid oedema score at the week 2 visit.

In this study Spearman correlation coefficient were calculated on the acoustical parameters separately at week two.

Figure 1 Visual scores of oedema of the arytenoid regions (score 1 normal arytenoids, score 3 most often seen oedema at the first examination, score 5 nearly closed larynx due to arytenoid oedema).



Results

The mean age of the 237 patients was 42 years.

In the lifestyle group there were 22 males and
56 females,

in the lifestyle + PPI group there were 17 males and 53 females,

in the lifestyle + PPI + alginate there were 26 males and 63 females.

Results

Table 1 summarizes the change from the first to the second consultation after two weeks using the MDVP program by Laryngograph and the scored arytenoid swelling as well as the follow up after 2-3 months (the three treatment groups are pooled).

From table 1 it is observed that the mean change between 1st and 2nd consultation for several of the parameters is statistically significant. For reading of a standard text there is a statistical significant change for intensity (%) and for frequency (%). For sustained tone there is a statistical significant change for shimmer (%).

The statistically significance of the changes at the 2nd consultation is sustained at the 3rd consultation and in addition, the EEG, QX % irregularity parameter is statistically significant changed from 1st consultation to the 3rd consultation after 2-3 months for sustained tone as well as reading.

Table 1 Summary of the arytoids region oedema visual score (1-5) and MDVP measurements: sustained tones in the speaking area and reading of a standard text by visits.

Parameter		1st consultation		2nd consultation			3rd consultation		
		N	Mean (SD)	N	Mean (SD)	Mean change (p-value)	N	Mean (SD)	Mean change (p-value)
Arytenoids region oedema visual score		237	2.71 (0.69)	196	2.19 (0.70)	-0.52 (<.0001)	147	1.96 (0.72)	-0.77 (<.0001)
Reading	Frequency (%)	235	10.73 (9.20)	194	9.43 (7.64)	-1.18 (0.0251)	144	9.51 (8.29)	-1.92 (0.0062)
	Intensity (%)	233	16.23 (4.91)	193	15.26 (4.13)	-1.02 (0.0002)	145	15.77 (4.27)	-0.80 (0.0246)
	Qx (%)	235	47.68 (6.03)	193	47.81 (5.75)	0.35 (0.2934)	145	47.51 (5.86)	0.10 (0.8057)
	Qx % irregularity	234	41.74 (14.8)	193	40.58 (15.1)	-1.07 (0.2717)	144	37.89 (15.7)	-4.52 (0.0003)
Tone	Jitter (%)	234	2.81 (8.31)	192	2.02 (5.73)	-0.77 (0.0635)	143	2.55 (6.93)	-0.31 (0.5979)
	Shimmer (%)	232	9.35 (8.04)	191	7.76 (4.38)	-1.37 (<.0001)	144	7.96 (4.56)	-1.41 (0.0003)
	Qx (%)	234	46.39 (8.60)	191	46.45 (7.19)	0.25 (0.5605)	143	47.08 (7.59)	0.63 (0.2707)
	Qx % irregularity	232	25.17 (22.3)	190	23.74 (21.9)	-2.10 (0.1385)	144	23.30 (20.2)	-3.92 (0.0142)

p-values are calculated in the ANCOVA model that includes baseline as covariate and visit as a fixed effect.

Results

Table 2 presents the Spearman correlation coefficient between changes in the acoustical MDVP measurements versus changes in the arytenoid swelling.

As can be seen from the table all the associations between changes in the MDVP measurements and the changes in arytenoid swelling are weak (less than 0.3).

Table 2. Spearman correlation between change in Arytenoid swelling and change in acoustical measurements: in MDVP of sustained tones in the speaking area and reading of a standard text

Parameter		2nd consultation		3rd consultation	
		Spearman n	P-value	Spearman n	P-value
Reading	Frequency (%)	0.17	0.0190*	0.04	0.6587
	Intensity (%)	-0.02	0.8107	0.06	0.5149
	Qx (%)	-0.11	0.1466	-0.11	0.1741
	Qx pct irregularity	0.09	0.2340	-0.08	0.3518
Tone	Jitter (%)	0.12	0.1065	0.22	0.0073**
	Shimmer	0.15	0.0416*	0.09	0.2714
	Qx (%)	0.05	0.4792	-0.10	0.2250
	Qx pct irregularity	0.22	0.0025**	0.18	0.0340*

*Statistically significant on 5% level, ** significant on 1 % level.

Figure 1 Visual scores of oedema of the arytenoid regions (score 1 normal arytenoids, score 3 most often seen oedema at the first examination, score 5 nearly closed larynx due to arytenoid oedema).

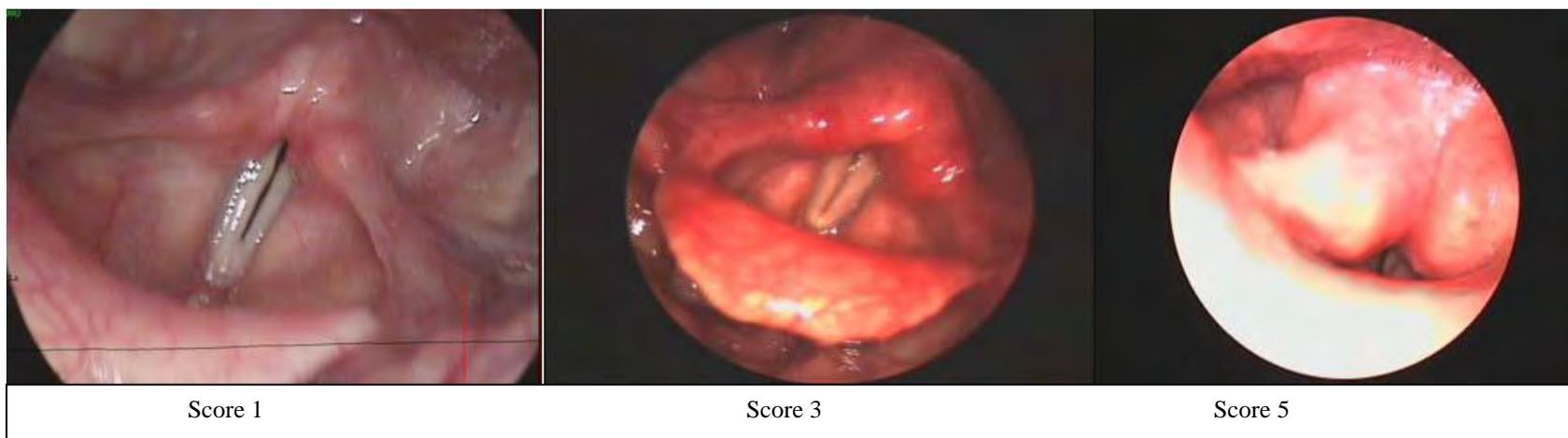
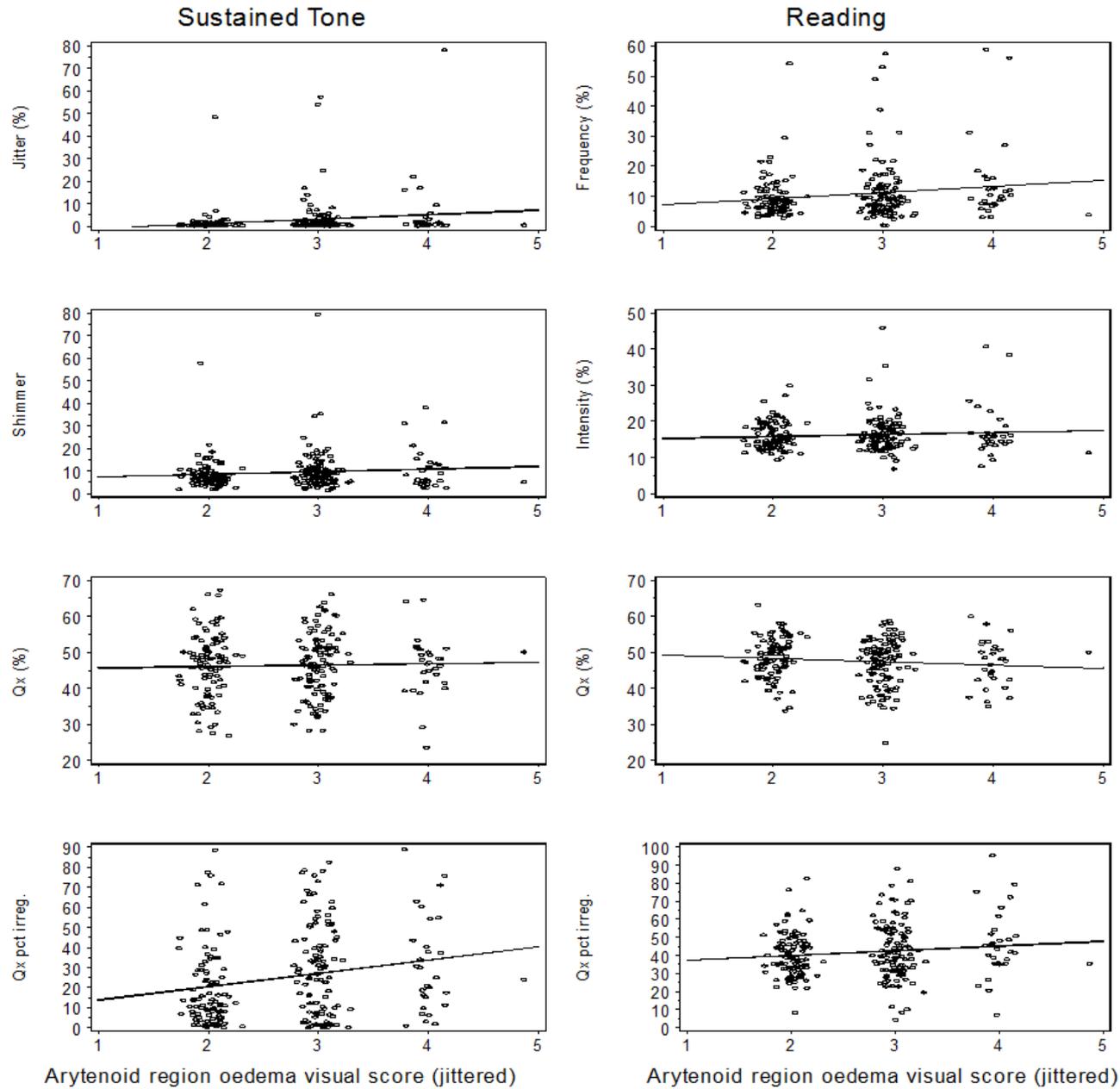


Figure 2 Scatter plots of measurements: sustained tones in the speaking area and reading of a standard text versus visual score of oedema of the arytenoid regions at baseline (1st consultation)

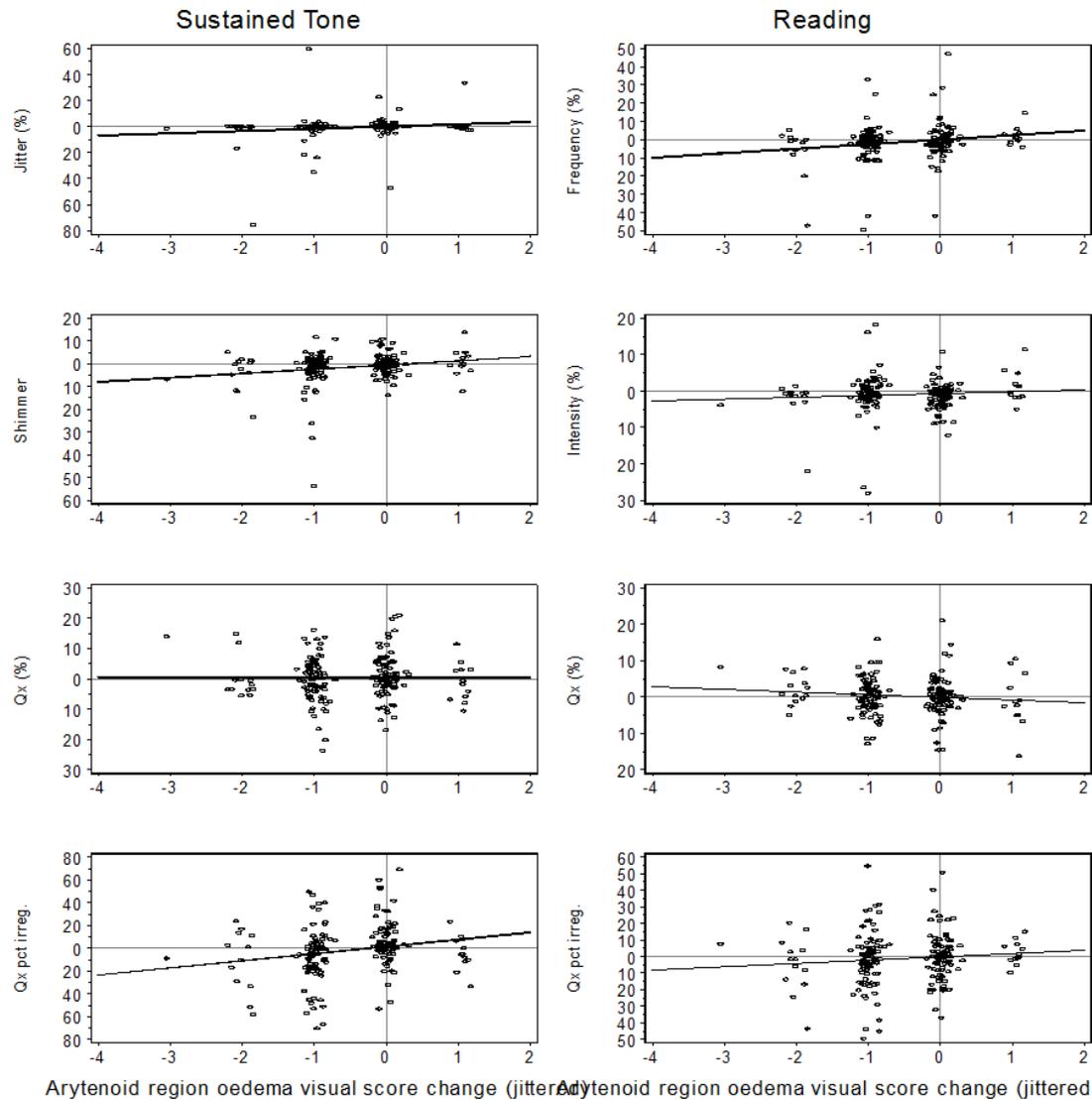


Results

Figure 3 scatter plots are presented for the changes from the first to the second examination after two weeks. Both sustained tones and reading of standard text are presented.

The scatter plot shows that a change in the voice measurements are generally not related to changes in the arytenoid swelling, but to a few aberrant measures.

Figure 3 Scatter plots of change in MDVP measurements: sustained tones in the speaking area and reading of a standard text versus change in visual score of oedema of the arytenoid regions from the 1st to the 2nd examination



Discussion

A randomized controlled trial of reflux with laryngeal complaints, and MDVP by Laryngograph Ltd., was carried out using sustained tones in the speaking area (Fo) and reading of a standard text.

The acoustical measures were only weakly associated with subjective complaints and the swelling of the arytenoid regions and can therefore not replace the visual inspection of the arytenoid regions with high speed films [17].

Discussion

The high-speed film

analyses are online pictures of arytenoid oedema with a visual score 1-5. Open quotients in front, middle and rear part of the vocal cords, kymography and EGG are routinely used in our clinic [16].

Döllinger et al. [18, 19] have presented several solutions on line for quantitative measurements of high-speed films, acoustial and vocal fold movement related. In our clinical experience they are extremely important.

Their set-up is optimal for further research of comparisons between high-speed films, acoustical analysis and subjective complaints of patients with reflux symptoms in the larynx, also in singers.

Discussion

The Glottis Analyse Tools online on high-speed films for vocal fold dynamics for each vocal fold with the Phonovibrogram is used in the clinic as shown in one of our patients (Table 3).

The use of arytenoid oedema visual scores 1-5, on high speed films seems to be better as a prognostic parameter than MDVP acoustical analysis.

In the future it will be possible to assure the oedema of arytenoid areas with optical coherence tomography as a supplementary diagnostic factor in speakers and in singers [20].

Discussion

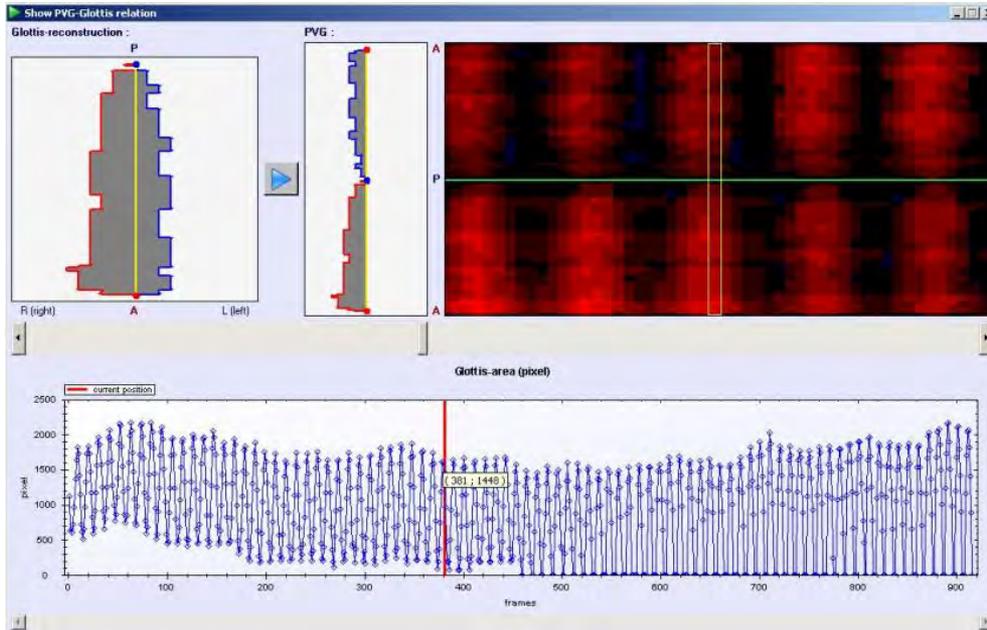
We have presented average oedema visual scores of the arytenoid region at the first examination compared with the second after two weeks.

There is a significant reduction of the oedema of the arytenoid region which is further reduced at the third consultation after 2-3 months in the study.

An acoustical reduction of shimmer was found after two weeks and also of reading frequency % and intensity variation %.

The parameter EGG QX % irregularity was highly significantly reduced at the follow up which corresponds to the sinus curves of voicing being more similar. This parameter is used very seldom. The idea is good and the parameter should be optimized to high-speed film and quantitative kymography films.

Table 3 Glottal Analyse Tools with high speed films. An increased control with contrast ensures accurate segmentation, and the area is calculated in each vocal fold cycle. This also ensures accurate jitter, shimmer and opening quotients.



Jitt(%)	0.542				
HNR(dB)	11.098				
Shim (%)	5.048				
		Mean	Std	Min	Max
ClosingQuotient(CQ)	0.4149	0.0602	0.2727	0.5455	
AsymetrieQuotient	0.4872	0.0721	0.3333	0.5833	
Stiffness	Left	0.4919	0.1902	0.254	0.9897
Stiffness	Right	0.4769	0.1664	0.2625	0.8411

Conclusion

The MDVP programs by Laryngograph Ltd as used for sustained tones and reading of a standard text does show improvement of shimmer percent on sustained tones and frequency and intensity variations % during reading of a standard text. QX % irregularity of EGG was a significantly changing factor only seldom used.

The acoustical changes were due to a few deviating measures.

The associations between changes in the MDVP measurements and the changes in arytenoid swelling were found to be weak.

Oedema of the arytenoid region was a better prospective factor for treatment of LPR/GERD than acoustical measures with MDVP.

- References on the web-side