

# Acoustical Voice Measurements did Change after Treatment in Patients with Laryngo-Pharyngeal Reflux: A Prospective Randomized Study Including MDVP (Laryngograph Ltd.)

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**Abstract:** A randomized prospective controlled study was made in order to find out if voice related acoustical measures show usable predictive pathologies in patients with laryngo-pharyngeal reflux (LPR). The used acoustical program was an advanced MDVP (multi-dimensional voice program) by Laryngograph Ltd. which routinely adjusts to well defined sustained tones measures as well as reading of a standard text and electroglottography. Three treatment groups for LPR were: Life style changes (avoid acid provoking food), and combined with proton pump inhibitors, and the third group also combined with alginate. There was no acoustical difference between the groups; they were therefore added to each other. A comparison between the first and second consultation after two weeks as well as follow up after three months did show significant jitter reduction of the measures of MDVP, and in reading of a standard text the frequency and intensity variations were also reduced. No change was found of electroglottography. The acoustical findings were not related to the oedema of the arytenoid region. The acoustical measures should be refined in the future with online measures on high speed films.

**Keywords:** Randomized controlled trials, laryngo-pharyngeal reflux, oedema of the arytenoid region, MDVP, standard text, electroglottography.

## INTRODUCTION

In our Cochrane review on laryngeal reflux (LPR) and hoarseness, studies were insufficient to document specific voice related acoustical relations to the larynx. Mostly, the amounts of patients were too low for statistical evidence [1]. Probably there is one disorder, GERD, which in some cases gives laryngeal complaints due to oedema of the arytenoid region (Figure 1) [2-4]. There is a lack of voice related acoustical evidence in randomized controlled trials between gastro oesophageal reflux disease (GERD) and LPR [5-10]. A meta-analysis did not give validated conclusions either [11-12]. With high speed films it is possible to document treatment effect with reduction of oedema of the arytenoid region, in this way we have new objective measures for prognostic evaluation of LPR. The aim of this prospective randomized study was to make an acoustical evaluation: that the speaking voice is a parameter of interest in LPR [13].

## MATERIAL AND METHOD

The required subjective symptom complaints duration of LPR for inclusion was at least 2-4 weeks. The objective presence of inter-arytenoid oedema with visual score 2-5, documented with high speed films, was also required for the inclusion to the study.

The LPR complaints with at least three of the following:

- Clearing your throat/excess throat mucus or postnasal drip
- Hoarseness
- 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

Reasons for exclusion were: under 18 years of age, no subjective complaints, and lack of the objective evaluation 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 first examination included registration of complaints, high speed films and randomization,

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**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).

followed by start of treatment. The second examination after two weeks was used for evaluation of treatment results and treatment was continued till the third examination after three months with a follow up, and where treatment could stop.

All participating patients signed a written consent, which was scanned and stored in the database. Patient treatment was randomized into three groups of treatment: 1. lifestyle correction (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. Life style correction + proton pump inhibitors (esomeprazol) 1 tablet daily 40 mg and a group 3 with supplementary alginate 1 tablet after the evening meal.

High speed films with description of inter arytenoid oedema were recorded with the standard equipment from Wolf Ltd. The Multi-Dimensional Voice Program (MDVP) was used for sustained tones, reading of a standard text and electroglottography (EGG) as developed in England by Fourcin and Abberton and used by Laryngograph Ltd. [14].

#### **Sample Size Consideration for the Prospective Randomized Controlled Study**

A total of 49 patients were needed in each group of lifestyle correction, lifestyle correction + proton pump inhibitor in the second group 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.

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 voice related acoustical analysis, subjective complaints, and inter arytenoids oedema scores on high speed films.

For each endpoint the hypotheses were tested:

An effect of life style correction based on voice related acoustical analysis, subjective complaints and high speed films.

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

A difference between treatment groups of lifestyle correction and lifestyle correction 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.

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

The subjective complaints had descriptive statistics for each LPR 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.

The study comprised a baseline visit with LPR complaints as the subjective inclusion criteria and a visual inter arytenoid oedema score (2-5) on high speed films with 4000 frames per second as the objective findings. 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 three months, both with the same analysis, and treatment as randomised and started at the 1<sup>st</sup> examination.

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

Spearman correlation coefficients were calculated on the acoustical parameters.

## RESULTS

No statistical voice related acoustical differences were found between the three treatment groups which consisted of lifestyle correction, lifestyle correction + proton pump inhibitor, and the third group with supplementary alginate, therefore they could be treated together. The average of symptoms collected as present or absent had a score of 4.37, 4.46, and 4.56 of the seven complaints respectively.

Table 1 A summary is presented of percent variation of fundamental frequency of sustained tones, reading of a standard text and EGG at the first, second and third consultation, arytenoid region oedema score was given at the top of the table. A reduction of reading frequency and intensity variation in percent was found at the second as well as third examination. A highly significant reduction of shimmer percent of sustained

**Table 1: Summary of Arytenoid Region Edema Seen of High Speed Films, Based on Edema Evaluation, Visual Score 1 –5 and MDVP. Sustained Tones and Reading on a Standard Text Were Analyzed Based on the Software**

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)
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)

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

**Table 2: Spearman Correlation Quotient between Arytenoid Swelling Changes and in MDVP Including EGG**

Parameter	2nd consultation		3rd consultation		
	Spearman	P-value	Spearman	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
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

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

tones was also found at the second and third examination. EGG changes were not found.

Table 2 Spearman correlation for percent change of the acoustical parameters was compared with oedema of the arytenoids at the second and third consultation. The better results of jitter at the third consultation were not found in reading. Statistically no change for the other parameters was found after LPR treatment. A comparison was here made of the Spearman correlation quotient between arytenoids swelling changes and MDVP including EGG at the second and third consultation. The jitter measures were due to a few aberrant variables. So the arytenoid oedema and the acoustical parameters did not change in a way that corresponds statistically.

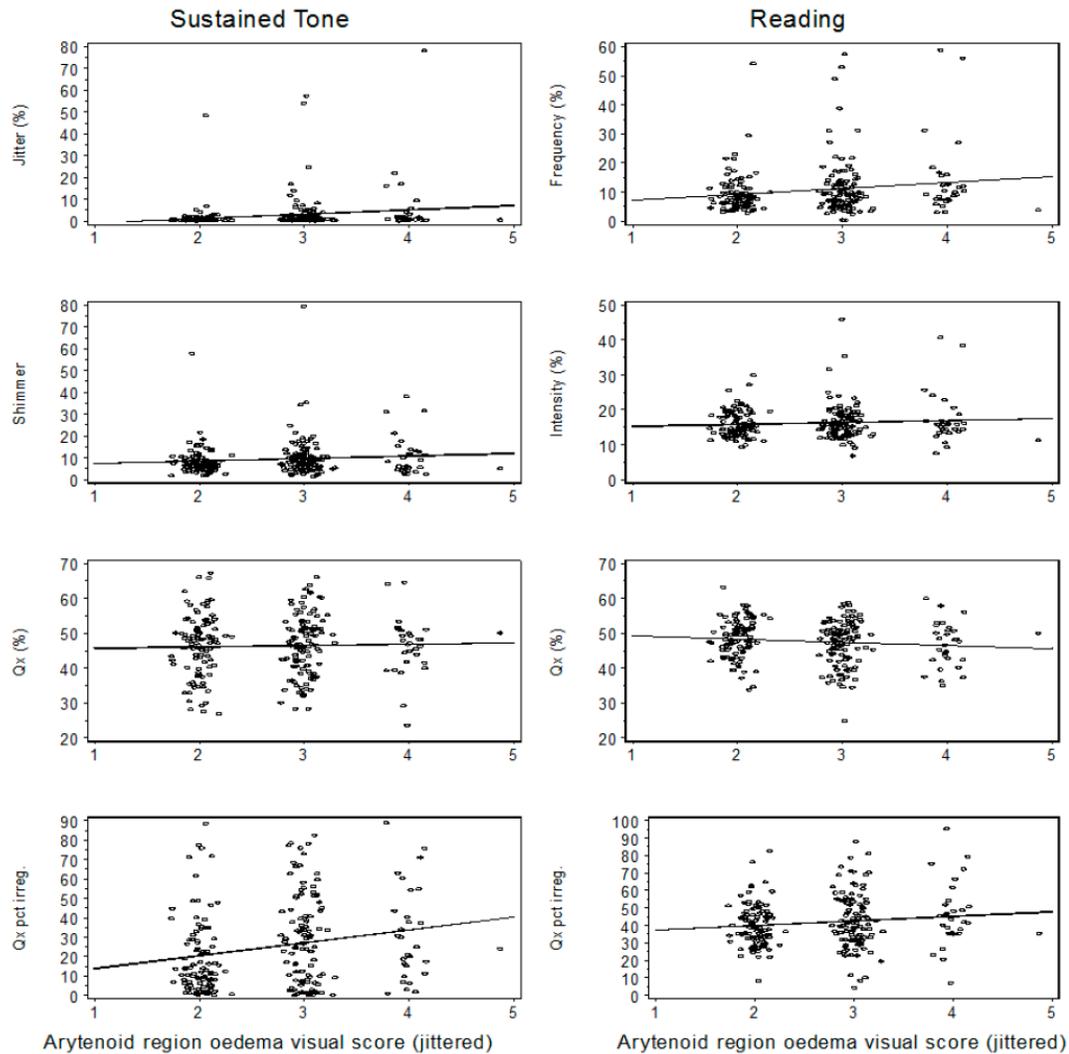
Figure 2 shows the distribution of voice related acoustical and electroglottographical measures in

percent for sustained tones and reading of a standard text at the first consultation as ordinate and oedema of the arytenoid region as abscissa.

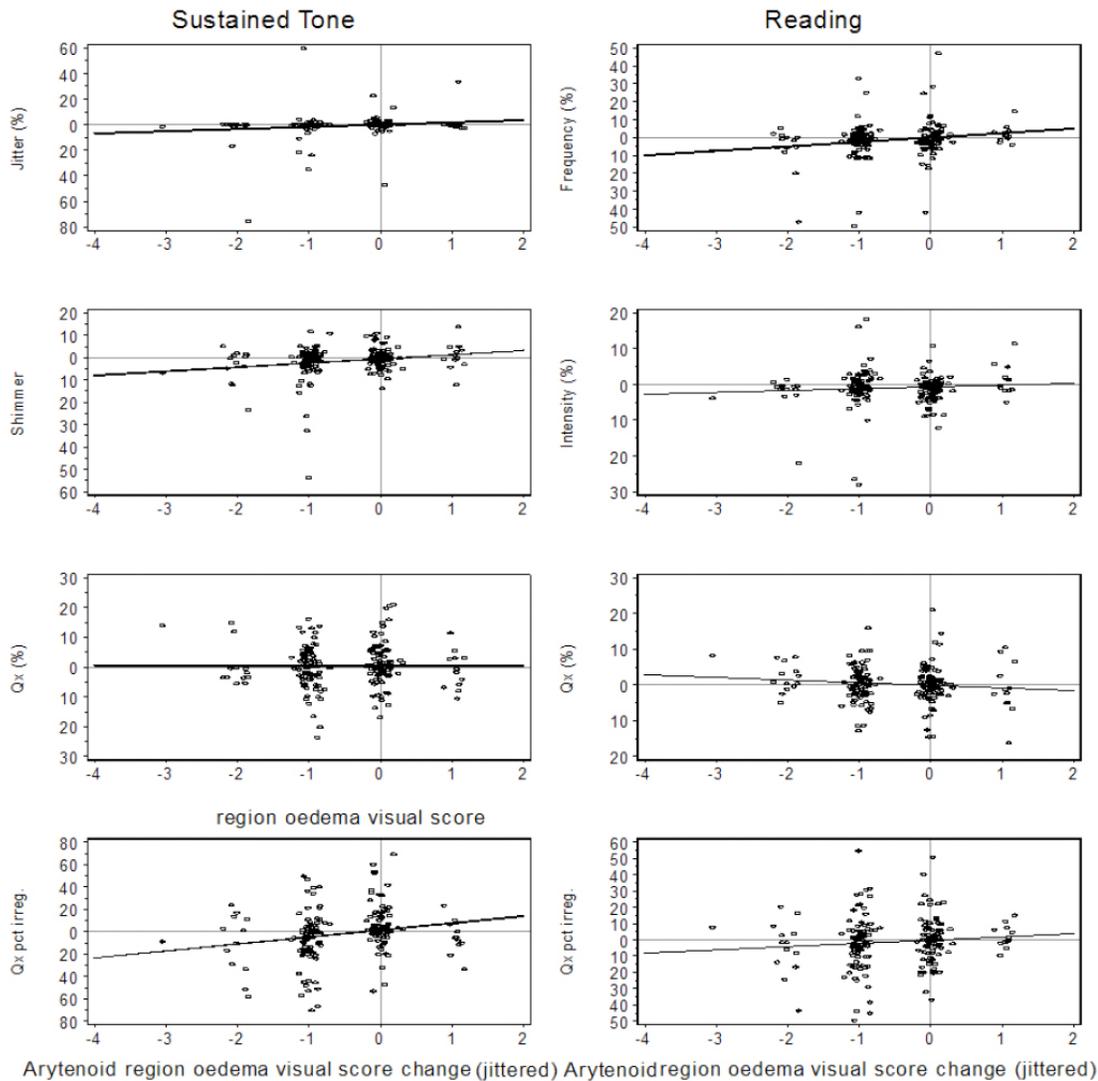
Figure 3 shows the distribution of changes of voice related acoustical and electroglottographical measures in percent from the first to the second consultation as ordinate and arytenoid oedema as abscissa.

**DISCUSSION**

We have made a prospective randomized controlled trial of LPR based on subjective complaints treated with lifestyle correction and two added medications, with high speed films as an objective inclusion parameter. No acoustical differences were found between the three groups by statistical calculations, therefore we combined them. The voice related acoustical measures were only weakly associated with the swelling of the



**Figure 2:** Distribution of acoustical and electroglottical measures at the first consultation as ordinate and oedema of the arytenoid region as abscissa.



**Figure 3:** Distribution of changes of acoustical and electroglottical measures from the first to the second consultation.

arytenoid regions based on the used measures, and could therefore not replace the visual inspection of the arytenoid regions at the second examination with high speed films. However, an interpretation could be that the acoustic quality improvements are very difficult to capture.

There was a significant reduction of the oedema of the arytenoid region at the second examination and a further reduction at the third consultation after 3 months in the study. Since high speed films and acoustical analyses have not been compared before references cannot be given for comparison, And as we have shown, mostly too small materials have been used earlier, for acoustical measures - and video stroboscopy and reflux [1].

A statistical significant reduction of frequency and intensity variation in percent in reading of a standard

text was found at the second as well as the third examination. A reduction of shimmer percent of sustained tones was also found at the second and third examination. Therefore it is suggested that acoustical focus on reflux treatment is made in patients with reduction of the two parameters.

The parameter EGG is interesting but without change. The parameter is found optimized in high-speed film and quantitative kymography films. Still no evidence of the value of the parameter in our LPR research study is found.

Table 3 presents the Glottis Analyse Tools, online on high-speed films for vocal fold dynamics for each vocal fold with the Phonovibrogram in one of our patients. It can be combined with high speed films for online measures, acoustical parameters and stiffness of vocal cords [15-18]. The principle is better than the

**Table 3: Glottal Analyse Tools with High Speed Films. An 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				
		<b>Mean</b>	<b>Std</b>	<b>Min</b>	<b>Max</b>
ClosingQuotient(CQ)		0.4149	0.0602	0.2727	0.5455
AsymmetrieQuotient		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

presented MDVP, which is not online with the films of the larynx.

The use of arytenoid oedema visual scores 1-5, on high speed films seems to be a valuable prognostic parameter. In the future it might be possible to evaluate the oedema of arytenoid areas with optical coherence tomography as a supplementary mucosal diagnostic factor in speakers and in singers, once all voice clinics have the high (cheaper) speed films as a clinical basic routine [19].

## CONCLUSION

In our MDVP study based on the advanced acoustical set-up by Laryngograph Ltd. referring to research by Fourcin and Abberton, a randomised prospective study of three different treatment aspects of LPR were made. No difference between the three treatment groups was found. There was an acoustical measured reduction in all groups of reading frequency and intensity variation and shimmer.

The relations between changes in the MDVP measurements and the changes in arytenoid swelling were found to be weak. In this study oedema of the arytenoid regions seen on high speed films seemed to be a better prospective factor for treatment effect than acoustical measures with MDVP by Laryngograph Ltd.

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