1.2.05 Benign organic voice disorders (Structural changes: nodules, polypus, vascular lesions, Reincke oedema, granuloma, cysts, sulcus vocalis)
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European Manual of Phoniatrics

Benign organic voice disorders

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Abstract

There has been a big focus on surgery of organic voice disorders. We have tried to divide the benign voice disorders in three groups: A group where surgical interference must be done, can be done and is preferably not done. Causality and provoking factors are discussed from our standpoint today. We are also trying to focus on upcoming factors for measuring, diagnosis and treatment, among others genetics and pharmacological treatment related to genetics and personalized medicine.

Introduction

The approach to diagnosis of organic voice disorders is changing all the time, understanding of personalized pharmaco-genetics and tissue engineering makes it possible to reduce enhanced surgery. Another newer approach is meta-analysis of randomized controlled trials. Two updated Cochrane reviews showed no effect of treatment of vocal nodules with neither speech therapy nor surgery [1], and larynges-pharyngeal reflux (LPR) studies were analyzed with too small materials [2]. A third way must be found, the suspicion being that benign vocal neoplams mostly are secondary especially to infection, and that genetic LPR has a much bigger role in provocations of vocal cord disorders than shown before.

Methods

In the clinic it seems that the complaints of the patients as the scientific basis have to be taken into account with e.g. voice handicap index (VHI [3]). VHI shows the personal situation of the patient. Perception tests (GRBAS [4]) are not evidence based among others because it has been shown that the musicality of the listeners is varying. Critics are also the case for many routinely used acoustical methods. No acoustical measures until now have been given as standards. We have shown that it is possible to differentiate between normal arytenoids regions and arytenoid edema in the larynx on high speed films, significantly related to the multi dimensional voice program (MDVP) of sustained tones and reading of a standard text [5]. In another study of LPR comparing subjective complaints of hoarseness and arytenoid edema we showed that they were highly related [6].
We have made a stratified overview of normal singer's parameters measuring air flow, jitter, shimmer,

reading variability and high speed measures with statistical measures calculated [7] (Table 1). So for documentation in our clinic the standards are sufficient and we can use these results routinely.
Still we recommend that measures are made for each country, since the languages in the European Union are not comparable for pathology, one of the results of the discussion in European research group COST 2103 of advanced voice assessment. No evidence based randomized controlled studies (RCT) were found in benign laryngology [8].

Material

With the understanding of pharmaco-genetics and voice related personalized medicine based on our Cochrane review, [9] selected valid averages of treatment of patients with organic benign voice disorders cannot be given. Evidence was not found for neither speech therapy nor surgery for vocal nodules [1]. This will probably demand multi-clinical approaches – in the various languages (countries) firstly and thereafter over the border of languages, secondly. Grouping of clinical cases are also difficult, organic disorders can be provoked by infections, allergy or environment with secondary bad voice habits [10]. Organic voice disorders can be age or hormone related [11] or part of a genetic syndrome [9].
Still the high speed films and video stroboscopy pictures can be systematically grouped to some extent, although causality can be different and the treatment too, high speed films with e.g. 4000 pictures per second being used for e.g. two second movement evaluation and video stroboscopy averaged for around 25 pictures per second for longer sequences of voicing, the old differentiation e.g. cysts/ nodules/ polyps being questioned.
There is no doubt that new pharmaco-genetic understanding makes surgery less obvious and that tissue engineering and knowledge of cell regulation [12] and fibroblast stimulation by activity of voice [13] document the need for training and lifestyle education [6] leaving less organic disorders for surgery of benign voice disorders. For potential malignant disorders and papilloma new approaches of medical treatment [14, 15] and understanding of virus as well as RNA engineering is of interest [16].
Updated randomized controlled studies (RCT) are too seldom, for example related to the well-known effect on benign swellings of the vocal cords treated with anti-histamines (e.g. fexofenadine up to 180 mg 3x a day) and cortisone locally on the closed vocal cords up to 400 mg 3x a day) , an impressive effect being showed of that medication on patients with dystonia – the types of dystonia possibly secondary syndromes [17].

Aspects of pathology

Therefore we demonstrate the organic disorders (Fig. 1) as potentially non-surgical cases analyzed genetically since no evidence has been found for surgery: secondary to lactose and gluten intolerance, low mannose binding lectin, allergies of inhalation, food, contact allergens, environmental stress especially of noise and pollution, reflux with dietary provocation or helicobacter provocation etc. – and cases where surgery is necessary (Fig. 2). None of the treatment methods are evidence based with randomized control trials till now. It is a necessity that meta-analysis in this area can be made on RCTs for specific diagnoses. Methodological studies should be used for pharmacogenetic diagnostics and treatment as well as surgical diagnostics and treatment- as well as surgical treatment. Base lines must include pharmaco-genetic aspects as well as power calculations and description of outcomes [18].
The literature of surgery of the vocal cords is as big as the pharmaco-genetic voice related personal treatment is small, and without statistical evidence usable for meta analysis at all.

Aspects of treatment of organic voice disorders

The pharmacogenetic approach includes systematic diagnosis of several hereditary genetic aspects and provocations often found (genetic gluten and lactose intolerance, mannose binding lectin insufficiency, inhalation and food allergens, environmental and infection factors (virus and bacteria) etc.)

Lifestyle change training and education needs evidence, based on knowledge of provocation and correct voicing.

The surgical approach is made with indirect or direct setup and equipment based on the surgeons´ patient material [19]. Well known approaches with indirect and direct cold instruments have shown success in operations on the vocal cords, based on further development of Kleinsasser instruments [19]. Development of newer laser instruments is promising as well as robots. The demand is an experienced surgeon, respecting the mucosal wave and the vocal muscle function. Procedures can be made with local or universal anesthesia.

Figure 1 shows a standard division of benign organic voice disorders and their structural changes.

Figure 2 shows our division of organic vocal disorders for medical treatment and operation.

Table 1 shows the software measures that are used routinely for documentation of results [7].

<u>Pharmacogenetic treatment</u>

Routine treatments: Antibiotics based on swabs in tight contact with micro biologists, anti-inflammatory treatments with antihistamines, local adrenalin, local cortisone in the upper airways and pharmacological virus treatment etc. to re establish the mucosal barrier of the upper airways. Lifestyle treatment with consciousness of environmental provocations and active response on provocations [10, 6, 17].

Future aspects relates to genetics, pharmaco-genetic repair of genes as well as epi-genes. Further understanding of the effect locally on the vocal cords of the antihistamine fexophenadin, local cortisone without lactose, and adrenalin inhaler etc. New software of light and electronic microscopy as well as optical coherence tomography for tissue evaluation is underway.

<u>Surgical treatment</u>

Routine treatments as mostly carried out has come to a standpoint, several advanced methods have been suggested especially using robots and laser surgery [19]. Benign neoplasms are not seen as often as in the past, taking pharmacogenetic treatment into account.

Future aspects includes mucosal repair and here it is also necessary to plan evidence based approaches. Cell repair with stem cell and tissue engineering is already used on vocal cord palsy and with botox in dystonia patients. Restoration of fibroblast and collagen matrix has been made on mice and rabbits. Genetic engineering is still a research area also in reflux [20].

<u>Education</u>

Routine treatments include dietary (especially reflux and lactose intolerance) and lifestyle adjustments to work and home as well as other disorders. It also includes respect for and avoiding provocation factors (dust, noise, shouting and others) [21].

Future aspects will take genetic aspects into account for example genetic loading of stem cells of defect collagen matrix of cells and many other syndromes to be co-ordinated with education. [22].

Training

Routine treatments: There is a large literature on training of voice. In our Cochrane review (1) of vocal nodules updated 2012, no evidence is found with RCTs on neither surgical operation nor speech training. In that review acoustical and physiological measures were included without any evidence of treatment effect in a model of randomized controlled trials. This does not mean that acoustical and physiological values should not be the basis for training. Models of randomized controlled trials should be planned with base lines, power calculation and outcome. There is no doubt that consciousness of the coordination of the voice related parts of the body is essential for the human wind instrument is necessary for patients with organic voice disorders also prophylactically against relapse. Personal coaches (logopeds, speech therapists, singing teachers, orthophonists) are still very necessary. Basic software for education can be downloaded made by several experts (e.g. Kathrine Verdolini to be downloaded via Youtube).

Future aspects: Personalized medicine and surgery of organic voice disorders has been overviewed, based on pharmaco-genetics. Personalized medicine/training is recommended taking results of genetic analysis into account [23].

Conclusion

Benign organic voice disorders are related to function of the vocal chords and nearby organ function as well as genes and epi-genes (provocational factors). Further understanding is necessary of the effect of e.g. gene repair and local steroids repair on the vocal cords directly, the effect of the antihistamine fexofenadine, other antihistamines and local adrenalin application derivate in the upper airways for repair and optimization of the mucosal barrier of the vocal cords and the larynx. Multicenter studies of randomized controlled trials are necessary for better evidence of treatment.

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Figure 1

			
	Nodules	Polyps	vascular lesions
Prevalence in populations	25% of hoarse patients	Not given	3,5% of population
Location	On the junction of the anterior 1/3 and the posterior 2/3	Mid cord location is characteristic	highly variable
Morphology	A mass of tissue that grows on vocal cords.	Smooth or round or have lobes	Prominent or enlarged vessels that exist on the vocal cord that cause hemorrhage of the lamina propia.
etiology	Arise from phonatory trauma and vocal misuse	Phonotrauma, physical stress of vocal cords	Vocal use, abuse and trauma
Sessile, Pedunculated	Sessile	Sessile or pedunculated	-
Edematous, vascular, fibrotic, myxoid	Edematous or fibrotic	Thin-walled dilated vessels and fibrinous exudates in edematous mucosa	Vascular

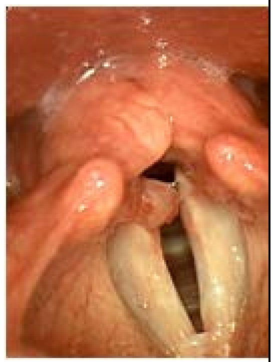
			
Reinkes edema	Granuloma	Cysts	Sulcus vocalis
Not given, mostly after the age of 40	Not given, related to underlying cause	Not known, but seems to recurrent among professional voice users attending throat specialists.	The incidence of sulcus vocalis is impossible to determine due to variation in presentation and diagnosis
Bi- or unilateral swelling of the vocal cords.	Located on the posterior third of the vocal cord, which corresponds to the vocal process of the arytenoid cartilage. Contact granulomas may occur unilaterally or bilaterally.	Located under the lining of the vocal cords, mostly in the middle of the vocal cords	A furrow or a trench in the vocal chord which can vary in depth
The Reinke's space between the lamina propria and vocal ligament is filled with loose connective tissue sheets	Mostly bilateral edemas with a granulated surface	Usually a spherical white or translucent mass located underneath the mucosa of the vocal cord	A thinning or absence of a special layer of tissue, called the superficial lamina propria, creating a "cleft".
Smoking, reflux or overuse/abuse of vocal cords	Factors that contribute to the development of granulomas include intubation, smoking, allergy, infections, postnasal drip, and chronic throat clearing.	Mucus retention cysts occur when a glandular duct becomes blocked and is unable to secrete. Epidermoid cysts result from developmental problems before birth or an injury to the mucous membrane.	Some physicians think that it is a developmental disorder, other that it is a long term result of vocal cord hemorrhage or cysts.
In principal, sessile	Mostly sessile	Sessile	Involves the whole vocal cord
myxoid	edematous	Mostly myxoid	Can be fibrotic

Figure 2

Group A (Preferably no operation): Diagnostic battery of infections also helicobactor and others, allergy and environment, pharmacogenetic battery including lactose and gluten intolerance and mannose binding lectin), training and education.

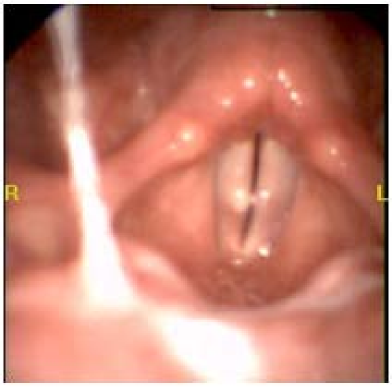
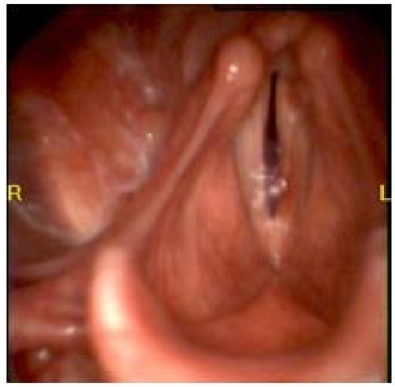
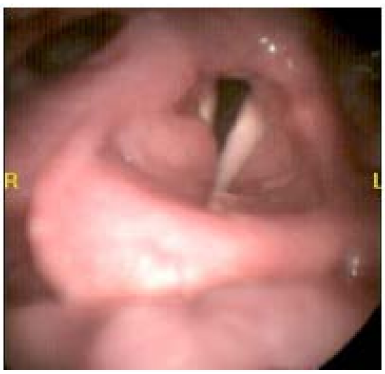
Group B (operation based on severity): Diagnostic battery, pharmacogenetic battery, training and education.

Group C (treated with operation): Diagnostic battery, pharmacogenetic battery, training and education.

Group A

Singing nodules 	Bleeding and haemangioma 	Edema and phlebectasia secondary to reflux, allergy and infection. 
Small Reincke Edema 	Posterior Granuloma 	AMONG OTHERS

Group B

Cysts of vocal chords 	Bigger polyps 	Papilloma 
Prolaps sinus Morgagni 	Sulcus vocalis 	AMONG OTHERS

Group C

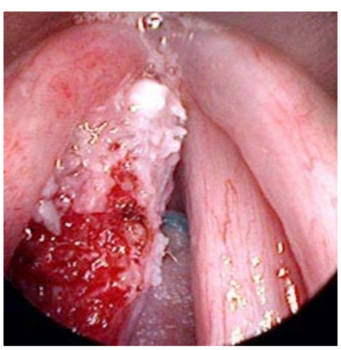
Vocal cord cancer 	Vocal chord paralysis (one sided/ double) 	AMONG OTHERS

Table 1

The tables shows our normal materials for clinical use in our laboratory of physiological and acoustical measurement (7).

18 healthy amateur female singers and 12 healthy amateur male singers between 20 and 40 years of age were analysed in a stratified cohort study. The 18 female and 12 male amateur singers had normal video stroboscopies and high speed films: The mucosa representing normality and no reactions of e.g. infections, allergies and others.

The arytenoid regions without any oedema or other reactions e.g. related to the swallowing process.

Multi-Dimensional-Voice-Program

The Multi-Dimensional-Voice-Program combined with video stroboscopy (MDVP) by the firms Key Elemetrics and Laryngograph were used :

A sustained note 'ah' and reading of a standard sentence: -' the blue spot is on the key again', and the story: 'the Northern wind and the Sun', respectively. Jitter and shimmer were measured for the sustained notes. Mean fundamental frequency, frequency- and intensity- variation percent were measured for the sentence.

For the firm Key Elemetrics also harmonics to noise ratio and degree of voicelessness were measured, and for the firm Laryngograph, also glottal closed phase (Qx%) of the electroglottogram (EGG), and cohesion factor (irregularity)% of the fundamental frequency and the EGG.

Rutine measures were made of phonation time, maximal and minimal tone ranges.

Long term average spectrograms (LTAS)

LTAS measurements up to 11.000 Hz were made with Laryngograph equipment. Calculations of harmonics were made.

Phonetograms

Phonetograms included calculations of the lowest note, the highest note, maximal dynamics and calculation of area of voicing in semitones times decibels (dB(A)).

Airflow measurements

Airflow measurements were made for sustained notes and consonant/vowels (Aerophone and Aerophone II by F J Electronics and Key Elemetrics) lung volume, peak flow, mean flow rate, phonation times, as well as the parameters of adduction/abduction rates pr second as an indication of the vocal fold movements pr second, and target flow rate parameters of the mid 50% of the sampled values measured during the loudest 6dB.

High speed digital imaging (HSDI)

HSDI based on the apparatuses by the firm Wolf, Germany, included qualitative measurements of kymography, acoustical curve and FFT up to 2000Hz. Quantitatively, the opening phase between the vocal cords in front, middle and rear parts and area opening was made based on segmentation calculation in % between the vocal cords. Supplementary EGG were made on line, but till now no on line quantitative measures can be presented of comparison of the EGG and the acoustical curves.

Standard deviations

Standard deviations and ranges were made. Multivariate correlations by pair were made and significance probabilities more than 0,5 were included. One way analysis of power (dB) was made by gender with summery of fit. A model for spectrograms of polynomial fit degrees = 5 was used for the variety fit of power (dB) by frequency (Hz) for sustained notes. For spectrograms of reading of a text the polynomial fit degree = 6 was used for bit variety fit of power (dB) by frequency (Hz). The statistics were made in a frequency area from 0-11.000 Hz and in 3 sub groups of frequency of 200-800 Hz, 2300-2700 Hz and 9.500-11.000 Hz. (SAS institute program, JMP 7 used in the clinic).

Airflow

Standard set-up for clinical use in ear, nose, throat clinics

The mean flow rate, vital capacity, peak flow and phonation times in 12 normal Danish males and 18 females between 20-40 years of age, on a sustained tone. The average mean flow rate showed a difference between males (204 ml pr. second) and females (178 ml pr. second).

	Average	Range		S.D.
		Lowest	Highest	
MEAN FLOW RATE ml pr second				
Male	0,204	0,031	0,527	
Female	0,178	0,106	0,318	
VITAL CAPACITY				
Male	5,138	3,460	8,876	
Female	3,723	2,615	4,219	
PEAKFLOW litres pr second				
Male	10,993	8,880	19,920	
Female	7,366	5,560	8,840	
Phonation time (in Aerophone)				
Male	15,0	5,6	23,4	4,6
Female	18,0	9,0	26,8	4,9

Table 1

Jitter and Shimmer

on sustained notes for 4 seconds, by MDVP and Laryngograph Ltd. The results of the two firms were correlated.

	Average	Range	
		Lowest	Highest
Average Fx (Sust.note)			
Male	140,048	116,040	169,400
Female	272,371	206,620	308,600
Jitter (Sust.note)			
Male	0,320	0,200	1,080
Female	0,541	0,140	2,080
Shimmer (Sust.note)			
Male	7,116	3,090	17,540
Female	8,227	2,010	18,690

Table 2

Frequency and intensity variation during reading

Frequency and intensity variation in percent during reading of a standard text, the Northern wind and the Sun.

	Average	Range	
		Lowest	Highest
Average Fx (Speech)			
Male	127,898	106,560	171,050
Female	227,405	198,260	262,700
Irregularity of frequenzy (Hz,Speech)			
Male	5,469	3,040	6,770
Female	5,448	2,620	7,550
Irregularity of intensity (dB,Speech)			
Male	18,047	13,950	20,900
Female	13,389	11,460	17,030

Table 3

No significant difference was found for fundamental frequency, frequency and intensity variation in reading and for a sustained note for the firms Key Elemetric and Laryngograph. The use of the term jitter and shimmer in reading of a standard text should instead in the future be replaced by frequency and intensity variation during reading, in percent.

Harmonics to noise and degree of voicelessness

Measures were made with the MDVP program, ranges and standard deviations.

	Average	Range		S.D.
		Lowest	Highest	
Harmonics to noise ratio				
Male	0,40	0,23	0,91	0,18
Female	0,37	0,21	0,860	0,220
Degree of voiceless ness				
Male	56,0	22,640	91,340	13,600
Female	66,0	25,260	86,900	18,100

Table 4

Laryngographic (EEG) measured closed phases (Qx%)

of the vocal cords on sustained tones /ah/ in on a comfortable tone in the speaking area for 4 seconds and during reading of the standard text.

	Average	Range	
		Lowest	Highest
Average Qx (Sust. note)			
Male	47,944	39,9	63,33
Female	46,032	37,65	60,94
Average Qx (Speech)			
Male	51,248	46,07	58,55
Female	49,239	39,99	57,46

Table 5

Cohesion factors of irregularity percents

With the Laryngograph Ltd. set-up, a calculation is made for a sustained tone /ah/ on a comfortable speaking level and during the reading of a standard text, and for fundamental frequency (Fx irregularity%) and EEG closed quotient percents (Qx irregularity%).

	Average	Range	
		Lowest	Highest
Cohesion factor % Fx (Sust. Note)			
Male	0,788	0,220	4,060
Female	0,415	0,090	1,000
Cohesion factor % Fx (Speech)			
Male	19,518	6,410	71,490
Female	8,525	7,360	14,890
Cohesion factor % Qx (Sust. Note)			
Male	7,987	0,400	31,030
Female	25,218	0,460	60,730
Cohesion factor % Qx (Speech)			
Male	40,209	28,350	82,010
Female	33,211	3,790	63,770

Table 6

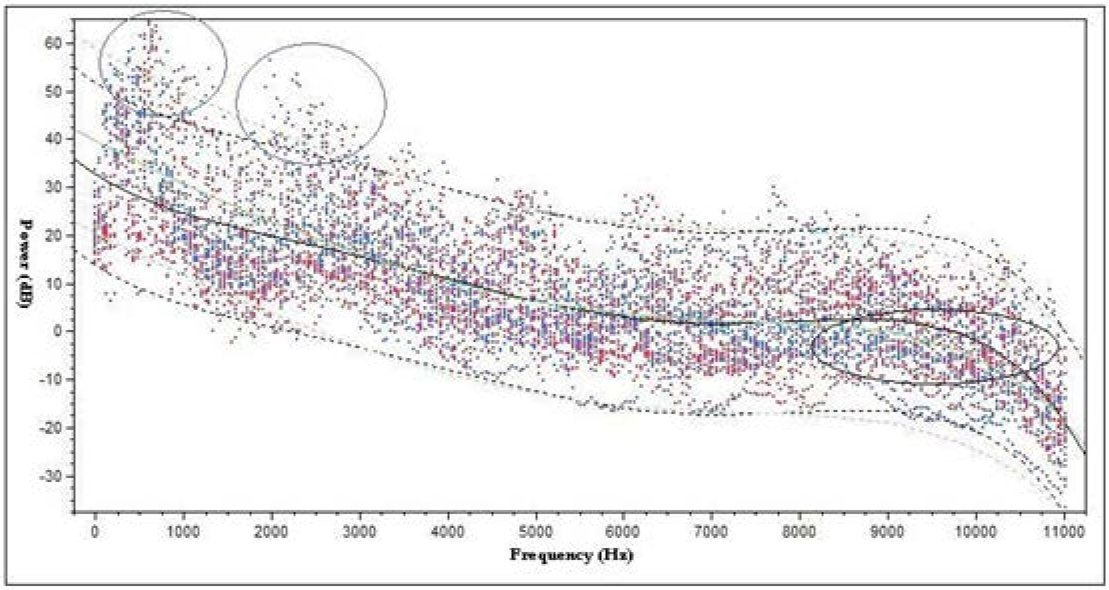
New set- up for medical, clinical use includes

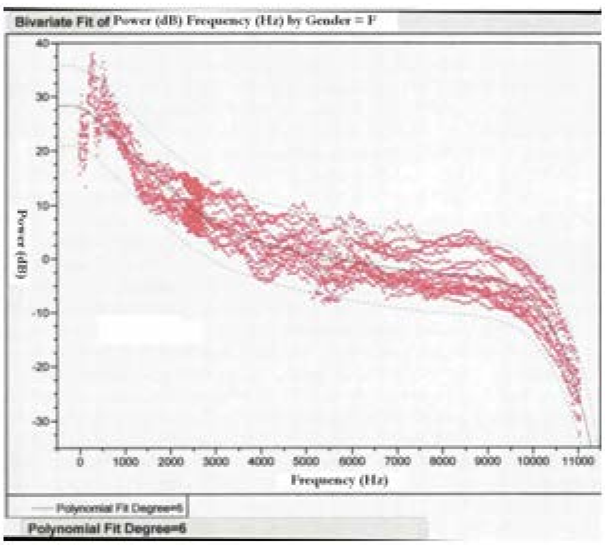
Long Time Average Spectrograms (LTAS) sustained tones

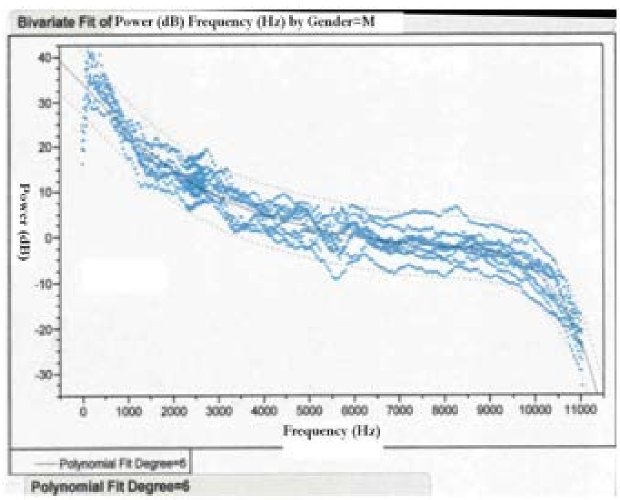
The LTAS results had significant different results of harmonics between males and females. The differences were found specifically at the areas 200-800 Hz, 2300-2700 and 9500-11000 Hz.

Sustained tones for 4 seconds of both males and females are presented in polynomial fit degree=5 areas are marked from 200-800, 2300-2700 and also 9500-11000.

With one way analysis of power by gender, a difference was found between resonance power, better for males at the area 200-800 Hz (40 versus 34 dB). At the area between 2300-2700 (23 versus 20 dB) the resonance power was also better for males.







Statistics showing LTAS calculations of gender differences between 9500 and 11000 Hz

At 9500-11000 Hz there was a slightly better result of intensity for females. Measurements from 9500-11000 Hz were also based on a polynomial fit degree=5 of sustained tones

Phonetograms

The calculated results were presented for phonetograms of the lowest tones, 87 Hz for males and 160 for females respectively, the highest tones, 716 and 1084 Hz, the maximal dynamic area 32 dB and 37 dB and the total area in semitones times decibels 714 for males and 822 for females. Ranges were also presented as well as standard deviations.

	Average	Range		S.D
		Lowest	Highest	
Lowest tone				
Male	87	73,4	98	31
Female	160	131	220	33
Highest tone				
Male	716	622	880	154,8
Female	1084	1568	1245	204,3
Maximal dynamic range				
Male	32	24	57	8,4
Female	37	20	41	9,01
Total area in semitones times decibels				
Male	714	406	1054	202
Female	822	432	1047	214

Table 7

Other airflow parameters

Some of the important airflow parameters based on the Aerophone II by FJ Electronics included abduction/adduction rate of the vocal cords in movements per second measured during voicing of a?a?a?a? as fast as possible. Another new measure is the target air flow rate: the average airflow rate of the mid 50% of the sampled flow values, measured during the loudest 6 db of the SPL curve, and real air pressure in cm water. The target flow rate was 0.24 in males and 0.17 ml per second in females. The adduction / abduction rate in males 8, 41 and in females 7.59, the real air pressure in males 8, 30 and in females 7, 83 cm H2O. Ranges and standard deviations were given.

	Average	Range		S.D
		Highest	Lowest	
Adduction –Abduction rate				
Male	8,41	11,87	5,64	1,70
Female	7,59	10,37	5,1	1,56
Target flow rate (l/sec)				
Male	0,24	0,45	0,17	0,117
Female	0,17	0,21	0,08	0,05
Target SPL (dB)				
Male	82,00	89,26	77,28	3,80
Female	79,43	87,12	70,86	6,36
Real air pressure (cmH2O)				
Male	8,30	12,22	5,15	2,23
Female	7,83	9,96	4,034	1,64

Table 8

High speed films

The open quotients of the high-speed films were calculated in % on segmentation, in front, centre and rear as well as the area of the general open phase, using the equipment and software from the firm Wolf. In front the open quotients were 0, 45 and 0, 48 in males and females respectively, in the centre 0, 51 and 0, 58 and rear 0, 59 and 0, 48. The open areas between the vocal cords were in males 0, 60 and in females 0, 68. Ranges and standard deviations were given.

	Average	Range		S.D.
		Lowest	Highest	
Open quotient front				
Male	0,45	0,14	0,92	0,32
Female	0,48	0,37	1,60	0,49
Open quotient centre				
Male	0,51	0,09	1,0	0,27
Female	0,58	0,12	1,0	0,29
Open quotient rear				
Male	0,59	0,07	0,99	0,32
Female	0,48	0,00	1,00	0,31
Area between vocal cords				
Male	0,60	0,04	1,0	0,43
Female	0,68	0,13	1,0	0,30

Table 9

Statistics related to the Multivariate Analysis with SAS JMP statistical program

A multivariate statistics made with SAS JMP statistical calculation showed many correlations between the new measures. The clinical value of the results is that it documents the voicing as a wind instrument, to be used in the clinical setting with patients with mucosal and neurological disorders, where the airflow regulation is compromised. 40 significant measures were calculated in this study of normal clients.

High speed digital imaging (HSDI) films e.g.:

The multivariate analysis showed in this normal material

r .8130, and p 0,0001 for HS open quotient front versus HS open quotient centre.,

r .6748, and p 0,0021 for HS open quotient front versus HS area between the vocal cords,

r .7574, and p 0,0003 for HS open quotient centre versus HS area between the vocal cords. A correlation of

r .4567,and p 0,0568 was found between the HS area between the vocal cord and the closed phase on the electroglottogram (EGG, Qx%) during reading of a standard text.

Phonetograms e.g.:

r -.6524, and p <0,0001 for the maximal dynamic range (dB) versus the phonetograms area in semitones times decibels

r -.6123, and p 0,0003 for the lowest tone (Hz) versus peak flow rate in litres/sec.

r -.5800, and p 0,0008 for the lowest tone (Hz) versus the vital capacity in litres.

r -.5743, and p 0,0017 for the highest frequency (Hz) versus the target flow rate in litres/sec.

r .3677, and p 0,0456 for the dynamic range in dB of the phonetograms versus the maximum phonation time in sec.

Aerophone II e.g.:

r .8461, and p < 0,0001 for peak flow (litre/seconds) versus vital capacity (litre)

r .5065, and p 0,0060 for max phonation (seconds) time versus mean air flow rate (litre/sec)

r .4594, and p 0,0107 for ad/abduction rate (cps) versus phonation quotient (litre/sec)

r .5027, and p 0,0123 for target flow rate (litre/second) versus target resistance

r .-3675, and p 0,0543 for ad/abduction rate (cps) versus mean flow rate (litre/sec)