Pathology of Voice-related Biomarkers in Laryngology

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Introduction

- Voice-related biomarkers are features related to the voice which have been validated and identified as associated with clinical outcomes. They can be used to diagnose a condition, grade the severity or the stages of a voice disorder, or for management and follow-up.

- For example, the auditory perceptual assessment of dysphonia and the glottic closure pattern were reported to be significant predictors of number of voice therapy sessions.
- Moreover, the hourglass glottic closure, predicted longer intervention duration in benign vocal fold lesions or laryngeal edema (Fujiki and Thibeault, 2022).

- The European Laryngological Society and the Union of the European Phoniatricians have suggested guidelines or statements for the baseline and pre- to post-treatment evaluations of voice quality (i.e. biomarkers).

- The changes in the biomarkers reported in these statements, along with examples of some other voice features in some laryngeal pathologies will be identified and explained in this presentation.

- The statements of the ELS and the UEP included:

- Perception (Grade, Roughness, Breathiness, Asthenia, and Strain).
- Videolaryngostroboscopy (mucosal wave symmetry, amplitude, morphology, and movements).
- Patient-reported voice quality assessment (30- or 10-voice handicap index),
- Acoustics (Mean F0, Jitter, Shimmer, and noise-to-harmonic ratio).

- Aerodynamics (maximum phonation time).

- Clinical instruments for comorbidities with voice disorders (**reflux symptom score**, dysphagia handicap index).

- Phonetogram (e.g., for singing students or singers with complaints in singing specially with negative stroboscopy).

- Auditory perceptual assessment is a basic and essential clinical parameter for voice assessment.

- GRBAS scale is the mild-moderate-severe grading of roughness, breathiness, asthenia and strain, in addition to the modified GRBAS scales (Kotby, 1986) including the grade**, character, pitch, register, loudness, glottal attack and comments on associated laryngeal functions (e.g., cough)** are used for diagnosis and follow up of pathological voice. Grade 0 is given in normal (non-dysphonic) voice.

- The Consensus auditory perceptual evaluation of voice (Cape-v) scale uses a 100-point scale for grading the strain, roughness and breathiness. It includes pitch, loudness, together with comments on resonance and features of voice (e.g., tremors, gurgly).

A correlation was found between the 2 scales for the assessment of voice disorders. (El-Adawy et al, 2011).

- The modified GRBAS scales (Kotby, 1986)

-The character:

It could be strained, leaky, breathy or irregular.

In hyperfunctional voice disorder where muscular tension is high, stained leaky character is usually heard.

A strained voice is often characterized by a second harmonic that is stronger than the first harmonic, with a long period of glottal closure during vibration.

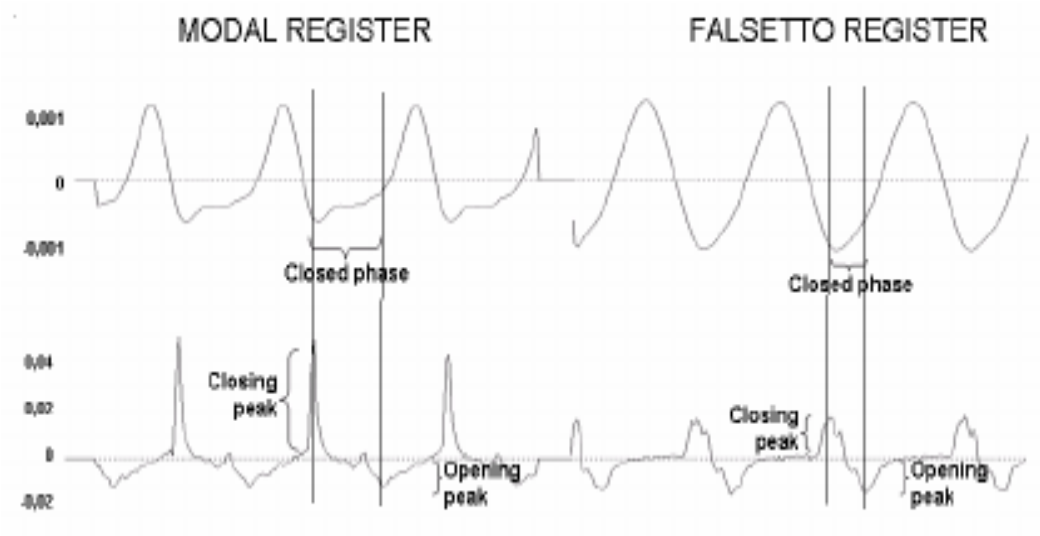
Breathy voice is commonly noticed in unilateral VF immobility or scarring (↑ size of the gap). Air escape could be associated with high subglottic pressure to increase the loudness

Irregular character could be noticed in minimal associated pathological lesions (MAPLs)[e.g., nodules, polyps, and Reinke edema], functional and organic voice disorders such as laryngeal changes in endocrine disorders (e.g., hypothyroidism). It could be heard as a result of VFs asymmetry in mass or tension. Irregularity could be observed when the cover layer stiffness is significantly reduced while maintaining the same subglottic pressure. Furthermore, a glottal gap could lead to irregular voice.

- Pitch (↑ , ↓ , diplophonic)

It could be reduced in MAPLs, diplophonic in mutational voice disorder, pitch range is reduced in thyroid gland dysfunction (Junuzović-Žunić et al., 2019)

The pitch of the voice is modulated primarily by fine changes in the tension of the vocal folds. Greater tension or stiffness in the vocal folds causes them to vibrate at a higher frequency during phonation. A reduction in the VF length leads to higher pitch (Dichter et al, 2018).



- Register

Falsetto, head, chest, modal/ breaks.

Falsetto register could be observed in some cases with unilateral VF immobility (Lundy and Casiano, 1995)

If one attempts to increase F0 by increasing CT activation alone, the vocal folds, with a small medial surface thickness, and a brief duration of glottal closure are likely to produce a falsetto-like voice production. It occurs with incomplete glottal closure and a nearly sinusoidal flow waveform, and a limited number of harmonics (Zhang, 2016).

The voice at the high end of the pitch range is often in a falsetto register.

The modal voice, which is used in conversational speech, is produced with an intermediate thickness of the vocal fold at the intermediate pitch range.

Vocal fry is produced often with increased vertical thickness and a long period of glottic closure. It occurs at the lower end of the pitch range (Zhang, 2021).

- Loudness

Reduced or fluctuating loudness is usually seen in laryngeal pathologies. For example, hyperthyroidism or hypofunctional dysphonia.

Increasing vocal intensity + ↑ subglottic pressure are associated with the high duration of the closed phase of the VF vibration cycle.

(Szkiełkowska et al., 2019)

- **Glottal attack** hard glottal attack is observed with hyperfunctional, MPLs.
- **Associated laryngeal functions** such as cough is influenced by some laryngeal lesions including disorders causing VF immobility.

- Videolaryngostroboscopy

- **Mucosal wave symmetry**

Asymmetry of the mucosal wave occurs in unilateral VF lesions including MAPLs, or in bilateral asymmetric lesions such Reinke's edema or leukoplakia.

- **Amplitude** (normal, mild, moderate, or severely decreased)

amplitude is decreased when the medial margin of VF mucosa moves laterally less than one third width of the visible portion of the VF. Reduced mucosal wave vibration were reported in MAPLs, non-organic dysphonia (e.g., hyperfunctional dysphonia), VF dehydration, VF scar, sulcus vocalis.

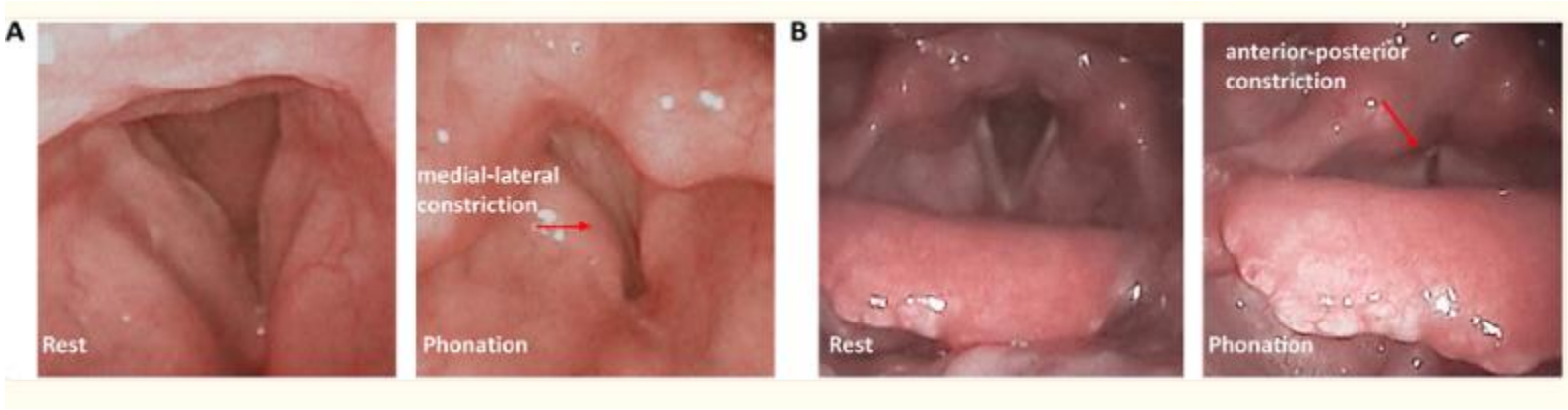
- **Morphology**

Comments on the morphology of the lesion or laryngeal disorder in essential.

For leukoplakia, non-homogenous color, irregular texture, and prominent thickness, vascularization perpendicular to the lesion& vessel loops predicted malignancy (Rzepakowska et al., 2019).

- **Movements** glottic closure (complete, posterior gap, anterior gap, hourglass, or incomplete) (Poburka and Patel, 2021)

- Sub and supra glottal compartments should be considered when voice is examined. Adduction of the supraglottal structures may lead to medial-lateral or anterior-posterior constriction of the airway immediately above the vocal folds, as often observed in muscle tension dysphonia.



- Patient-reported voice quality assessment (30- or 10-voice handicap index)

The score is high in laryngeal pathology. It was reported to improve after voice therapy measures.

- Acoustics (Mean F0, Jitter, Shimmer, and noise-to-harmonic ratio).

- **F0**

It could be reduced in many organic, MAPLs, and non-organic voice disorders or raised in other disorders (mutational).

It depends on length, depth, thickness, stiffness and stress conditions of the vocal folds. F0 increase with low length and higher stiffness and stress. F0 increase by increasing contact time of VF and higher subglottic pressure (Zhang, 2016).

- Jitter is the periodic variation from cycle to cycle (duration)

The voices of patients with pathologies often have a higher percentage of jitter.

It is affected mainly by the lack of control of vibration of the VF.

- **Shimmer** relates to the amplitude variation of the wave in the voice.

In voice disorders the percentage of shimmer increases.

The shimmer changes with the reduction of glottal resistance and mass lesions on the vocal cords and is correlated with the presence of breathiness.

- **Noise to harmonics ratio (dB)** is the ratio between the non-periodic to the periodic component of the voice. It was reported to increase in many voice disorders. Breathiness and roughness of voice were correlated with the NHR.

ELS & UEP

The following acoustic measurements should be included in the voice quality assessment of voice professionals: standard deviation of F0 (STD), range of intensity (dB), minimal intensity (dB), and maximal intensity (dB).

The acoustic parameters need to be measured on a sustained vowel /a/ considering the 3-middle sec on same dB level when the patient acts as own control, possibly also at different levels of 60, 70, and 80 dB. The microphone is at 4 cm from the mouth.

Jitter and shimmer were reported to be influenced by the intensity of voice signal, the vowel being selected for analysis, and the frequency of phonation (Brockmann-Bauser et al., 2018). Furthermore, they cannot be applied to severe dysphonic voices with high aperiodicity.

Cepstral analysis has been reported to be used to overcome these limitations of the time-based measures.

- Cepstrum

Is the Fourier transform representation of the log magnitude of the spectrum, Cepstral analysis is a measure of acoustic analysis to quantify the fundamental frequency and harmonic organization in voice (Sujitha *and* Pebbili, 2022).

Cepstral Peak Prominence (CPP) estimates aperiodicity or additive noise without the identification of cycle boundaries. Thus, can be identified in sustained vowel productions and in connected speech.

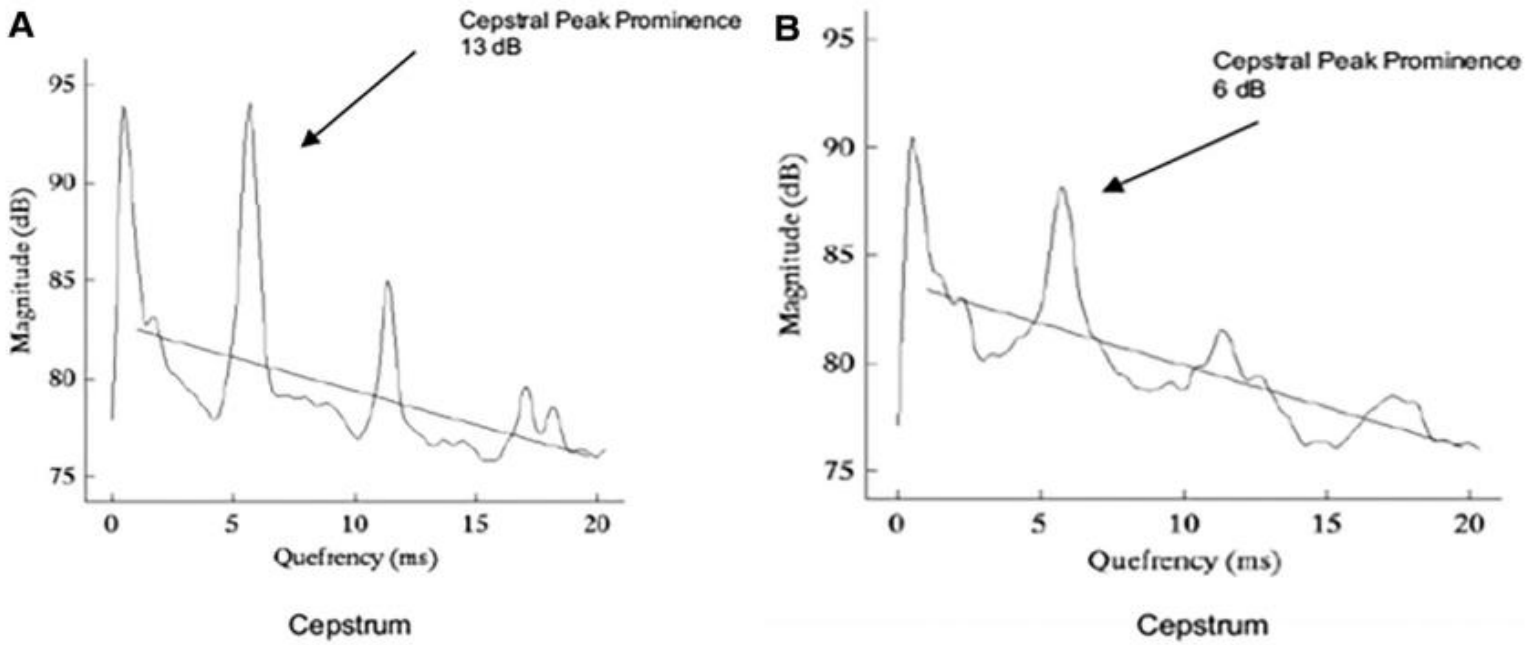


Figure : Cepstral representation in normal voice and moderately dysphonic voice

- A voice signal which is periodic will have a high-amplitude CPP (in dB).
- Low amplitude CPP represents weakly periodic or an aperiodic voice signal (Watts and Awan, 2011).

- sCPP is another advanced cepstral measure which occurs in every 2 milliseconds instead of every 10 milliseconds to reduce artifacts.

- However, Brockmann-Bauser et al. (2021) reported that CPP measure should be developed for alternative vowel types (with the same vowel used for comparison i.e. /i/ before with /i/ after). They advised to detect age changes in CPP in connected speech better than vowels.

ELS & UEP Statements

- Aerodynamics (maximum phonation time, the phonation quotient, the mean flow rate, and the subglottal pressure are the most used aerodynamics).

- **Maximum Phonation Time** (MPT) is the maximum time in seconds that a person can sustain a vowel produced in a single breath with comfortable pitch and loudness. It measures glottal efficiency by depicting the ability of the vocal folds to adduct efficiently and to vibrate through rapid opening and closing cycles. Presence of laryngeal pathologies will result in reduction of glottic efficiency hence reduced the MPT. it is used to assess simple respiratory functions and can be performed anywhere without special instruments.

Obesity affects the MPT in that as BMI increases, the MPT decreases. (Al-Yahya et al., 2022)

- Clinical instruments of comorbidities with voice disorders (dysphagia handicap index, reflux symptom score which change after medications targeting this problem). *(Lechien, 2023).

- Phonetogram or voice range profile (for singing students or singers with complaints in singing, specially with negative stroboscopy).

Patients are asked to produce maximum variations in fundamental frequency at minimum and maximum intensity levels while producing a vowel in ascending and descending pitch glides to represent the voice capacity

Improved laryngeal muscle strength and tone, as well as improved balance among laryngeal muscle effort, respiratory effort and control, might result in an increase in the vocal capacities (Am et al., 2018).

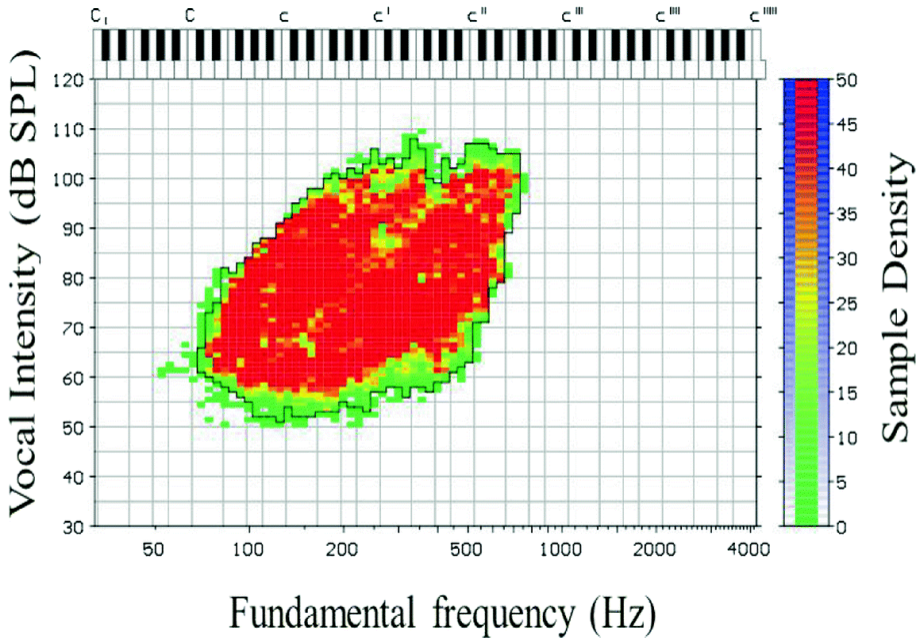


Figure: An example of phonetrogram (Jičínský and Mareš, 2019).

- Maximum Flow Declination Rate (MFDR).

It indicates the fastest rate of change of the air flow during the closing phase. It is an indirect estimate of maximum vocal fold closing velocity and possibly related to the relative magnitude of vocal fold collision forces. It is measured by flow glottogram. It has been reported to have a positive correlation with increased vocal intensity. It is also related to vibrational amplitude ratio and vocal tract inertance (Titze, 2006).

"Needs further investigations to detect its change in different laryngeal pathologies".

- **Open Quotient and Closed Quotient**

- It is the time the VFs are separated from each other divided by the duration of the whole glottal cycle. It is estimated by kymography and EGG.

The open quotient (OQ) in hypofunctional dysphonia was higher than OQ in hyperfunctional dysphonia in anterior and middle but not he posterior parts of the VF. It was observed to be high in leukoplakia. Dysphonic voice has a higher value of OQ than normal voice because of the long open phase interval.

A variation of open quotient with vocal intensity in speech and singing was reported (Bernardoni et al., 2005).

- A low closed quotient was noticed in mutational dysphonia (Szkiełkowska et al., 2019).

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Thank You
Questions and/or Discussion