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ORIGINAL SCIENTIFIC REPORT

Transcutaneous Laryngeal Ultrasonography for Laryngeal Immobility Diagnosis in Patients with Voice Disorders After Thyroid/Parathyroid Surgery

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Abstract

Background Transcutaneous laryngeal ultrasonography (TLUS) was recently developed to assess recurrent nerve palsy after thyroid/parathyroid surgery, with variable rates of efficiency. The aim of the current study was to evaluate this technique using subjective estimation and post-processing quantitative data.

Methods Fifty subjects presenting with a recurrent nerve palsy and 50 "controls" presenting with voice, swallowing, or breathing disorders following thyroid/parathyroid surgery were prospectively included. All of them underwent a flexible laryngoscopy, considered the gold standard, and a ten-second TLUS clip within the 10 days following surgery. In addition to the subjective interpretation of vocal fold motion, two quantitative criteria taking into account motion symmetry (symmetry index, SI) and amplitude (mobility index) of the two hemi-larynges were defined on TLUS acquisitions in adduction and abduction.

Results The subjective interpretation provided a sensitivity of 100% and a specificity of 96%, compared to the gold standard. The quantitative criteria provided a sensitivity and specificity of both 82%, when based on SI solely. When combining SI and mobility index, the sensitivity reached 94%, but the specificity fell to 66%.

Conclusions Visual assessment of recurrent nerve palsy using TLUS after thyroid/parathyroid surgery appeared a high sensitive and specific test compared to flexible laryngoscopy. Quantitative criteria are promising and need to be refined to better describe the whole TLUS video clip.

Introduction

Thanks to improvements in imaging technologies, some organs that were initially not considered areas of expertise of specific techniques are now being explored more

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thoroughly. Two-dimensional (2D) ultrasound imaging for the visualization of the laryngeal tract is a good example of this widening utilization. Indeed, transcutaneous laryngeal ultrasonography (TLUS) used to analyze airway vocal fold anatomy and motion has been on the rise from 2010 [1–3]. A recent study shows its potential in detecting recurrent nerve palsy before thyroidectomy [4]. Compared to other imaging techniques (CT, MRI), TLUS has the advantage of a lower cost, an easy use at patient's bedside especially in intensive care units, and the capacity of real-time motion analysis during breathing or phonation thanks to high temporal resolution [5–8]. TLUS is now acknowledged as an interesting tool to explore the airways during the perioperative period, in case of emergency and in critical care settings [9]. However, to date, the sensitivity, specificity, positive and negative predictive values of TLUS for detecting vocal fold motion impairment, difficult preoperative airways, or predicting post-extubation stridor are highly variable among studies [10, 11].

In the present study, we focused on the capacity of TLUS to diagnose laryngeal motion impairment. Indeed, while TLUS seems easily accessible to non-specialists [12], there is still debate to determine whether it is an accurate and reliable tool in the detection of recurrent nerve palsy, in either the pre- or postoperative period of thyroid surgery [13–16]. For example, Wong and al [13] found that the postoperative sensitivity, specificity, positive predictive value, and negative predictive value of TLUS in detecting abnormal laryngeal motion were 93.3, 97.8, 77.8, and 99.4%, respectively, while Borel et al. [16] described a sensitivity of 33%, a specificity of 95%, a positive predictive value of 42%, and a negative predictive value of 89% for the postoperative diagnosis of the same pathology. These results are questionable. An important factor of discrepancy, apart from the type and generation of US scanner, may be the technique used to assess laryngeal motion. Indeed, the authors used different anatomical landmarks such as the false vocal folds, the true vocal folds and/or the arytenoids [1, 2, 17, 18], different acquisition planes [19] (axial or lateral view), and different testing conditions [7] (free breathing, phonation, Valsalva maneuver). Another parameter that is not controlled for in many of the studies cited before is the way mobility is assessed. Most of the time, the operator describes his/her subjective impression of motion, with good correlation rates with clinical assessment by flexible laryngoscopy in some cases [13]. Thus, to question whether this variability factor could be controlled for, we have recently published objective and quantitative measures of the laryngeal tract motion in healthy subjects using TLUS [20], based on a dedicated home-made software [21]. An axial plane was used to define three landmarks (the two arytenoids and the most anterior and medial part of the thyroid cartilage, see Methods) during free breathing. We were able to distinguish abduction from adduction movements, and showed that each hemi-larynx was symmetrical in size (comparison of hemi-surfaces) during these movements. We then hypothesized that a difference in surface for a same individual would predict a unilateral vocal fold paralysis.

The aim of the present study was, therefore, to test the software using subjective evaluation and, objective and quantitative measures of the laryngeal tract motion in a population operated on for thyroid/parathyroid surgery and see how accurate this tool was to predict unilateral vocal fold paralysis. We predicted that in case of unilateral recurrent nerve lesion (RNL), the surface of the immobile side would not vary between adduction and abduction and that a difference could be observed between the right and left sides.

Materials and methods

This prospective trial was approved by the local Institutional Review Board for Protection of Human Subjects, Comité de Protection des Personnes (CPP), Paris VI, as a noninvasive study that did not modify the usual perioperative follow-up of patients.

Subjects

From November 2012 to September 2013, adult patients who consulted in the Endocrine surgery department, Pitié-Salpêtrière Hospital, Paris, France for thyroid (total thyroidectomy or lobectomy, with or without lymph node dissection) or parathyroid surgery were informed of the research protocol and received a formal notice. For those who accepted, subjects gave their written consent during the preoperative assessment. It was verified that patients did not present with preoperative dysphonia or any other clinical sign of laryngeal immobility. Those who had had previous cervical dissection or any suspicion of voice disorder performed a systematic preoperative vocal fold examination (flexible laryngoscopy). Any abnormal motion was considered an exclusion criterion. Postoperatively, only patients who presented with swallowing disorder, dyspnea, hoarseness and/or dysphonia ($n = 100$), and for whom the larynx was not ossified (see Methods) were finally included in the present study.

Double-blind assessment of vocal fold mobility

After a maximum of 10 days after surgery, all included patients saw an ENT specialist who performed a flexible laryngoscopy in order to explain their symptoms, and underwent a TLUS during their postoperative hospital stay, between Day 1 and Day 2, performed by an independent operator (see below for acquisition methods). The two practitioners were not aware of the results of each examination; both gave their subjective qualitative impression of laryngeal immobility/mobility. Cases of paresis (limited abduction and adduction, without full paralysis) assessed by flexible laryngoscopy were excluded. To serve our purpose of testing the sensitivity/specificity and validity of our new tool, only cases of total immobility were included in this first series, similarly to other studies on the same subject.

An external examiner collected the subjective assessments and placed on the acquired TLUS loops three laryngeal landmarks to be used by the dedicated software to measure laryngeal surfaces (see paragraph below). According to the results of the flexible laryngoscopy, considered the gold standard for RNL diagnosis [22], patients were prospectively included into two groups of 50 subjects each: (1) with a recurrent nerve lesion (RNL+) and (2) with no laryngeal immobility (RNL−). Non-US assessable vocal tracts (Fig. 1) were excluded. It concerned 16 cases (14%), all were men (mean age 57 ± 15 years), nine of them presented with a RNL+. As already reported [23, 24], these cases were in relation with thyroid cartilage calcification.

Translaryngeal ultrasonography acquisition, definition of landmarks and objective measures

The TLUS was performed by a surgeon, using a portable machine, SonixTouch® (UltraSonix™, Richmond, BC, Canada) with a 7–14-MHz linear probe. The acquisition protocol was the same as that described in Bergeret-Cassagne et al. [20]. In brief, subjects were lying on the back, neck slightly extended, with the probe placed over the laryngeal prominence of the thyroid cartilage, including the arytenoids in the axial view. The images were acquired in B-mode, during normal breathing at rest. Typical values for acquisition were: frequency 10 MHz, depth of field of view 4 cm, mechanical index 0.6, gain 45%, and dynamic range 85 dB. A video clip of 10 s (30 images per second) was then recorded in order to include one complete respiratory cycle at least. Two images corresponding to physiological abduction and adduction during the same breath cycle were selected. The three following landmarks were placed (Fig. 2): The first landmark corresponded to the anterior insertion (A) of the two vocal folds on the thyroid cartilage, and the two other landmarks to the center of the right (R) and left (L) arytenoid cartilages. The left and right surfaces (S_L and S_R) corresponding to the areas of each hemi-larynx defined by the bisector of the angle RAL were measured on each image (in abduction and adduction). From these measurements, a symmetry index (SI) was defined as the mean value of the standardized surface differences in abduction (S^{ab}) and adduction (S^{ad}):

$$SI = \tfrac{1}{2}\left[\left|{S_L}^{ab} - {S_R}^{ab}\right|\left({S_L}^{ab} + {S_R}^{ab}\right) + \left|{S_L}^{ad} - {S_R}^{ad}\right| / \left(S_L^{ad} + S_R^{ad}\right)\right]. \quad (1)$$

Furthermore, left and right mobility fraction indices were defined as the relative variation of area between abduction and adduction, and the lowest value between left and right mobility fraction indices was defined as the lower mobility index (LMI):

$$LMI = \mathrm{Min}\left[\left({S_L}^{ab} - {S_L}^{ad}\right)/{S_L}^{ab}, \left({S_R}^{ab} - {S_R}^{ad}\right)/{S_R}^{ab}\right]. \quad (2)$$

The dedicated software [20, 21] calculated SI and LMI automatically.

Quantitative criteria to define RNL

In a previous study based on different subjects, we showed in 50 healthy volunteers that standardized surface differences in abduction (S^{ab}) and adduction (S^{ad}) were close to zero [20] because of a symmetrical functioning of both hemi-larynges, and that SI was lower than 10% in 46 cases over 50. Thus, we first tested the criterion SI > 10% as an indicator of RNL+. To increase the sensitivity of RNL+ detection, LMI < 10% was added as a second criterion.

Statistical analyses

Data analysis was conducted using JMP® statistical software (SAS institute, Cary, NC, USA). Mean values and

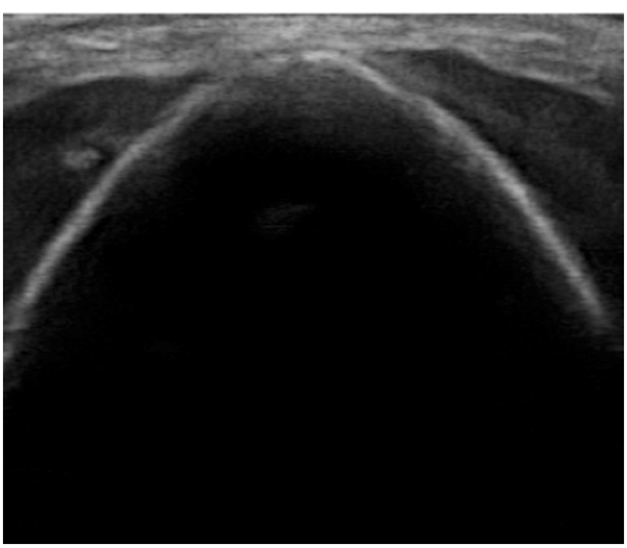

Fig. 1 Translaryngeal ultrasound image for which the vocal tract is not seen due to cartilage ossification

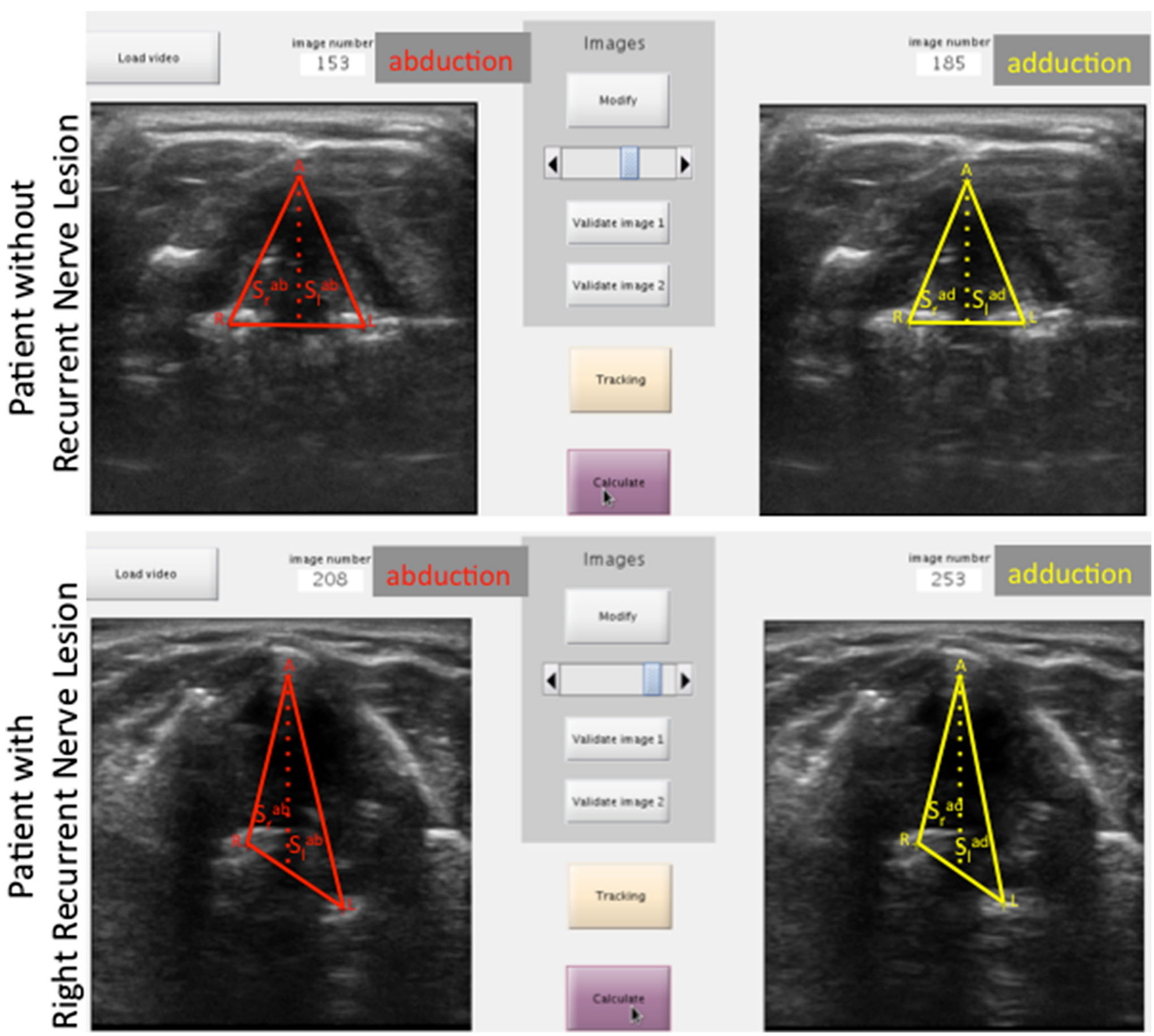

Fig. 2 Illustration of quantitative indices from translaryngeal ultrasound images. Left panel: abduction images and selected points of interest (thyroid cartilage A, left arytenoid L, and right arytenoid R) resulting in S_L^{ab} and S_R^{ab} areas. Right panel: adduction images and selected points of interest resulting in S_L^{ad} and S_R^{ad} areas. Upper row: patient without recurrent nerve lesion, SI = 2.5%, LMI = 15%. Lower row: patient with recurrent nerve lesion, SI = 22%, LMI = 4%

standard deviations were computed for each group (RNL+ and RNL−) and were compared using Student's *t* tests.

Results

Subjects

The surgical procedures performed are detailed in Table 1. Mean age (52 ± 15 years for the RNL+ group, 51 ± 13 years for the RNL− group) and body mass index (24.5 ± 4.1 for the RNL+ group, 24.3 ± 4.6 for the RNL− group) were not statistically different between the two groups. Gender repartition (M/F) was 4/46 for the RNL+ group and 2/48 for the RNL− group.

Diagnosis of RNL: flexible laryngoscopy versus TLUS subjective visual assessment

Table 2 shows the confusion matrices of RNL assessed by flexible laryngoscopy and TLUS. This table shows that TLUS subjective visual assessment described two cases of

Table 1 Surgical procedures ($n = 100$)

Surgical procedure	Patients (n)
Total thyroidectomy	59
Total thyroidectomy and lymph node dissection	27
Lobo-isthmectomy	9
Parathyroid surgery	5

Table 2 Confusion matrix between flexible laryngoscopy (FL) and translaryngeal ultrasound visual assessment (TLUS-VA) for positive (RNL+) and negative (RNL−) recurrent nerve lesions

	RNL+ using TLUS-VA	RNL− using TLUS-VA
RNL+ using FL	50	0
RNL− using FL	2	48

recurrent nerve lesion that were not according to the flexible laryngoscopy. They were two false-positive cases. Consequently, TLUS subjective visual assessment of RNL provided a sensitivity of 100% and a specificity of 96%, a positive predictive value (PPV) of 96% and a negative predictive value (NPV) of 100%.

Diagnosis of RNL: flexible laryngoscopy versus TLUS quantitative criteria

The mean symmetry index (SI) was significantly larger in the RNL+ group compared to the RNL− group (20.4% ± 13.8% vs 6.7% ± 4.7%, $p < 0.0001$). The mean lower mobility index (LMI) was significantly smaller in the RNL+ group (2.2% ± 17.4% vs 20.5% ± 14.8%, $p < 0.0001$).

Tables 3 and 4 show the confusion matrices of RNL assessed by flexible laryngoscopy and TLUS quantitative measures. Table 3 shows that using SI with a cutoff value of 10% (SI > 10%) alone led to nine false-positive cases and nine false-negative cases providing a sensitivity of 82%, a specificity of 82%, a PPV of 82%, and a NPV of 82%.

When combining SI > 10% and LMI < 10%, the number of false-positive cases increased to 17, but the number of false-negative cases ($n = 3$) was low (Table 4). The detection of RNL then reached a sensitivity of 94%, a specificity of 66%, a PPV of 73% and a NPV of 92%.

Table 3 Confusion matrix between flexible laryngoscopy (FL) and the symmetry index calculated from TLUS (TLUS-SI) for positive (RNL+) and negative (RNL−) recurrent nerve lesions

	RNL+ using TLUS-SI	RNL− using TLUS-SI
RNL+ using FL	41	9
RNL− using FL	9	41

Table 4 Confusion matrix between flexible laryngoscopy (FL) and the combined use of the symmetry index (SI) and the lower mobility index (LMI) for positive (RNL+) and negative (RNL−) recurrent nerve lesions

	RNL+ using TLUS-SI/LMI	RNL− using TLUS-SI/LMI
RNL+ using FL	47	3
RNL− using FL	17	33

Discussion

Voice disorders after thyroid/parathyroid surgery are quite common, as they may concern up to 50% of patients [25, 26]. They significantly impact professional or personal quality of life in 25% of cases [26]. Among the main etiologies, nerve lesions regrouping injury to the external branch of the superior laryngeal nerve or to the recurrent nerve are the most frequent [27–30]. While the diagnosis of superior laryngeal nerve palsy is difficult [31, 32], laryngeal immobility secondary to recurrent nerve paralysis is easily detected by observing the mobility of the vocal folds with a flexible laryngoscope. This latter examination has been considered the gold standard to assess RNL, allowing for 99% of diagnoses [33]. However, when practiced by non-trained specialists, this examination can be sensed invasive and painful [34].

Thanks to advances in imaging technologies and in particular in TLUS, high temporal resolution and real-time motion analysis of the vocal tract during breathing or phonation are now possible [5–8, 24]. TLUS offers lower cost, availability at bedside, noninvasiveness, and innocuousness compared to other techniques [3]. It has consequently gained an increased interest in RNL detection after thyroid surgery. Indeed, the technique seems quite accessible for non-radiologists, with a fast learning curve of 10–20 examinations [12]. However, the reliability of this technique in determining RNLs is still questioned, with teams recommending TLUS as a valuable alternative to flexible laryngoscopy [13, 14] and others advising against it in the pre- and postoperative period, even when performed by radiologists trained in the USA [15, 16].

To rule out confounding factors such as training, operator skills, subjectivity, and try to answer the question of statistical power of TLUS in assessing RNL, we developed a dedicated software. This software only requires indicating three landmarks on an axial B-mode plane: the two arytenoids and the most anterior and medial part of the thyroid cartilage, during free breathing [21]. Identification of motion features (in adduction and abduction) is then automatized. This tool was initially validated in a sample of fifty healthy subjects and provided three main results: (1) the larynx opens and closes symmetrically (no significant surface difference between two triangles defining each hemi-larynx), (2) abduction and adduction were always discernable, and (3) trained and non-trained operators obtained similar results, proving reduced inter-operator variability [20].

The present study tested this new tool in a series of subjects presenting with RNL assessed by flexible laryngoscopy. Only total immobility of the vocal folds was considered valid, limited movements (paresis) reported by the ENT specialist were excluded from this study, as TLUS needs to be first validated in true paralyses. Subjective interpretation of vocal fold motion and two quantitative criteria were compared to validate TLUS accuracy in RNL diagnosis just after surgery. The studied population was recruited on immediate postoperative dysphonia in order to increase the possible number of RNLs, and to avoid bias: The practitioner performing the TLUS could not suppose the result by just hearing the patient's voice. The strengths of our results also rely on systematic flexible laryngoscopy for all included subjects, similar conditions of testing as all assessments were performed before the tenth day following surgery [35], and an important number of RNL cases ($n = 50$, similar to $n = 44$ in Wong et al. [12] and $n = 53$ in Wong et al. [35].

With the proposed TLUS acquisitions using normal breathing conditions, the subjective evaluation of RNL reached a sensitivity of 100% with only two false-positive cases. These latter could be explained by the mild amplitude of adduction–abduction in breathing at rest. Our excellent sensitivity may be explained by the short delay of maximum 2 days between surgery and TLUS. The specificity rate could thus be optimized using either Valsalva or phonation maneuvers [7]. The same assessment obtained poor sensitivity rates in other hands presumably because true vocal folds were tracked [16] while they are difficult to identify and follow by US examination. Indeed, as previously published by our group [20] and others [18, 36], arytenoid cartilages are reliable landmarks to assess vocal fold motion. In our sample, the laryngeal tract was not US accessible in men only (14% of all subjects). Because thyroid surgery concerns mainly women (81% in our series), this issue of thyroid cartilage calcification is relative compared to other neck surgeries. This practical limitation should be further investigated to increase the usefulness of the technique.

Sensitivities and specificities for RLN diagnosis were lower when quantitative indices were tested (sensitivity and specificity of 82% for SI alone, and sensitivity of 94% and specificity of 66% for SI and LMI associated). This discrepancy with the visual subjective findings could be explained by several factors. Indices were based on two frozen pictures from the video loop. These pictures, representing the arytenoid cartilages in their extreme abduction and adduction positions, were freely chosen by the observer. Results could be improved by including more frames based on a real-time motion tracking system. Moreover, when combining the two indices, SI and LMI, the sensitivity reached 94% and was significantly increased ($p = 0.04$, MacNemar's test), suggesting that to improve the automatic detection of RNL, it would be necessary to extend the number of studied criteria. Future work will address these issues to offer an automatic diagnosis of RNL.

Conclusion

TLUS subjective visual analysis of laryngeal motion in patients presenting with post-thyroidectomy/parathyroidectomy voice disorders is a successful tool to detect patients with recurrent nerve palsy, when arytenoids are taken as landmarks. This assessment requires a short but certain learning curve. Automated symmetric and mobility indices are promising even if they were not sufficient to replace an expert in the diagnosis and follow-up of patients. Next steps will focus on the refinement of quantitative automatically computed indices to improve their sensitivity and specificity rates.

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Compliance with ethical standards

Conflict of interest Dr. Frouin, Dr. Bergeret-Cassagne, Dr. Russ, and Pr. Tresallet indicate that they are co-inventors of a patent entitled "Procédé de traitement d'images en vue de déterminer un degré de mobilité des cordes vocales," Application WO2015173109A1.

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