

# Eucapnic voluntary hyperpnoea and exercise-induced vocal cord dysfunction

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**To cite:** Turmel J, Gagnon S, Bernier M, *et al.* Eucapnic voluntary hyperpnoea and exercise-induced vocal cord dysfunction. *BMJ Open Sport Exerc Med* 2015;**1**:e000065. doi:10.1136/bmjsem-2015-000065

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjsem-2015-000065>).

Accepted 17 November 2015

## ABSTRACT

**Introduction:** Exercise-induced bronchoconstriction (EIB) is a common condition in endurance athletes. Exercise-induced vocal cord dysfunction (EIVCD) is a frequent confounder of EIB. The diagnosis of EIVCD may be challenging and can be missed as the problem is often intermittent and may only occur during intense exercise. Eucapnic voluntary hyperventilation (EVH) is the best test to detect EIB. This pilot study aimed to assess if EVH could be helpful in the diagnosis of EIVCD associated or not to EIB in athletes.

**Methods:** A nasolaryngoscopy was performed during a 6 min EVH test, in 13 female athletes suspected to have VCD, aged 21±7 years. Image analysis was conducted by two Ear Nose and Throat surgeons in random order.

**Results:** During the EVH, three athletes showed incomplete paradoxical vocal cords movement, without inspiratory stridor. However, 12 athletes showed marked supraglottic movement without inspiratory stridor. In two athletes, this supraglottic movement was severe, one showing a marked collapse of the epiglottis with an almost complete obstruction of the larynx by the arytenoid cartilage mucosa. In 3 of the 12 athletes with supraglottic movement, severe vibration of the mucosa covering the arytenoid cartilages was also observed.

**Conclusions:** EVH challenge in athletes can provide information on various types of glottic and supraglottic obstruction in reproducing laryngeal movements during hyperventilation. Our findings make us suggest that exercise induced upper airway obstructions should be named: Exercise-induced laryngeal obstruction (EILO). Then, EILO should be divided in three categories: supraglottic, glottic (EIVCD) and mixed (glottic and supraglottic) obstruction.

## BACKGROUND

Endurance athletes frequently report exercise-induced respiratory symptoms and show a high prevalence of exercise-induced bronchoconstriction (EIB).<sup>1–4</sup> EIB is described as a transient narrowing of the airway during or, most often, after exercise.<sup>5–7</sup> Symptoms of EIB may include dyspnoea, phlegm production, chest tightness, shortness of breath, wheezing and cough. However, other clinical entities can produce similar symptoms.<sup>8 9</sup>

## Summary box

- The eucapnic voluntary hyperventilation challenge in athletes can provide information on various types of glottic and supraglottic obstruction in reproducing laryngeal movements during hyperventilation.
- The supraglottic movement induced by hyperventilation can be severe in some athletes, showing a marked collapse of the epiglottis with an almost complete obstruction of the larynx by the arytenoid cartilage mucosa.
- Exercise-induced laryngeal obstruction should be divided in three categories: supraglottic, glottic (exercise-induced vocal cord dysfunction) and mixed (glottic and supraglottic) obstruction.

Exercise-induced vocal cord dysfunction (EIVCD) is a frequent confounder of EIB. EIVCD is the most common cause of upper airway obstruction during exercise.<sup>10 11</sup> It may present either as an abnormal adduction of vocal cords, during inspiration or early expiration. Symptoms of EIVCD are often intermittent, but recurrent and include sensations of throat tightness, inspiratory stridor, cough and/or choking.<sup>12</sup> It frequently presents itself as a noisy breathing and dyspnoea that occur at any level of exertion and symptoms are characterised by sudden onset and rapid resolution with the exercise cessation. Contrary to asthma, EIVCD has no refractory period and some athletes can experience repeated episodes immediately on restarting physical activity.<sup>13</sup>

A prevalence of EIVCD ranging from 5 to 27% in patients referred for exercise-induced dyspnoea has been reported<sup>14–17</sup> and a similar incidence was reported among athletes.<sup>10 18–24</sup> EIVCD is often associated with EIB (>50%)<sup>25 26</sup> and mostly occurs in adolescents<sup>11</sup> and young adults (20–40-years-old), with a predominance in females.<sup>16 17 25</sup> EIVCD does not seem sport-specific,<sup>13</sup> but tends to be more common in athletes participating in outdoor (8.3%) than indoor sports (2.5%).<sup>27</sup>



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The aetiology of EIVCD is unclear. It may be associated with chronic rhinosinusitis,<sup>28</sup> gastroesophageal reflux (GER),<sup>29–30</sup> sleep apnoea and asthma.<sup>8–31</sup> Moreover, many factors can trigger paradoxical vocal cord movement such as inhalation of allergens, pollutants, cold and dry air or exercise.<sup>28–32</sup> In athletes, anxiety relative to the pressure of high expectations may subconsciously lead to laryngeal closure and choking.<sup>10</sup>

EIVCD can be suspected by a flattening of the inspiratory flow-volume loop, airway obstruction and/or inspiratory stridor.<sup>3</sup> However, no technique has shown good sensitivity and specificity<sup>33–35</sup> and it is still difficult to diagnose EIVCD.<sup>36</sup>

Direct visualisation of the upper airway by fiberoptic laryngoscopy is the gold standard for making a diagnosis of VCD or EIVCD.<sup>33–37</sup> It can show an adduction of vocal cords during inspiration, reveal evidence of upper airway inflammation or pharyngeal erythema and also exclude other pathologies.<sup>38</sup> However, performing a resting laryngoscopy in a currently asymptomatic athlete may not reveal paradoxical motion of vocal cords. Bronchoprovocation test with methacholine or exercise have been used to trigger VCD<sup>34–39</sup> and laryngoscopy during exercise can also be performed.<sup>40–41</sup> However, exercise laryngoscopy is complex to be performed in many clinics and it can be difficult to reproduce the intense physical and emotional setting of athletes in an artificial environment.<sup>42</sup> Thus, new methods to evaluate EIVCD are needed.

Eucapnic voluntary hyperpnoea (EVH) is the best test to detect increased airway responses to exercise and support the diagnosis of EIB.<sup>43</sup> The advantage of this test is that it can be done in the laboratory without exercising while it reproduces the high minute ventilation that occurs during exercise. We report the results of a pilot study which aims to assess if EVH may be useful to identify EIVCD in athletes with a high degree of suspicion of such problem.

## METHODS

### Participants

Out of 352 athletes regularly followed at our centre, 41 (12%) had a confirmed or suspected diagnosis of EIVCD of whom 13 agreed to participate in the study. Six had a confirmed diagnosis of EIVCD, based on the following criteria: (1) presence of breathing difficulties during exercise with the presence or not of an inspiratory stridor, (2) symptoms appear suddenly during exercise, (3) symptoms stops or diminish quickly when the exercise is stopped, (4) adduction of the vocal cords during inspiration, visualised by laryngoscopy. Athletes were aged between 14 and 35 years and trained in a competitive sport. Written informed consent was obtained from each participant and/or their parents or guardians before inclusion in the study. The protocol was approved by the local Ethics Committee.

### Study design

All participants attended the laboratory on two occasions. On a first visit, a physical examination was performed followed by a medical questionnaire regarding health condition, family history of disease, medication and experience in sport. In addition, questionnaires about GER symptoms and airway sensory hyperactivity were filled by the participants. A methacholine inhalation test was then performed with a flow-volume curve, performed at baseline and at maximal fall in forced expiratory volume in 1 s (FEV<sub>1</sub>). Finally, if not done in the past 2 years, allergy skin prick tests were done. If a methacholine challenge had been performed in the last year, these results were used for this study.

On a second visit, a nasolaryngoscope was properly installed after local anesthesia and a resting laryngoscopy was performed by the Ear Nose and Throat surgeon (ENT). Thereafter, the pre-EVH flow-volume curve was performed and the 6 min EVH test was done, with continuous video recording laryngoscopy.

### Questionnaires

A questionnaire on present and past history of respiratory symptoms, medical conditions, as well as a recording of the type and frequency of exercise performed was filled. Particular attention was devoted to the description of symptoms during exercise.

### Reflux symptoms index

The Reflux Symptoms Index (RSI), a self-administered nine-item instrument, was used to assess for laryngopharyngeal reflux.<sup>44</sup> A score greater than 9, on a maximal score of 45, is considered abnormal, suggesting laryngopharyngeal reflux.

### Chemical sensitivity scale for sensory hyper-reactivity

The chemical sensitivity scale for sensory hyper-reactivity (CSS-SHR) questionnaire was used to quantify the affective and behavioural consequences of odour intolerance.<sup>45</sup> Selected from a larger number of items about odour intolerance, the CSS-SHR questionnaire consists of 11 statements/questions that are particularly sensitive in discriminating participants with an airway sensory hyper-reactivity syndrome from control participants.<sup>46–47</sup> The sum of all 11 items makes up the individual's total CSS-SHR score (range from 1 to 55 points; a score  $\geq 43$  points indicates severe odour intolerance).

### Flow volume curves

The FEV<sub>1</sub> and forced vital capacity (FVC) were assessed from flow-volume curves performed according to the American Thoracic Society (ATS) specifications using an ATS-approved spirometer.<sup>48</sup> Predicted values were derived from Knudson *et al.*<sup>49</sup> The best of three reproducible measurements was used for analysis.

### Methacholine inhalation test

The tidal-breathing method described by Juniper *et al*<sup>50</sup> was used to determine airway hyper-responsiveness (AHR) to methacholine. After baseline measurements of FEV<sub>1</sub> and FVC, each participant inhaled 0.9% saline followed by doubling concentrations of methacholine between 0.03 and 16 mg/mL to obtain a 20% decrease in FEV<sub>1</sub> (PC<sub>20</sub>). Methacholine aerosols were generated from a Wright nebuliser with an output of 0.13 mL/min and were inhaled for 2 min at 5 min intervals. FEV<sub>1</sub> was measured at 30 and 90 s after each inhalation and every 2 min until it started to improve. An acceptable-quality FEV<sub>1</sub> was obtained at each time point; otherwise the FEV<sub>1</sub> manoeuvre was repeated. AHR was defined as a PC<sub>20</sub> ≤ 16 mg/mL.

### Allergy skin test

Each participant had an allergy skin test unless performed within the past 2 years, to determine his atopic status. Skin-prick tests were performed with a battery of 26 common airborne allergens. Normal saline and histamine were used as negative and positive controls, respectively. Skin weal diameters were recorded at 10 min as the mean of two perpendicular measurements. A positive response was defined as a skin weal diameter ≥ 3 mm.

### Nasolaryngoscopy

Five minutes before the laryngoscopy, the nasal cavity was anaesthetised with topical lidocaine (1%) and xylometazoline (0.1%) applied by cotton-tipped swabs in the nares. The posterior pharynx was not anaesthetised intentionally in order to avoid any anaesthesia of the vocal cords. A flexible video-naso-pharyngo-laryngoscope (VNL-1170K/1171K, VNL-1070STK/1570STK, VNL-1190STK, Pentax Medical, Mississauga, Ontario, Canada) was directed to the posterior pharynx several centimetres above the glottis in order to prevent stimulation and adduction of the vocal cords.

Observation of the vocal cords was first made at rest before EVH challenge. The participant was asked to make the sound 'E,' cough and breathe rapidly for approximately 15 s each. The possible adduction of the supraglottic structures and vocal cords were assessed during the EVH challenge at each inspiratory phase of the respiratory cycle, at the same level of ventilation for 6 min.

### Eucapnic voluntary hyperpnoea

The EVH test was performed according to the method described by Anderson and Brannan.<sup>43</sup> Briefly, participants inhaled a dry-air mixture containing 21% O<sub>2</sub>, 5% CO<sub>2</sub> and the balance with N<sub>2</sub> at room temperature for 6 min. The target ventilation was 30 times the FEV<sub>1</sub> according to the baseline FEV<sub>1</sub>. To get a valid test for the diagnosis of EIB, the participant must ventilate at least 21 times the baseline FEV<sub>1</sub>. FEV<sub>1</sub> was measured before the test and at 3, 5, 10 and 15 min after the EVH test. At each time interval, FEV<sub>1</sub> was measured twice,

and if there was a >10% difference between the two measurements, a third FEV<sub>1</sub> was performed. After the test, the highest of the two reproducible values was used to calculate the maximal decrease in FEV<sub>1</sub>. A maximum post-EVH fall in FEV<sub>1</sub> of >10% from baseline value sustained during at least 5 min or observable at two consecutive time points was considered positive for EIB.

Presence of respiratory symptoms (wheeze, cough, dyspnoea, choking sensation, chest tightness and stridor) and their severity, during the EVH, were also recorded on a modified Borg scale (0–10).

### Interobserver evaluation

All video recordings were reviewed by two experienced ENT investigators. Each data set was anonymised and presented to the observers in random order. Observers performed their evaluation separately and they then combined their assessments and agreed on a final evaluation for each participant. Movement at the glottic and the supraglottic level were assessed at rest and during the 6 min EVH. The findings were rated as: (1) vocal cord adduction (yes/no), (2) vocal cord adduction (complete/incomplete), (3) supraglottic movement (yes/no), (4) severity of the supraglottic movement (slight/moderate/severe), (5) vibration of the supraglottic movement (yes/no), (6) respiratory distress (yes/no), (7) audible inspiratory stridor (yes/no), (8) laryngeal anatomy (normal/abnormal) and (9) laryngeal function (normal/abnormal).

## RESULTS

### Participants' characteristics

The participants' characteristics are summarised in table 1. The mean age of the athletes was 21±7 years. On average, they trained for 12±6 h per week. Six athletes were sensitised to common airborne allergen and nine had a diagnosis of asthma. Only two athletes reported rhinitis and one had GER disease (GERD) and was treated with proton pump inhibitors (PPI).

### Questionnaires

All athletes reported respiratory symptoms (wheeze, cough, dyspnoea, chest tightness and phlegm) and inspiratory stridor during exercise with a mean Borg score for the severity of symptoms of 5±3. In all athletes, these symptoms disappeared a few minutes after the cessation of the exercise. In four of the athletes these symptoms affected their exercise performance and occurred a mean of 2±2 times per week.

The RSI showed a mean score of 5.3 (0–20), on a maximal possible score of 45. Only three athletes had an abnormal score, that is, more than 9, suggesting laryngopharyngeal reflux. The sensitivity index to chemical agents and odours showed a mean score of 26<sup>16–34</sup> on a maximal possible score of 55. None of the athletes had an abnormal score that is, more than 43, which would have suggested airway hypersensitivity syndrome.



**Table 1** Participants' characteristics

Characteristic	
Participants (n)	13
Sex (M:F)	0:13
Age (years)	21±7
Sports	
Cycling	3
Cross-country skiing	4
Long track speed skating	2
Triathlon	1
Synchronised swimming	1
Taekwondo	1
Swimming	1
BMI (kg/m <sup>2</sup> )*	22±1
Training (h/week)*	12±6
Asthma medication	
β <sub>2</sub> -agonists (n (%))	5 (38)
Inhaled corticosteroids (n (%))	4 (31)
Diagnosis of rhinitis (n (%))	2 (15)
Rhinitis medication	
Antihistaminic (n (%))	0 (0)
Nasal steroids (n (%))	1 (8)
Diagnosis of GERD (n (%))	1 (8)
PPI (n (%))	1 (8)
Atopy	
Animals (n (%))	4 (31)
Tree pollens (n (%))	5 (38)
Grass pollens (n (%))	4 (31)
House dust mites (n (%))	5 (38)
FEV <sub>1</sub> (L)*	3.5±0.4
FEV <sub>1</sub> (% predicted)*	103±13
FVC (L)*	4.4±0.6
FVC (% predicted)*	116±17
FEV <sub>1</sub> /FVC (%)*	81±7
PC <sub>20</sub> ≤16 mg/mL (n (%))	8 (62)
PC <sub>20</sub> (mg/mL)	6.0 (0.3–16.0)
EVH positive (ie, EIB) (n (%))	2 (15)
Asthma (n(%))	9 (69)
Maximal fall in FEV <sub>1</sub> after EVH (%)	6.8 (1.5–15.0)
Minute ventilation during EVH (lpm)	83 (59–100)
Number of times the FEV <sub>1</sub> †	24 (16–30)

\*Data are presented as means±SD.

†The target minute ventilation is 30 times the baseline FEV<sub>1</sub>. Airway hyper-responsiveness to methacholine (PC<sub>20</sub>≤16 mg/mL) and/or maximal fall in FEV<sub>1</sub> after EVH≥10%; BMI, body mass index; EIB, exercise-induced bronchoconstriction; EVH, eucapnic voluntary hyperpnoea; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; maximal fall in FEV<sub>1</sub> after EVH, expressed as mean(range); PC<sub>20</sub>, concentration of inhaled methacholine causing a 20% decrease in the forced expiratory volume in 1 s, expressed as geometric mean (range); GERD, gastroesophageal reflux disease; PPI, proton pump inhibitors.

### Spirometry findings

Ten athletes performed methacholine challenge, as part of the study, and among them none demonstrated fluttering of the inspiratory curve of the flow volume loop. Inspiratory curve of the flow volume loop, before and after the EVH challenge, was also normal in all participants.

### Laryngoscopic findings

All athletes had normal laryngeal anatomy and normal laryngeal function at rest. One athlete showed opening of the upper oesophageal sphincter a few times during the EVH challenge.

None of the athletes had audible inspiratory stridor or respiratory distress during the EVH challenge. Three athletes showed incomplete adduction of the vocal cords movement. However, 12 athletes showed mild supraglottic movement. In two athletes, this supraglottic movement was severe, one showing a marked epiglottis posterior collapse with an almost complete obstruction of the larynx by the arytenoid cartilage mucosa. In three athletes with supraglottic movement (1 mild and 2 severe), marked vibration of the arytenoid cartilage mucosa was also observed.

The mean minute ventilation during the EVH was 83 (59–100) L/min, which correspond to 24<sup>16–30</sup> times the baseline FEV<sub>1</sub>. Ten athletes reported respiratory symptoms (wheeze, cough, dyspnea, chest tightness and phlegm) during the test with a mean Borg score for the severity of symptoms of 3±1. However, none of the athletes reported choking sensation or a sensation of tightening of the throat, but three felt like they had an inspiratory stridor during the test.

### DISCUSSION

Our study suggests that videolaryngoscopy during an EVH challenge may not be the most appropriate test to induce VCD. However, this test can discriminate between types of exercise-induced laryngeal obstruction (EILO): supraglottic dysfunction (obstruction), vocal cords dysfunction (EIVCD) or mixed dysfunctions (glottic and supraglottic), in reproducing laryngeal movements during hyperventilation that resting laryngoscopy does not reveal. Thus, the EVH challenge may serve as a complementary tool in the diagnosis of patients with exercise-induced respiratory symptoms, as it is important to differentiate these conditions from EIB, their treatments are different.<sup>51 52</sup>

Christensen *et al*<sup>53</sup> also showed that EVH testing can be used to induce EILO, and has a potential diagnostic applicability. As a result of these observations, we can think that the inspiratory stridor reported by athletes participating in this study, during field exercise, could be due not only to EIVCD. It could be also attributable to larger and floppy arytenoid cartilage mucosa that combined with hyperventilation may result in inspiratory collapse of the supraglottic structures. That could eventually cause complete obstruction of the larynx such as laryngomalacia observed in infants. For those athletes with a severe supraglottic involvement, a laser supraglottoplasty might be of some interest as suggested by Maat *et al*.<sup>52</sup>

Although some athletes clearly have EIVCD or asthma, both conditions may coexist. In half of the participants with EIVCD, EIB or asthma is also present<sup>54</sup> and up to

30% of patients with asthma have coexistent VCD.<sup>25</sup> In our study, 9 (69%) of the athletes had asthma.

The larynx and the vocal cords are innervated by sensory receptors which can be stimulated by many irritants.<sup>55 56</sup> VCD can be due to glottic closure reflex induced by repetitive irritant exposure to which athletes are often exposed in their training environment.<sup>28</sup> For example, chlorine inhalation causing VCD has been described and deserves special consideration in swimmers.<sup>57</sup> Several other inhaled irritants such as strong odours, perfumes, ammonia and particles matter have been identified as causative agents in VCD.<sup>28 58</sup> For this reason, we used the CSS-SHR in our study in order to identify if some athletes had odour intolerance suggesting airway sensory hyper-reactivity syndrome that could possibly cause VCD. However, we did not observe abnormal CSS-SHR score in this study.

Furthermore, GER and laryngopharyngeal reflux (LPR), associated or not with symptoms, are frequent in endurance athletes and can trigger EIVCD.<sup>28 59</sup> These conditions can cause laryngeal lesions such as oedema, erythema and granulomas to the glottic and supraglottic structures.<sup>60</sup> In our study, we evaluated, through RSI score, if athletes had GER symptoms. Only three athletes had GER symptoms which is not surprising as many patients with irritant-induced VCD will not report classical symptoms of GER,<sup>40</sup> but which is not in keeping with another study reporting that 84% of patients with VCD had abnormal RSI scores.<sup>27</sup> These findings may be explained by the fact that our participants are younger. In addition, previous report showed that 66–95% of patients with VCD have laryngeal findings, such as inflammation, consistent with GER.<sup>38 59</sup> However, in our study, none of the athletes exhibited laryngeal findings suggesting GER or LPR, but one athlete was treated with PPI.

Isolated fluttering of the inspiratory curve of the flow volume loop while the patient is symptomatic is consistent with extrathoracic obstruction, which is the most commonly described abnormality in VCD.<sup>34</sup> However, flow volume loop abnormalities are uncommonly noted on spirometry<sup>10</sup> and particularly in athletes, as their symptoms occur generally only during high-intensity exercise, making the usefulness of spirometry conflicting.<sup>26 61</sup> In our study, none of the athletes showed abnormal inspiratory loop before or after the EVH test, neither during the methacholine challenge. Furthermore, bronchoprovocation tests such as methacholine provide inconsistent results in regard to change in flow volume curve appearance. Only 40–50% of patients in whom VCD is highly suspected will have symptoms with methacholine provocation.<sup>62 63</sup> For this reason, the appearance of the flow volume loops should not influence the decision to perform or not laryngoscopy.<sup>64</sup>

In our study, we did not observe EIVCD during the EVH challenge in athletes suspected or already having such diagnosis, which may be explained by many

reasons. EVH is done with dry air at room temperature, which does not reproduce every environmental conditions such as temperature, humidity, as well as the pollutants or allergens contained in air during field training. Moreover, EIVCD is more often observed during competition possibly due to the stress and anxiety of a competitive event, as a relationship between VCD and psychological stress has been shown.<sup>59</sup> EIVCD can also be related to psychological disorders or to personality traits.<sup>65</sup> In addition, athletes may become used to the EVH challenge, as all athletes had already done this test before. Thus, they probably had less apprehension and stress in regard to that test. Finally, some athletes may not have sufficient ventilation during the EVH test, to trigger VCD. The performance during the EVH test is effectively influenced by individual factors such as attitude and expectations. Thus, the motivation and the effort to achieve the target ventilation may vary.

## CONCLUSION

Reported exercise-induced respiratory symptoms are common in endurance athletes, but these symptoms are often treated as EIB and upper airway obstruction are not often considered and therefore rarely diagnosed. Patients with EIVCD are frequently misdiagnosed as having poorly controlled EIB and their response to asthma treatment is poor.<sup>66</sup> Failure to diagnose EIVCD may lead to unnecessary healthcare utilisation, inappropriate medication use<sup>25 67</sup> and hospitalisation.<sup>68</sup> In athletes, suboptimal performance and discontinuation of sports are unfortunate additional consequences of misdiagnosis.

Although EIVCD was not specifically diagnosed using EVH, by reproducing the hyperventilation-induced laryngeal movement, the EVH allowed identifying laryngeal obstructions, which are not always observed during a resting nasolaryngoscopy. The exercise-induced inspiratory stridor reported by athletes may be associated with EIVCD or movements of different severities of the supraglottic structures. The latter observations lead us to suggest that EILO can be divided into subcategories: supraglottic obstruction, glottic obstruction (VCD) or mixed obstruction (glottic and supraglottic).

Actually, we need to find a method to quantify the larynx obstruction observed in EILO, in order to objectively assess test results and to define criteria for diagnostic purpose, to evaluate effects of treatment and to further assess which patients might benefit from reduction surgery. Maat *et al*<sup>69</sup> had previously proposed a scoring system which is rather subjective and allowed large interobserver variability. Christensen *et al*<sup>53</sup> have created software (EILOMEA) to calculate specific distances and areas in the larynx from a still frame of the laryngoscopic recording, but this software need to be validated.

**Acknowledgements** The authors thank all the athletes who participated in the study, Mrs Kristi Huff, National Territory Manager-ENT at Pentax Medical for

the loan of equipment, Dr Jean-Philippe Vézina for his help in the images analysis, as well as the Conseil des Sports de Haut Niveau de Québec (CSHNQ) for their support in the accomplishment of this project.

**Competing interests** Disclosure of potential conflicts of interest of L-PB. L-PB consider to have no conflict of interests but wish to declare what can be perceived as 'potential' conflicts of interests Advisory Boards: GlaxoSmithKline, Novartis. Conferences (honoraria): AstraZeneca, GlaxoSmithKline, Merck, Novartis. Sponsorship for investigator-generated research: AstraZeneca, GlaxoSmithKline, Merck Frosst, Schering. Sponsorship for research funding for participating in multicenter studies: most of these studies are performed in the context of the Canadian Investigative Collaboration with the NCE: AllerGen, Altair, Amgen, Asmacure, AstraZeneca, Boehringer-Ingelheim, Genentech, GlaxoSmithKline, Novartis, Ono Pharma, Pharmaxis, Schering, Wyeth. Support for the production of educational materials: AstraZeneca, GlaxoSmithKline, Merck Frosst, Boehringer-Ingelheim, Novartis. Governmental: Adviser for INNESS, the Quebec National Health Institute, Member of the Quebec Workmen Compensation Board Respiratory Committee. Organisational: Chair of the Canadian Thoracic Society Respiratory Guidelines Committee, Chair of the Global Initiative for Asthma (GINA) Guidelines Dissemination and Implementation Committee.

**Patient consent** Obtained.

**Ethics approval** This study was approved by the Institut Universitaire de Cardiologie et de Pneumologie de Québec's Ethics Committee.

**Provenance and peer review** Not commissioned; internally peer reviewed.

**Data sharing statement** No additional data are available.

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