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Exercise-associated dyspnea and stridor: thinking beyond asthma

J.H. Hull, PhD, FRCP, Krystelle Godbout, MD, FRCPC, Louis-Philippe Boulet, MD, FRCPC



PII: S2213-2198(20)30145-8

DOI: <https://doi.org/10.1016/j.jaip.2020.01.057>

Reference: JAIP 2688

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 5 December 2019

Revised Date: 21 January 2020

Accepted Date: 21 January 2020

Please cite this article as: Hull JH, Godbout K, Boulet LP, Exercise-associated dyspnea and stridor: thinking beyond asthma, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.01.057>.

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**2020-1-21**

*For Theme issue on Sports Allergy, JACI-In Practice*

**Title: Exercise-associated dyspnea and stridor: thinking beyond asthma**

**Sub-title:** Breathing issues in non-asthmatic subjects

**Authors:**

J. H. Hull<sup>1</sup>, PhD, FRCP

Krystelle Godbout<sup>2</sup>, MD, FRCPC

Louis-Philippe Boulet<sup>2</sup>, MD, FRCPC

**From :**

1 Department of Respiratory Medicine, Royal Brompton Hospital, London

2 Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval

Address for correspondence:

Louis-Philippe Boulet MD FRCPC

Institut universitaire de cardiologie et de pneumologie de Québec - UL

2725, Chemin Sainte-Foy

Québec (Québec), Canada, G1V 4G5

Tel.: 418-656-4747 Fax: 418-656-4762

Email: [lpboulet@med.ulaval.ca](mailto:lpboulet@med.ulaval.ca)

**Key-words:** Stridor, Exercise-induced dyspnea, Dysfunctional breathing

**List of abbreviations:**

EIB: exercise-induced bronchoconstriction

EILO: Exercise-induced Laryngeal Obstruction

ILO: inducible laryngeal obstructions

PVFM: paradoxical vocal fold motion

VCD: Vocal Cord Dysfunction

**Conflict of interest:** **JHH:** has none to declare. **KG:** Fee for consulting and advisory boards: AstraZeneca, GSK, Novartis, Sanofi-Regeneron. Conference fees: AstraZeneca, Boehringer-Ingelheim, GSK, Merck, Novartis **LPB:** I have no conflict of interest in regard to this publication. My potential general COI are: Research grants for participation to multicentre studies: AstraZeneca, Boston Scientific, GSK, Hoffman La Roche, Novartis, Ono Pharma, Sanofi, Takeda. Support for research projects introduced by the investigator: AstraZeneca, Boehringer-Ingelheim, GSK, Merck, Takeda. Fee for consulting and advisory boards: AstraZeneca, GSK, Novartis, Merck, Sanofi-Regeneron. Nonprofit grants for production of educational materials: AstraZeneca, Boehringer-Ingelheim, GSK,

- 45 Merck, Novartis, Teva. Conference fees: AstraZeneca, GSK, Merck, Novartis, Teva.  
46 Support for participation in conferences and meetings: Novartis, Takeda.

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**Abstract: (202 words)**

Breathlessness during sport can be caused by a variety of cardiorespiratory conditions, but when associated with stridor, usually arises from an upper airway etiology. The term exercise-induced laryngeal obstruction (EILO) is now used to describe the phenomenon of transient glottic closure occurring in association with physical activity.

Exercise related laryngeal closure is most commonly encountered in athletic individuals and likely affects between 5-7% of all young adults and adolescents. The diagnosis of EILO is not always straightforward as features can overlap with exercise-induced asthma / exercise-induced bronchoconstriction. EILO can therefore remain misdiagnosed for years and most patients receive inappropriate asthma therapy. In contrast with asthma, EILO symptoms are usually most prominent at maximal exercise intensity and resolve quickly on exercise cessation. It is important to recognize that EILO and asthma can co-exist in a proportion of athletes. .

The gold standard test for diagnosing EILO is continuous laryngoscopy during exercise (CLE) testing, although eucapnic voluntary hyperpnea testing has also been utilized. Various surgical or pharmacological interventions can be used to treat EILO but first-line treatment is breathing technique work. Further research is needed to establish the optimal treatment algorithm and more work is needed to increase awareness of this important clinical entity.

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## **Introduction and definitions (2,999 words)**

Exercise-induced breathlessness may be caused by a variety of respiratory conditions but when associated with wheezes, it is most often attributed to the presence of asthma or exercise-induced bronchoconstriction (EIB). In recent years, however, it has become increasingly apparent that other airway-centric etiologies such as those involving the larynx and upper airway, are equally relevant as causes of this clinical presentation.

The first descriptions of abnormal 'functional' laryngeal closure causing breathlessness and wheeze are attributed to Christopher et al.<sup>1</sup> over 30 years ago. This description of paradoxical (i.e. inward movement occurring on inspiration) movement of the vocal cords was termed vocal cord dysfunction (VCD). Since this time, a great number of terms have been used to describe similar phenomena of abnormal laryngeal function and more recently an international consensus group proposed the term "inducible laryngeal obstruction (ILO)", to describe an inappropriate and transient obstruction of the larynx that arises in response to an external trigger. The terminology also acknowledges the fact that in many cases laryngeal closure occurs because of structures distinct from the vocal cords and thus VCD is a misnomer. When ILO develops in the context of exertion it is termed exercise-induced laryngeal obstruction (EILO)<sup>2</sup>.

The aim of this review is to provide a pragmatic overview of the epidemiology, clinical features and treatment of EILO, to help clinicians encountering athletes with breathing difficulties.

## **Prevalence of stridor and inducible laryngeal obstruction**

The impact of VCD has been recognized for some time. Newman reported a series of 95 adults (84% women) who had been hospitalised with laryngeal symptoms and diagnosed with VCD (average age of 39 years)<sup>3</sup>. Fifty-three of them (56%) had co-morbid asthma<sup>3</sup>. In this study, patients with VCD and without co-existing asthma were predominantly

young females whom had been misdiagnosed with asthma for an average of almost 5 years prior to assessment. Medical utilisation was high in this group.

In a large data series review of VCD, there was an approximately 2:1 female predominance, 71% were adults and the remaining 29% were predominantly adolescents<sup>4</sup>. In a study of 94 patients diagnosed using the continuous laryngoscopy exercise (CLE) test, average age was 15 years, and 68% were female similar to other adolescent group<sup>5</sup>. Exercise appears to be a more common inducer of laryngeal obstruction in younger age groups; however, this might be a biased by different exercise habits in term of type and duration at different ages.

Several studies in adolescents and young adults in northern Europe, that focused on exercise laryngeal closure have indicated that the prevalence of EILO appears to be in the range of 5-7%<sup>6</sup> with a preponderance in females<sup>7, 8</sup>, adolescents and young athletes<sup>6, 9, 10</sup>. In 146 adolescents who reported exercise-induced dyspnea on a large-scale questionnaire, prevalence of EILO visualized on exercise testing was 5.7% while 19.2% had EIB<sup>6</sup>. Rundell *et al.* reported a prevalence of inspiratory stridor during exercise of 5.1% in US based athletes, often with concomitant asthma, although usually mild<sup>11</sup>.

### **Etiology and pathophysiology**

Breath sounds are generated by vibrations created when air molecules collide with each other and with the bronchial wall in the presence of turbulent airflow or vortices<sup>12</sup>. Stridor, a high-pitched musical sound, is produced when turbulent airflow is located in the upper respiratory tract. It differs from wheezes essentially by its greater audibility over the neck than chest wall. Its location in the respiratory cycle indicates the level of obstruction<sup>13</sup>. Inspiratory stridor is the most commonly heard and is associated with obstruction located at the extra-thoracic level (larynx, either glottic or supraglottic). Less frequently, it can be expiratory in intrathoracic tracheobronchial dynamic obstruction

(tracheomalacia, external compression) or biphasic when the lesion is fixed (e.g. tracheal stenosis).

When exertional dyspnea is associated with noisy or loud breathing, physicians have historically thought of asthma +/- EIB. However, in the absence of demonstrable airway hyper-responsiveness or response to asthma treatment, EILO should be suspected and assessed. Other causes of dyspnea and stridor include structural lesions or external compression of the upper airway and proximal tracheobronchial tree, cardiac disease such as hypertrophic cardiomyopathy and exercise-induced anaphylaxis.

Dysfunctional breathing is another common but overlooked cause of exertional dyspnea although not associated with stridor or wheezes. It is poorly understood and ill-defined, but literature has been reviewed in 2016 in order to provide common nomenclature and classification for future research<sup>14</sup>. The breathlessness sensation universally felt in dysfunctional breathing is thought to be related to asynchrony in muscle contractions or abnormal breathing patterns, including thoracic dominant breathing<sup>15</sup>. When clear hyperventilation with hypocapnia is present, abnormalities in relation with the ventilation regulatory systems are also likely to be involved. They may include an overactive reticular activating system, which regulates breathing patterns, increased sensitivity for CO<sub>2</sub> and a hypersensitive fear network<sup>16</sup>.

During exercise, in order to facilitate ventilation and decrease airway resistance, the larynx physiologically opens in an active muscular process and the epiglottis rotates anteriorly towards the base of the tongue, stretching the aryepiglottic folds and providing additional opening<sup>17, 18</sup>. A slight adduction of the aryepiglottic fold at maximal ventilation is however frequently observed in patients and is therefore considered a physiologic finding<sup>19, 20</sup>. At the glottic level, it is the combined contraction of the posterior cricoid (PCA) and cricothyroid muscles, synchronized with and ahead of the diaphragm contraction, that results in maximal inspiratory vocal cord abduction<sup>21, 22</sup>.

EILO occurs when the normal mechanisms responsible of opening the larynx during exercise fail. The narrowed larynx creates a bottleneck, increasing airflow resistance and creating turbulent flow, causing dyspnea and stridor. In most patients, the dynamic obstruction occurs initially at the supraglottic level<sup>23</sup> with medial rotation of the aryepiglottic folds and/or the cuneiform tubercles<sup>20</sup>. A secondary adduction of the vocal cord (glottic level or vocal cord dysfunction) happens in most but may be the sole or primary obstructive mechanism in a limited number of patients.

The precise pathophysiology of EILO is unknown but it is likely multifactorial and heterogeneous amongst suffering individuals. Our current understanding of the mechanisms involved include anatomic, neurologic, behavioral and comorbid elements.

#### Anatomic

Mechanical factors are related to airway size and pliability and likely to be relevant in many EILO cases. Fluid dynamics have taught us with the Bernoulli's Principle that as the velocity of airflow in a tube increases, the negative pressure and inward force within that tube also rise<sup>24</sup>. Depending on airflow velocity, turbulence and the strength of the supporting structures, the tube will sooner or later cave in. In the larynx, this impending dynamic collapsibility with increasing ventilation is influenced by the aperture size and laryngeal support provided by laryngeal cartilages, muscles and ligaments. An increased flaccidity of these structures or weakness of the PCA-muscle (vocal cords abductor) would result in inspiratory laryngeal collapse with increasing ventilation, therefore EILO. Congenital laryngomalacia is perhaps the most obvious example of this theory and has indeed been linked to some EILO cases<sup>25, 26</sup>. Larynx aperture size also theoretically impacts collapsibility. Adolescents are known to have a narrower supraglottic space<sup>27</sup> and are indeed overrepresented in EILO epidemiology<sup>6</sup>. However, as previously mentioned, EILO is also more frequent in females<sup>9, 23</sup> but no gender difference has been

described in larynx proportion<sup>27</sup>. Sex differences seen throughout accelerated growth in adolescents<sup>28</sup> could perhaps explain the female predominance but other factors described below could also be involved.

### **Neurologic**

The laryngeal adductor reflex protects the airway from aspiration by involuntarily triggering glottis closure with mechanical or chemical stimulation of the supraglottic mucosa<sup>29</sup>. Upregulation in the sensitivity or intensity of this protective loop could lead to a reflex-induced ILO<sup>30, 31</sup> and the increased ventilation seen during exercise, particularly in a cold and dry environment, trigger this reflex. evidences to fully support this theory are lacking despite anecdotal reports of EILO, occurring more frequently in winter sports and outdoor athletes<sup>32</sup>. A recent study also demonstrated a surprising decreased laryngeal mechanosensitivity in patients with EILO<sup>33</sup>, but this could have been explained by gastro-esophageal reflux (GER, see below)<sup>34</sup>

### **Behavioral**

Psychological and behavioral factors have been hypothesized as potential contributors to EILO development. This theory arises from the reported panic reactions seen during crisis and association of ILO and psychiatric conditions such as anxiety and conversion disorders<sup>35, 36</sup>. However, exercised-induced ILO should be distinguished from ILO occurring at rest on this subject as the former is more mechanically related and has not been specifically associated with psychiatric disorders<sup>37</sup>. Also, panic behaviors seen in EILO are most likely reactions to the choking sensation provoked by glottis closure rather than causal events.

### **Comorbid Conditions**

Asthma, GER and nasal disease have been epidemiologically related to ILO and are therefore hypothesized as contributors to its development although the underlying mechanisms are still hypothetical and the association perhaps non-causative<sup>23</sup>. Indeed,

in severe asthma, ILO may be an adaptative process to regulate airflow outtake and reduce airway collapse on expiration. That would certainly explain the proportional reduction in glottis opening seen in obstructive diseases as the forced expiratory flow in one second (FEV<sub>1</sub>) decreases<sup>38</sup>. However, although expiratory closure may be beneficial by creating intrinsic positive end-expiratory pressure (PEEP)<sup>39</sup>, inspiratory laryngeal obstruction should be considered maladaptive as it increases the work of breathing. As for GER and rhinosinusitis with post-nasal drip, they have been thought to promote EILO by creating an hyperexcitable laryngeal state with heightened mechanical and chemical sensitivity. Literature confirming this theory is limited in rhinosinusitis<sup>40</sup> and in GER, with studies demonstrating an increased threshold for mechanical stimulation<sup>33, 41</sup>.

## **Clinical management**

### **Assessment**

The assessment of an athlete with unexplained exertional breathlessness and wheeze should begin with a thorough clinical history. This acknowledged, it is now well recognized and widely published that a clinical-based approach to diagnosis alone can often be imprecise in this context<sup>42</sup> (i.e. taking a history is not sufficiently accurate). This is likely due to the fact that an athlete's self-report of wheezy-type sounds, cough and breathing discomfort can arise from either EIB, EILO or indeed simply exaggerated forms of dysfunctional breathing. A seminal study in elite winter sports athletes showed that these symptoms and indeed a constellation or combination of symptom groups was very poorly predictive for the diagnosis of EIB with only a 50% positive predictive value<sup>43</sup>.

These limitations accepted, there are some key features that can help differentiate EILO from EIB and other causes of exertional breathing difficulty (Table 2, Figure 1). Classically, athletes with EILO will report that their symptoms are most prominent at maximal exercise intensity, and then start to settle fairly rapidly on exercise cessation. Olin and colleagues confirmed the fact that EILO usually occurs at workloads >80% of an individual's maximum exercise capacity<sup>44</sup>. This contrasts with EIB, whereby the typical

symptoms are most prominent on exercise cessation (hence explaining why spirometry is assessed in the post-exercise-period to confirm a fall in lung function)<sup>45</sup>. Athletes with EILO also tend to notice an audible inspiratory sound and others surrounding them (e.g. coaches or competitors) can also hear this sound. The latter is unusual with EIB and certainly loud polyphonic wheezes are rarely reported by observers.

In the process of assessment it would seem intuitive to ask an athlete whether their breathing difficulty and/or wheeze was occurring on inspiration or expiration. Detailed studies of lung mechanics have shown that patients with obstructive lung disease report the sensation of an 'unsatisfied inspiration' which likely explains why this particular approach to clinical differentiation has been found to be a poor discriminator. Moreover, at least anecdotally, it is common to see athletes who report wheeze on expiration while on CLE testing there is only a loud inspiratory sound. This may relate to difficulty recalling the nature of sounds during vigorous exercise and should prompt requests from the athlete for a 'selfie-type' video recording of a strenuous training session to assist in making the diagnosis; in order to then share this video at a clinic consult (see <https://www.uptodate.com/contents/exercise-induced-laryngeal-obstruction> for example). The reviewing clinician can then assess the true nature of the wheeze and its pattern of onset.

The current most widely accepted 'gold standard' diagnostic technique to confirm the cause of exercise-associated stridor and specifically EILO is the CLE test<sup>46</sup> (Figure 2 – CLE in action). This test involves insertion of a flexible laryngoscope via the nostril and secured in the posterior oropharynx on specialist headgear. This placement thus allows for continuous visualisation of the laryngeal inlet throughout an exercise bout and the ability to characterize (i) the location of any obstruction (ii) its severity and pattern of onset (iii) its relationship to the symptoms an athlete develops. The CLE test has significantly progressed understanding of EILO, demonstrating that most young individuals with exercise-associated stridor, the problem is arising from closure of the

supraglottic structures (i.e. arytenoids) as opposed to purely the vocal cords. This discovery has informed treatment decisions and prompted a change in nomenclature from the historical used term exercise-associated vocal-cord dysfunction (i.e. this is a misnomer in most cases)<sup>47, 48</sup>. The CLE test can also be used to provide immediate biofeedback to the patient and more recently has proven beneficial as a therapeutic laryngoscopy during exercise (TLE)<sup>47</sup>. An additional advantage of CLE is that it can be applied in a number of different sport-specific settings, with successful reports of its application during swimming<sup>49</sup>, rowing<sup>50</sup> and in outdoor ambulatory running and cycling settings<sup>51</sup>.

Surrogate methods for diagnosing EILO include assessments of inspiratory flow attenuation during spirometry or a cardiopulmonary exercise test. Unfortunately these tests have been shown to have limited specificity and sensitivity, perhaps due to the fact that EILO develops during peak exercise and obtaining adequate airflow measurements at this juncture is challenging<sup>52, 53</sup>. Laryngoscopy during indirect bronchoprovocation testing (e.g. EVH) may offer some promise<sup>54</sup> by enabling simultaneous assessment of EILO and EIB. Unfortunately the data to date suggests that there can be difficulties maintaining sufficient laryngoscopic visualisation due to increased secretion accumulation<sup>55</sup>. Further work is needed to refine CLE testing but also to evaluate novel and less invasive means of detecting and characterising EILO.

### **Treatment**

The last decade has seen transformational progress in the way exercise-associated stridor is treated. Historically this condition, especially in young individuals, was in many cases viewed as related to performance anxiety or to the impact of certain psychological stressors on breathing. Over time, however, our improved understanding of the likely mechanisms underpinning EILO have acted to facilitate interventions that can reduce laryngeal closure and minimize symptoms.

307

308 A key therapeutic development has been borne out by the appreciation that EILO most  
 309 likely develops, or is at least exacerbated, by the pressure changes that occur across the  
 310 laryngeal inlet<sup>56, 57</sup>. This is a narrow structure and a location of considerable airflow  
 311 resistance change with heightened turbulence. Thus, any propensity to laryngeal  
 312 weakness or structural predisposition to closure is heightened during a state of  
 313 increased airflow (i.e. vigorous exercise). With this knowledge comes the ability to  
 314 develop techniques and a therapeutic approach that acts to modulate and attenuate the  
 315 early 'high velocity' stages of inspiration, with a presumption that this will lessen the  
 316 physical airflow state that promotes collapse in the laryngeal inlet. Several authors have  
 317 now published their own techniques in this area<sup>58-60</sup> and have been collectively termed  
 318 the EILO-biphasic inspiratory techniques, utilizing airflow modulation with either teeth  
 319 clenching or temporary closure of the mouth with opposition of the lips and teeth (see  
 320 reference for video demonstration)<sup>58</sup>. The Hull 'Hoover' technique encourages athletes  
 321 to work around conceptualising and creating an audible sound replicating the word  
 322 'hoover' to modulate airflow both on inspiration and expiration. Overall, these  
 323 techniques have been shown to be efficacious in a large proportion of patients and  
 324 particularly in runners and cyclists<sup>58</sup>.

325

326 The other key advance in this field is the acceptance that surgical intervention has an  
 327 established role in the management of some cases of therapy-resistant EILO<sup>61 62</sup>. In  
 328 cases of EILO with predominantly supraglottic obstruction, a laser supraglottoplasty may  
 329 be undertaken to remove arytenoid tissue or encourage its fibrosis. Several  
 330 international series have now been published demonstrating the overall effectiveness of  
 331 this type of intervention, although a recent systematic assessment confirmed the need  
 332 for further, more robust, and well controlled prospective analysis<sup>63</sup>.

333

334 In any comprehensive therapeutic assessment, it is important to discuss the nature of  
 335 the diagnosis with the patient/athlete which can be therapeutic in terms of explaining

why asthma is not present nor indeed relevant (unless there is overlap of conditions) and to address other factors or contributory issues<sup>64</sup> (NB - No athlete should be given a short-acting beta-2 agonist alone now, according to the last Global Initiative for Asthma (GINA) 2019 report). There are now good patient information documents and infographic tools available<sup>65, 66</sup>. Coaching and preparedness training for competition is a key part of any successful breathing control strategy and likewise removal of triggers or upper airway irritants (e.g. GERD or sinonasal disease) is mandatory<sup>67</sup>. The role of other treatments such as inspiratory muscle training and inhaled therapy with anti-cholinergics is yet to be established, but may be on an individual basis. An overall summary of the approach to treatment is provided in Tables (1 and 2).

## **Conclusions and recommendations**

The presence of EILO with or without asthma needs to be considered in the presence of dyspnea and stridor on exercise. The type and level of obstruction and contributing factors should be determined. The diagnosis of EILO often remains a challenge but a direct laryngoscopy during exercise or EVH can provide an objective demonstration of this phenomenon. Various treatments have been proposed but speech therapy is typically offered as first line treatment and surgical intervention is a recognized therapeutic option in highly selected cases. More research is needed on this condition, but a key priority remains increasing awareness of this important and prevalent cause for exertional breathlessness.

**Table 1 Steps in the successful approach to exercise-associated stridor**

| Treatment step |                                                             | Important process                                                                                                     | Outcome                                                                                                                                                                               |
|----------------|-------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>1</b>       | Diagnosis of EILO +/- EIB                                   | Use robust objective test methodologies such as CLE and EVH testing. Do not make a clinical-based diagnosis alone     | Explain the outcome to the patient / athlete and explain what treatment options are most beneficial. Remove treatments that are not needed (i.e. stop inhalers if no evidence of EIB) |
| <b>2</b>       | Evaluation of contributing factors and psychological issues | Discussing the cause of symptoms is an important step. Discuss and anticipate race / competition strategies.          | An athletes will be better preperared with treatment strategies.                                                                                                                      |
| <b>3</b>       | Laryngeal irritants removal                                 | Consider clinical evidence of GER and sinonasal disease +/- arrange testing if needed. Discuss upper airway hydration | Remove irritants and encourage athletes to be cognizant of environments / triggers that may drive their symptoms.                                                                     |
| <b>4</b>       | Specialist laryngeal breathing control techniques           | Techniques may take time to be acquired and can be delivered in a direct biofeedback session.                         | Specialist laryngeal relaxation techniques can often control EILO but can take time to learn.                                                                                         |
| <b>5</b>       | Surgical approach                                           | Good case selection in an expert centre and in context of failed conservative (therapy-based) approach                | Athletes typically will need to rest 4-6 weeks post procedure and success rates are variable and dependent on good case setecion.                                                     |

**Table 2****Differential diagnosis of EILO**

Asthma  
Exercise-induced bronchoconstriction +/- asthma  
Cardiac diseases  
Anatomical abnormalities of the larynx  
Tracheal stenosis  
Exercise-induced anaphylaxis  
Dysfunctional breathing  
Anaphylaxis

**Figure 1. Clinical characteristics of EILO and EIB. EIB, exercise-induced bronchoconstriction; EILO, exercise-induced laryngeal obstruction.**

Ref: Steffan Arthur Griffin et al. Br J Sports Med 2018;52:1211-1212

*Permission granted*

**Figure 2. Continuous laryngoscopy during exercise test to detect exercise induced laryngeal obstruction in the laboratory A) and in-field exercise setting B).**

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Hull James <J.Hull@rbht.nhs.uk>

Thu 2/6/2020 03:37 AM

To: Louis-Philippe Boulet <lpboulet@med.ulaval.ca>

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**Subject:** Re: JACI: In Practice - Items needed for INPRACTICE-D-19-01275R1

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LS-Ph

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**Date :** mercredi 5 février 2020 à 16:31

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Regards  
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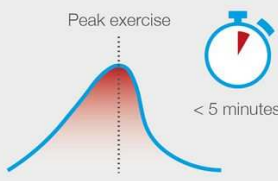
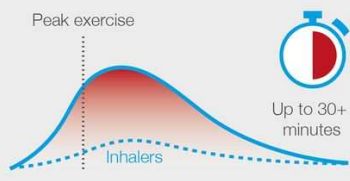
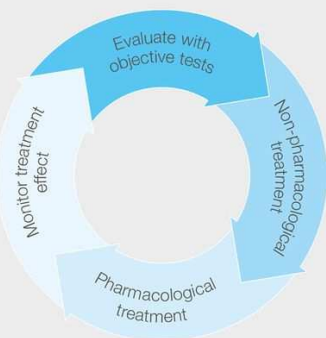
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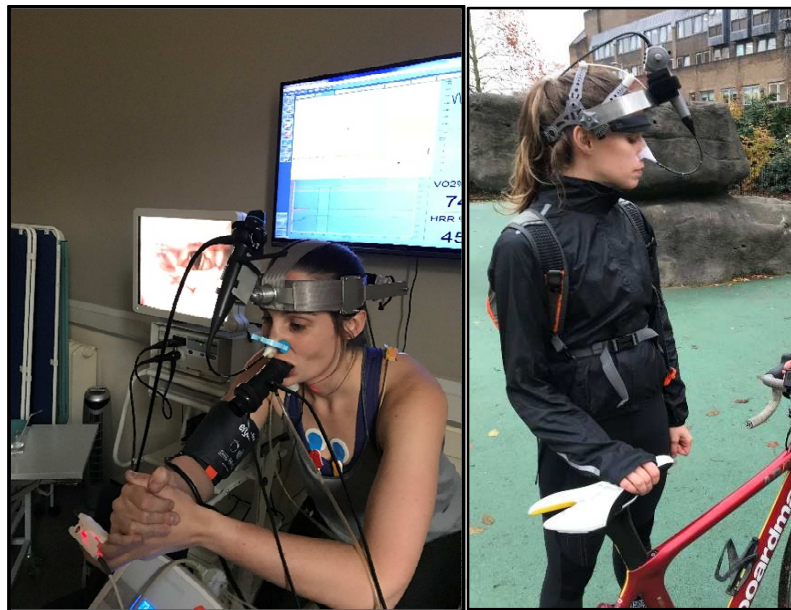
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|                                  | EILO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | EIB                                                                                                                                                                                                                                                |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Symptom intensity                |  <p>Peak exercise</p> <p>&lt; 5 minutes</p> <p>Breathlessness and wheeze</p>                                                                                                                                                                                                                                                                                                                                                                                    |  <p>Peak exercise</p> <p>Up to 30+ minutes</p> <p>Inhalers</p> <p>Breathlessness and wheeze</p>                                                                  |
| Localisation and symptom quality |  <ul style="list-style-type: none"> <li>• Inspiratory stridor</li> <li>• Throat tightness</li> <li>• Inhalers (<math>\beta</math> agonists) do not work</li> </ul>                                                                                                                                                                                                                                                                                              |  <ul style="list-style-type: none"> <li>• Inspiratory and expiratory symptoms</li> <li>• Chest tightness</li> <li>• Cough following exercise cessation</li> </ul> |
| Management                       | <ul style="list-style-type: none"> <li>• Discuss diagnosis, impact on performance</li> <li>• Mitigate environmental triggers</li> <li>• Improve laryngeal hygiene</li> <li>• Manage co-morbidities (allergy, EIB, reflux)</li> </ul> <div> <ul style="list-style-type: none"> <li>• Optimise breathing control at high intensity</li> <li>• Laryngeal relaxation</li> <li>• Consider use of inspiratory muscle training</li> <li>• Pharmacological treatment (anticholinergics)</li> </ul> </div> <div>Surgical treatment (selected cases)</div> |                                                                                                                                                                 |



A)

B)