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Is Dysfunctional Breathing Preventing Effort Induced Asthma Exacerbation?

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Abstract

Introduction:

The aim of this study is to analyse patients who were prescribed respiratory physiotherapy for dysfunctional breathing (DB) and exercise-induced asthma (EIA), as defined by a fall of FEV1 of ≥ 10%, in comparison to those with DB but negative exercise test defined as a fall of FEV1 of < 10%. Our hypothesis is that children or adolescents develop dysfunctional breathing patterns with obvious clinical signs, causing premature exercise interruption, to protect them from an EIA exacerbation. This is important as any treatment would involve on the one hand to address the dysfunctional breathing, whilst on the other hand the treatment of EIA.

Method:

Retrospective case series of patients followed at the respiratory outpatient clinic at the children's hospital Lausanne HEL. We studied the physiotherapeutic and medical records of those paediatric patients who were referred for dysfunctional breathing from the respiratory consultation to the physiotherapy department and analysed in case reports the patients presenting an association of EIA and DB more in detail.

Results:

The 5 patients with the association of both entities had a similar symptomatology to the sample presenting only DB. Even though EIA remained not optimally controlled for a longer period of time in most of the patients, there were only a few emergency consultations with a symptomatology evoking DB rather than EIA. In general, the predominant symptomatology was more suggestive of DB than EIA.

Conclusion:

Our hypothesis could not be confirmed or infirmed, due to the small numbers of cases. Our study suggests that DB might be playing instinctively a role in preventing EIA exacerbations, but the endpoint should be an effective treatment of both entities. A prospective study, conducted in a larger group, would be necessary to clarify if there is indeed a role played by this association.

Introduction

Asthma is the most common chronic illness in paediatric age, with a worldwide prevalence of about 14%, varying between regions, for example >20% in Europe and North America and <5% in India. In countries with low or middle income, the prevalence grew higher in children born in the nineties and early 2000 (1993-2003), but in countries with high income levels the asthma prevalence remained relatively stable (1). Variation in the prevalence is not only present on a global level, but it also exists on a smaller scale, with differences between nations, cities and even neighbourhoods. The exact cause of this variation is not entirely clear, but different factors, such as genetics, environment and socioeconomic status are suspected to play a role in the susceptibility to develop asthma. (1,2)

Asthma represents a high burden in health as well as in economic terms. Death caused by asthma is rare, representing less than 1% of the total deaths worldwide, occurring mainly in the old aged population. (1)

But what is asthma? According to the most recent guidelines published in 2015, asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation (3). But there is not only one type of asthma. Asthma is rather a symptom complex of cough, wheezing, chest tightness, prolonged expirium and/or shortness of breath, than a single entity. It thus exists as a variety of different phenotypes. The classification of asthma has varied through the years (Table 1). At first, the classification has been based on two elements: allergic *versus* non-allergic asthma, whether the patient presented an allergic sensitisation or not. A classification by the Tucson Children's Respiratory Study (TCRS) in 1995 has then identified four time-based subtypes of "wheezing" asthma: transient, early onset, persistent and late onset. Also other classifications, with 5 (PIAMA) to 6 (ALSPAC) different categories have been recently proposed (4), based on the wheezing frequency reported by patients, and lately, a classification based on asthma endotypes and phenotypes and the underlying pathophysiology, with a multitude of categories and sub-categories has been suggested (5).

<table>
<tr><td>First asthma classification</td><td colspan="4">Non-allergic</td><td colspan="4">Non-allergic</td></tr>
<tr><td>Tucson Children’s Respiratory Study (wheezing phenotypes)</td><td colspan="2">Transient</td><td colspan="2">Early onset</td><td colspan="2">Persistent</td><td colspan="2">Late onset</td></tr>
<tr><td>ALSPAC (Wheeze temporality)</td><td>Never or infrequent</td><td colspan="2">Transient early</td><td>Prolonged early</td><td>Intermediate</td><td colspan="2">Late</td><td>Persistent</td></tr>
</table>

Table 1 : asthma classifications (adapted from Carlsen et al. (5)*)*

We focus only on one type of asthma for this study, namely exercise-induced asthma (EIA). In the reviewed literature, contradictory elements appeared. In a recent article of May 2015, it is stated that EIA is a misleading term and therefore not a subtype of asthma, because exercise is not an independent risk factor for asthma itself, but a trigger for bronchoconstriction in patients with underlying asthma and therefore, the term “exercise-induced bronchoconstriction” (EIB) should be preferred (6). In other articles, EIA is considered as a subtype of asthma, defined as “symptoms and signs of asthma occurring in an asthmatic after exercise” and EIB is defined as “reduction of FEV1 (forced expiratory level in 1 second) of ≥10% after a standardised exercise test” (5). This same definition of ≥10% reduction in FEV1 after an exercise test is used to define EIA instead of EIB (2). Although the ≥10% FEV_1 reduction cut-off is the most commonly reported in the literature, a higher cut-off of ≥15% is also used, due to its higher specificity (7).

However, in our study EIA and EIB will be considered as synonyms, because asthma is a phenomenon characterised by the narrowing of airways by a triggering element (infection, allergy, etc.) which, in this case, is exercise.

The underlying pathogenic mechanism of EIA is not completely understood but it is supposed that the increase of ventilation may be the triggering factor. Indeed, during exercise, the demand of oxygen is higher than in resting state. Thus to supply the needed quantity of oxygen, the ventilation will be increased. Normally, however, the inhaled air is neither at 37°C nor contains the humidity present in the airways. Thus warming up and humidifying will occur during the flow through the upper airways resulting in net heat and water loss of the airways. Two theories could explain exercise-induced asthma. The first theory is on a thermal basis. The cooling of the airways may lead to a reflex parasympathetic nerve stimulation, which will result in bronchoconstriction and a concomitant vasoconstriction to attempt to reduce the heat loss. When exercising is stopped, all the primary mechanism of increased ventilation stops and also its consequences (cooling and drying of the airways) disappear, leading to a rise in the airway temperature. This rise in temperature will induce a vasodilation as consequence leading to a subsequent mucosal oedema and smooth muscle constriction, reducing the bronchiole calibre and increasing airway resistance (5,8). This first theory however does not account for the role of mediators which have been found to play a role in exercise-induced asthma, such as leukotrienes. Further, studies have suggested that exercise-induced asthma can be induced by inspiring dry air at a temperature of 37^{o}C, while inspiring air saturated with water induces less bronchoconstriction (8). The second theory is based on an osmotic phenomenon. Water loss in the bronchial mucosa leads to an increase of osmolality in the mucus layer, inducing a water movement from the inside of the cells to the mucus. This leads to a decrease of intracellular water, which can lead to the release of mediators, either newly secreted or preformed ones such as histamine, also leading to bronchoconstriction (5,8).

The symptoms experienced during EIA are not different than in other asthma forms. Typically, the symptoms described after exercise would be cough, wheezing and shortness of breath, speaking in favour of asthma, whatever the form. If these symptoms are experienced only in exercise-related situations, EIA must be suspected as diagnosis (2,5).

One of the best tests available to diagnose EIA is the free running test, because it is the one to most likely provoke EIB, as other exercise testing, like running on a treadmill, cycling or swimming are less provocative. Free-running tests should be standardised in regard of humidity and temperature and have a concomitant heart rate monitoring. Heart rate monitoring is important, as it allows to determine the exercise performed by the patient. The exercise load for an exercise test should be maximal, meaning the heart rate of the patient should be measured at 95% of the real maximal value (not the theoretical one) (5). Alternative tests such as metacholine bronchial challenge or mannitol test may evoke the presence of EIA, but any link to exercise is not proved. The exercise test is considered positive if the decrease in forced expiratory volume in one second (FEV_1) is ≥10%. Exercise-testing, like free-running test, has a higher specificity than methacholine bronchial challenge for the diagnosis of asthma, but bronchial challenge testing has a higher sensitivity (5). Another test evoking EIA is the bronchoreversibility test, which is considered positive if there is an increase of 12% or more after inhalation of a bronchodilator. There are no definitions of EIA including forced expiratory flow at 25-75% of pulmonary volume (FEF 25-75), which is evocative for small airways disease, but it does not help in clinical decision making (9). Effort testing has a high specificity and lower sensitivity for the diagnosis of asthma, contrary to the bronchial challenge tests, which have more sensitivity than specificity (2,5).

The treatment of EIA is similar to them for allergic asthma. It is based on two categories of medicaments: controller and reliever treatment. Controller treatment relies on three types of drugs, namely inhaled corticosteroids (ICS), leukotriene receptor antagonists and cromones. ICS are the current baseline treatment for asthma, by their anti-inflammatory properties, and they allow an optimal control of the symptoms with an adapted dose in one to a few weeks (5,7). Other classes of control treatment are the leukotriene receptor antagonists (Montelukast) and cromones. Particularly Montelukast might be useful to treat EIA, but the treatment's efficiency has to be reviewed regularly (5,10). The reliever treatment is not a standalone treatment, such as the treatment mentioned above, but is used as pre-treatment before exercise, in addition to the baseline treatment. Available drugs for this treatment are inhaled short- or long-acting β2-agonists, or anticholinergic drugs as inhaled ipratropium bromide (5,7).

The symptoms of bronchoconstriction usually occur in a relative short time-lapse, particularly during endurance, reaching its maximum a few minutes after the exercise is stopped. The symptomatology experienced by the patient is not specific. EIA can be classified in a large section called exercise-induced dyspnoea (EID), which regroups other possible causes of dyspnoea, such as vocal cord dysfunction, exercise induced laryngomalacia, exercise-induced hyperventilation and others (11). These entities can be regrouped under the term dysfunctional breathing (DB).

Dysfunctional breathing is described in the literature, but not totally understood. This term has no clear definition and is often ambiguously used, with a multitude of synonyms, such as hyperventilation syndrome (HVS), somatoform breathing disorders, vocal cord dysfunction (VCD) and many others, each synonym having its own definition. Even well-known entities such as VCD have different names (factitious asthma, functional stridor, etc.). A recent article focusing on DB proposed the following definition: "alteration in the normal biomechanical patterns of breathing that result in intermittent or chronic symptoms, which may be respiratory and/or non-respiratory"(12). The multiple terms used to describe DB were classified in that article in two forms: thoracic DB (T-DB) and extra-thoracic DB (ET-DB). T-DB is a problem in the respiratory pattern of the patient, sometimes associated with hyperventilation and its consequences (hypocapnea, dizziness, etc.) or not. ET-DB describes an association between the altered breathing patterns and, additionally, an involvement of the upper airways, such as paradoxical vocal cord dysfunction (12). Furthermore, this article suggests one more sub classification of DB, further distinguishing between functional and structural DB. Functional DB implies that the structure and the function of the airways are normal, on the contrary of structural DB in which a structure abnormality is present, for example a stenosis of the upper airways. The aetiology of functional DB remains unclear and may be due to physiological or psychological causes, largely influenced by the autonomic system. Stress has been proven to alter function of the diaphragm by flattening, hypertonicity and immobility. Such changes could also be suspected in the upper airways. This response to stress is considered normal and appropriate. DB can be a persistence of this stress response, although the underlying stress situation is not anymore present (12). T-DB and ET-TB, although being similar entities, show differences in the symptoms, like wheeze (inspiratory or expiratory) and throat tightness in ET-DB and chest pain in T-DB, related to the difference in thoracic or extra-thoracic location (Table 2). But some of the symptoms, such as shortness of breath, sighing and difficulty with breathing in are common to both entities. Also further symptoms were described in other studies, such as chest tightness, frequent yawning, hyperventilation and breathlessness during effort (12,13). These symptoms are not specific for DB only, but are also present in other diseases, particularly such as asthma, and there is no available test to specifically diagnose DB. Therefore, DB can mimic other diseases or can co-exist with them.

Only a limited number of studies tried to assess the prevalence of DB, and most of them suggested that it is common, in the general population, as well as in the asthmatic population. The majority of these studies do not give a precise prevalence value. A study by Thomas et al. (14) and another by de Groot et al. (13) determined the prevalence of DB in asthmatic populations in adults and children, respectively. To determine the prevalence, the Nijmegen Questionnaire, which evaluates suggestive symptoms for dysfunctional breathing, has been used. The Nijmegen Questionnaire's

Table 2: Frequently met symptoms (adapted from Carlsen et al.(5) *and Barker et al.*(12)*)*

	EIA	T-DB	ET-DB
Wheeze	✓		✓
Sighing		✓	✓
Chest tightness		✓	
Hyperventilation		✓	✓
Chest pain		✓	
Shortness of breath	✓	✓	✓
Yawning		✓	✓
Cough	✓		

validity of use in an asthmatic population has been recently tested by Grammatopoulou et al. and was found to be valid not only in a general population (15). A score over 23 points is suggestive for DB and a score between 18 and 23 cannot exclude DB. 29% of the tested adult asthmatic population had symptoms suggestive of DB and 5.3% of the paediatric asthmatic population had symptoms suggesting DB and 11% with "possible" DB (12–14). A recent study by D'Alba et al. also studied the prevalence of DB in an adolescent population, with a prevalence of 2.5% in a non-asthmatic population *versus* 25.8% in the asthmatic population (16). Despite the prevalence differences, these three studies concordantly found that DB is more frequent in female than in male participants. An older study from 1986 turned the question the other way around and studied the prevalence of asthma in a population with DB. The prevalence in this population was at 80% (17).

The treatment of DB is primarily based on breathing retraining by physiotherapists or other professionals (12,18). The goal of breathing retraining is to normalise the altered breathing patterns, but this can only be achieved in the long run. Besides the breathing pattern, the aim of such treatment is to normalise the respiratory rate and/or tidal volume. This treatment is the same for both types of DB, as well as T-DB and ET-DB. In addition to the retraining of breathing, psychological support can be useful for some patients, in the form of cognitive behavioural therapy (12). Other studies suggest that treating the associated disease would be sufficient and that DB should be treated specifically only if the underlying lung disease cannot be treated effectively (19). A review from the Cochrane Collaboration from 2013, led by Barker et al., tried to identify studies on breathing retraining in children and their implications. Only few studies were found and most of them were performed in an adult population. Due to the lack of evidence by studies, breathing retraining in children cannot be recommended basing on the literature, but the study suggests that an improvement can be observed clinically (20).

The association of DB with asthma and other respiratory impairments are described in the literature, but not completely understood. Most of the articles on this subject focus on studying adult populations, while the paediatric population is studied only in a few articles and the studies principally focus on allergic asthma, rather than EIA.

The aim of this work is to study those patients prescribed respiratory physiotherapy for DB and EIA as defined by a fall of FEV1 of ≥ 10%, in comparison to those with DB but negative exercise test defined as a fall of FEV1 of < 10%.

Methodology

Literature

The articles for this study have been found by searching in Pubmed, Embase and Web of Science with the following search terms:

Dysfunctional breathing in children with asthma

dysfunctional[All Fields] AND ("inhalation"[MeSH Terms] OR "inhalation"[All Fields] OR "breathing"[All Fields] OR "breathing in"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields])

Exercise induced asthma children

("asthma, exercise-induced"[MeSH Terms] OR ("asthma"[All Fields] AND "exercise-induced"[All Fields]) OR "exercise-induced asthma"[All Fields] OR ("exercise"[All Fields] AND "induced"[All Fields] AND "asthma"[All Fields]) OR "exercise induced asthma"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields])

Dysfunctional breathing asthma

dysfunctional[All Fields] AND ("respiration"[MeSH Terms] OR "respiration"[All Fields] OR "breathing"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields])

For the theoretical part, two books were used as reference

- Carlsen K-H, Gerritsen J. Paediatric Asthma. European Respiratory Society; 2012

- Eber E, Midulla F. ERS Handbook of Paediatric Respiratory Medicine. European Respiratory Society; 2013.

Retrospective descriptive case series study

The study is based on medical and physiotherapeutic records referred to respiratory physiotherapy unit in the Children’s Hospital of Lausanne (Hôpital de l'Enfance Lausanne, HEL) for suspicion of dysfunctional breathing between January 2011 and May 2015.

The data collection in the medical records focused on three issues:

- General information, such as age, gender, BMI, family history

- Respiratory symptoms, spirometry and exercise tests (free running test). The exercise-test used is an outdoor free-running test without continuous heart rate monitoring and with spirometry after 3, 5, 10 and 15 minutes after the exercise was stopped. Heart rate is assessed after the test; in addition humidity and outside temperature are noted as it is the running distance. The aimed time of exercise was 6 minutes, but exercise was stopped by the patient when needed respectively with occurrence of symptoms. The definition of a positive test is a fall in FEV1 ≥ 10%. Positive broncho-reversibility is defined as increase of FEV1 % predicted of ≥ 12% ten minutes after inhalation of short acting bronchodilator (Salbutamol)(5). The standard measuring times for spirometry after exercise test were at 3, 5, 10 and 15 minutes post-effort. Additional, allergic tests and fractional exhaled nitric oxide (FeNO) where available.
- Treatment

In the physiotherapeutic records, it focused on the observations made by the physiotherapist and the respiratory symptoms presented by the patients during the treatment sessions.

The anonymity of the patients is guaranteed throughout the study.

Ethic

The study has been approved by the local Ethic Commission on Research (ECR) in March 2014 (protocol number 85/14) and the access to the records has been granted by the hospital's medical direction and the ECR.

Results

During the study period, a total of 28 patients were referred to the respiratory physiotherapy unit for DB. Out of these 28 patients, 9 patients were excluded, since it was impossible to access their medical records, as they were referred directly by paediatricians and not by the respiratory physicians. In addition, no pulmonary function tests were available in these 9 patients.

The analysed data are based on the remaining 19 medical records of children referred to the respiratory physiotherapy division of the HEL for suspicion of dysfunctional breathing.

Sample Characteristics:

The sample of patients addressed for respiratory physiotherapy was a predominantly non-athletic population. A general overview of the sample is presented in Table 3. The values depicted in this table, represent the data collected during the respiratory consultation in which the first exercise test was performed. The post-exercise (PE) values represent the maximal drop of FEV1, independently of the time it occurred after exercise stop.

The post-effort (PE) values represent the maximal decrease of FEV_1 and FEF 25-75 observed during the test, independently of the time after which it occurred.

Our sample comprised 15 (78.9%) female patients and 4 (21.1%) male participants. Most of the patients were adolescents with a mean age of 12.84 years and median age of 13.00 years, the youngest patient being 7 years old and the eldest 16 years old. The mean body mass index (BMI) in the group of patients was 20.06 kg/m^2 in a range of values from 16 to 25.11 kg/m2. The distribution of the patients in percentiles is illustrated in Figure 1. Fifteen (78.9%) of the patients were of normal weight (P3-P90), two (10.5%) overweight (P90-P97), one (5.3%) obese (>P97) and one (5.3%) underweight (<P3).

Patient	I	II	III	IV	V	VI	VII	VIII	IX	
Age	14	14	15	10	13	15	15	11	13	
Gender	F	F	F	F	F	F	M	F	F	
BMI	16	16.8	19.54	17.3	18.17	19.4	19	16.3	20.4	
BMI percentile	<3	3 – 10	25 – 50	25 – 50	25 – 50	25 – 50	25 – 50	50	50 – 75	
Allergic Tests	x	0	1	1	1	1	x	x	0	
Resting FEV1 (L)	3.17	3.16	3.35	3.34	3.09	2.91	2.04	2.92	2.33	
Resting FEV1 (%)	110	118	113	102	117	86	92	111	106	
Resting FEF 25-75 (L)	3.1	3.55	3.96	3.08	4.03	2.66	3.84	3.22	3.18	
Resting FEF 25-75 (%)	87	105	108	77	121	65	135	97	112	
PE FEV1 (L)	x	2.81	2.28	1.69	1.62	1.93	3.58	x	2.19	
PE FEV1 (%)	x	-4.00%	-32.00%	-8.00%	-6.00%	-34.00%	-4.00%	x	-6.00%	
PE FEF 25-75 (L)	x	3.03	2.15	1.63	2.36	1.52	3.87	x	3	
PE FEF 25-75 (%)	x	-6.00%	-46.00%	-23.00%	-14.00%	-43.00%	-8.00%	x	-6.00%	

Patient	X	XI	XII	XIII	XIV	XV	XVI	XVII	XVIII	XIX
Age	12	7	12	14	14	13	14	16	12	10
Gender	F	M	F	F	F	F	F	M	M	F
BMI	19.8	16.55	21.17	22.8	22.2	21.3	23.9	25.11	20.9	24.5
BMI percentile	75	75	75 – 90	75 - 90	75 - 90	75 – 90	75 – 90	90	90	>97
Allergic Tests	0	0	1	0	0	x	1	x	0	0
Resting FEV1 (L)	4.59	3.04	2.48	1.91	2.55	1.8	3.31	3.71	1.99	2.39
Resting FEV1 (%)	110	90	101	92	92	91	101	96	68	96
Resting FEF 25-75 (L)	5.07	3	3.43	1.5	3.02	3.13	4.53	4.2	2.37	3.43
Resting FEF 25-75 (%)	111	73	110	58	87	121	116	98	65	115
PE FEV1 (L)	2.85	1.93	2.94	2.65	2.95	2.5	3.18	4.35	1.8	2.44
PE FEV1 (%)	-8.00%	1.00%	-7.00%	-16.00%	-12.00%	-2.00%	-4.00%	-5.00%	-25.00%	-2.00%
PE FEF 25-75 (L)	3.83	1.61	2.68	2.5	2.51	2.73	4.2	4.76	1.13	3.26
PE FEF 25-75 (%)	-5.00%	7.00%	-14.00%	-30.00%	-19.00%	-10.00%	-7.00%	-6.00%	-67.00%	-5.00%

PE = Post effort X = missing data 1 = positive 0 = negative = positive effort test

Table 3: summarized results of 19 patients referred to physiotherapy rehabilitation in the HEL

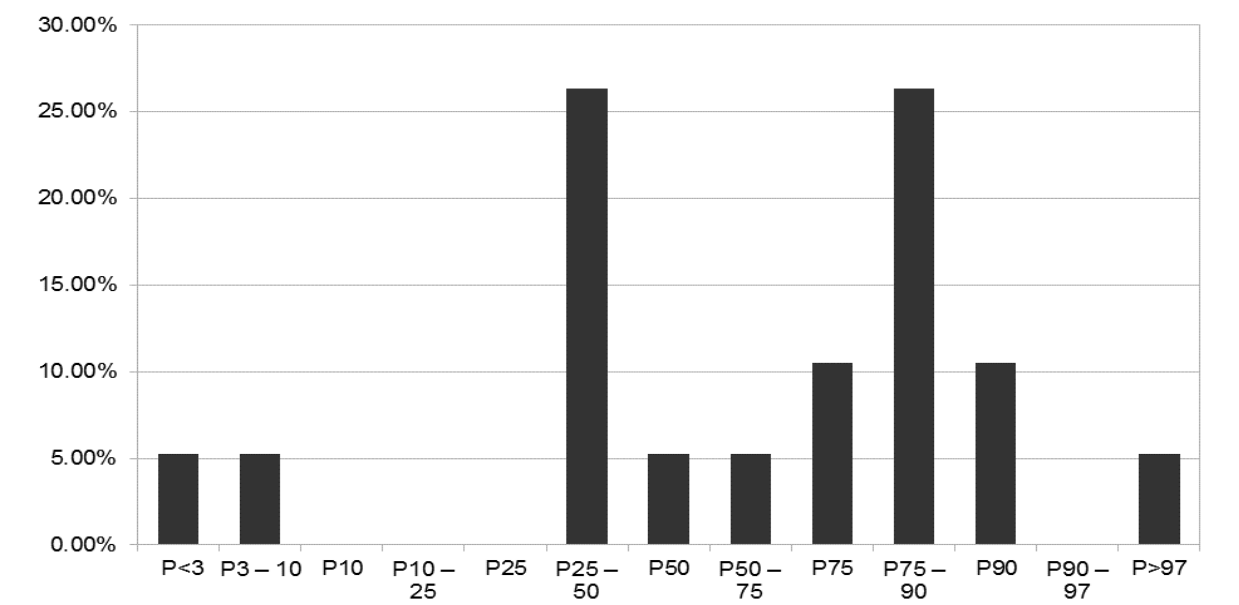


Figure 1: Patient BMI percentile repartition

Allergy testing:

Allergic tests were performed in most patients and are presented in Figure 2. Most of the tests were negative (42.1%), but about one third (31.6%) came back positive. Allergic tests were not performed in (26.3%) of the patients. One third of the positive tests were performed in the subgroup presenting EIA associated with DB. The other two thirds of positive tests were performed in the sample with DB only.

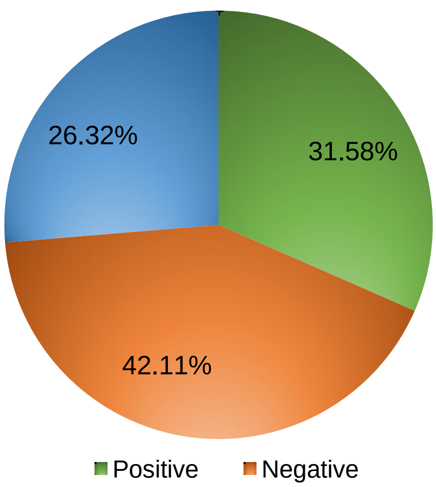


Figure 2: Allergic tests

Symptomatology:

More respiratory specific data had also been collected. An overview of the symptoms' prevalence is presented in Figure 3. This symptom list has been chosen based on the symptoms described in the introduction for exercise-induced asthma and for dysfunctional breathing, representing the most frequently met symptoms in these pathologies. The symptoms are not unique to exercise, but might be part of general asthma symptoms and with possible occurrence at rest also. The symptoms mainly found during exercise are breathlessness, dizziness and hyperventilation. The number of symptoms presented by the patients in our sample varied from minimum 1 to maximum 5 per patient, without a clear difference between weight classes. The subgroup with the association of DB and EIA reported slightly more symptoms (min 1 – max 5) than the subgroup with only DB (min 1- max 4).

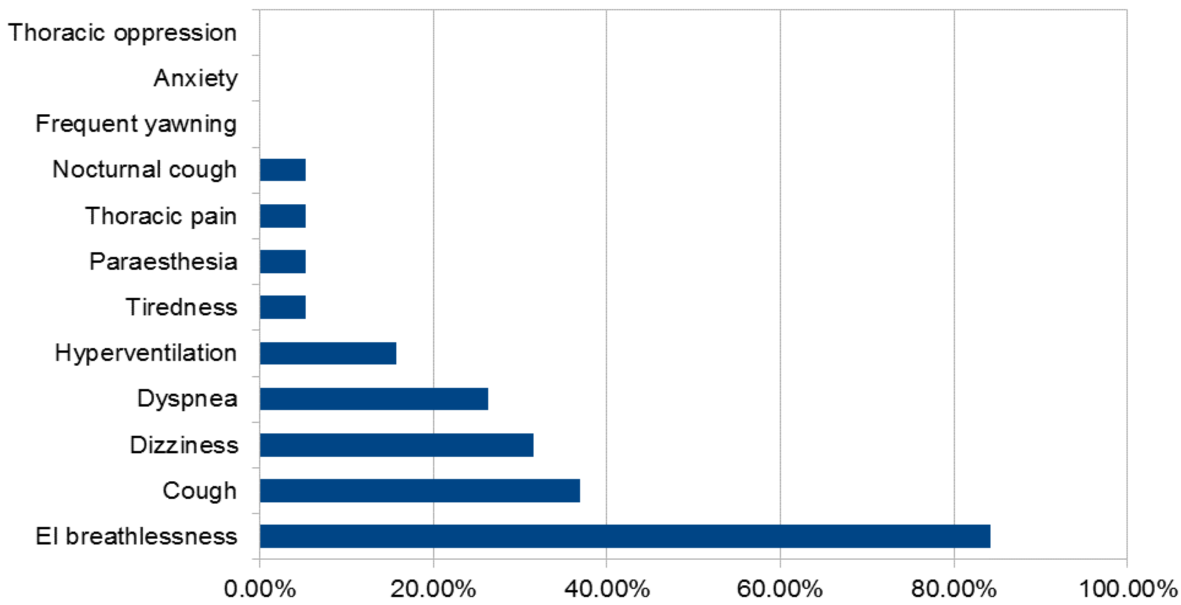


Figure 3: symptoms presented by the patients in the general sample

Exercise-testing:

Figure 4 shows the results of the exercise tests' analysis.

The prevalence of EIA in our sample was 26.3%, with five patients out of the 19 having a positive exercise test. The patient sample with positive exercise-testing is similar compared to the whole sample in the following points: The male-female proportions are the same (80% female – 20% male in the EIA&DB group *vs* 79.0% female – 21.0% male in the general sample). The mean age is slightly higher with 14 years compared to the whole sample. The mean BMI is also comparable to the whole sample.

Broncho-reversibility tests were performed in 8 patients (42.1%), thereof 5 (62.5%) were performed in patients presenting EIA associated to DB and 3 (37.5%) in patients with DB only. All the tests performed in patients presenting DB only were negative, on the other hand, the tests performed in patients with the association of DB and EIA were all positive (*i.e.* FEV_1 increase of ≥12%).

These five cases will be discussed in more details separately in the individual case presentations to illustrate the possible association between exercise-induced asthma and dysfunctional breathing and the role of physiotherapy, allied to conventional asthma treatment.

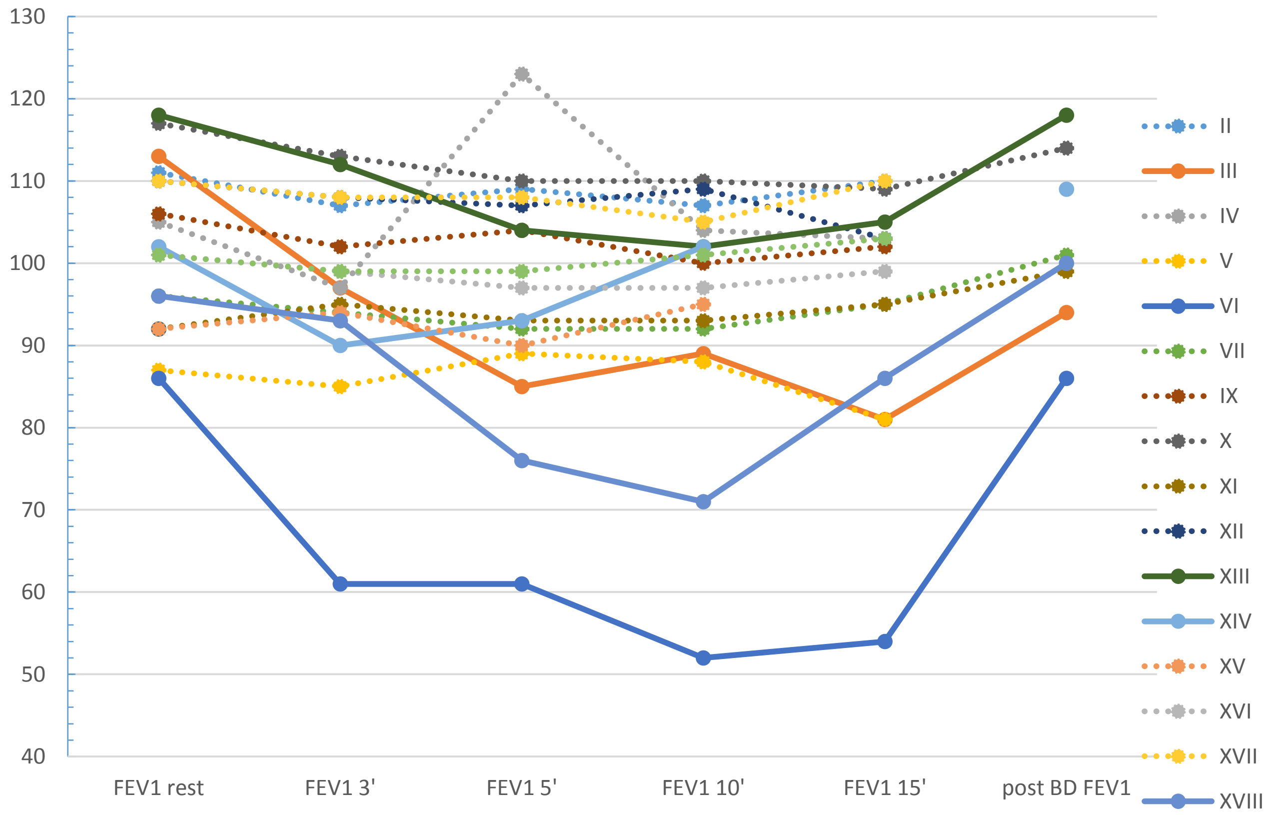


Figure 4: FEV_1 of perfomed exercise tests (plain lines: patients with asthma)

Case presentations

The five identified cases with the association of EIA and DB are presented in detail in the "Annex" section.

Discussion

Out of 19 patients referred for respiratory physiotherapy for DB, we identified 5 patients who had also positive exercise tests, *i.e* a drop in FEV1 of ≥10%, signing an associated EIA.

Compared to a study from 1986 by Demeter et al. (17), where in a group of 47 adult patients with hyperventilation syndrome, which is a synonym for DB, 38 patients had positive asthma testing (prevalence of asthma: 80%), we find a much lower prevalence of 26.3% in our sample.

However, major differences between the studied populations exist. We focused on a paediatric respectively adolescent population and looked for a specific entity of asthma, while the above mentioned study focused on an adult population and looked for asthma in general. Nevertheless, it is the only study found in the literature which assessed a prevalence of asthma in a DB population, and not a DB prevalence in an asthmatic population. The prevalence of EIA in our group could be underestimated due to false negative exercise-tests. Exercise-testing has a good specificity to diagnose EIA, but a lower sensitivity in comparison to metacholine bronchial challenge, which has a better sensitivity than specificity (5).

The remaining 73.7% of the patients in our group had an “isolated” form of DB, without any other respiratory condition. These patients were often referred to the respiratory outpatient clinic by their treating paediatrician, who suspected asthma, showing that DB can mimic other respiratory pathologies. For these fourteen patients, the treatment consisted essentially in respiratory physiotherapy with a good evolution and regression of symptoms. The large predominance of female patients in our group (79.0%) is in accordance with the observations made by other studies in the literature, which also found that DB is more frequently in female patients than in male patients, no matter if the studied population is adult or paediatric (12,14).

The patient’s symptomatology in our sample had a repercussion on their daily life. It didn’t allow them to participate fully in exercise activities, such as school sports, dancing and other activities. At rest, most of the patients did not experience any symptoms or the rest symptoms were not the same as those experienced during exercise.

The symptoms found among both groups with and without EIA were nonspecific, without a clear constellation in one group or the other. The main symptom found in both group was EI breathlessness, which isn’t surprising, since both entities, DB as well as EIA, can manifest through this symptom. In the group of five patients with an association of DB and EIA, two patients didn’t show exercise-related breathlessness, although intuitively it is expected that the combination of both conditions would lead to a higher expression of such a symptom. This might be due to insufficient exercise during the test. The second most frequent symptom encountered in our sample was cough. Two studies of Carlsen et al. (5) and Barker et al. (12), suggest that this symptom is more typical for EIA patients rather than DB patients. In our study, cough was present in 37% of the patients, which is more than the frequency of EIA in our patients. After a closer look, only one patient in the DB/EIA group presented cough and all the other patients presenting cough were in the DB only group. Other symptoms which manifested in our sample such as dizziness (31.5%), dyspnea (26.3%) and hyperventilation (15.8%) were interesting to compare. Dyspnea occurred solely in the group with EIA- DB association with a frequency of 4 out of 5 patients. In one case, it was the only symptom reported by the patient (case 4). The other two symptoms, hyperventilation and dizziness, were associated as expected and, as described in the literature, with a linking causality. Hyperventilation is the “trigger” symptom, leading to hypocapnea, resulting in respiratory alkalosis. This phenomenon of alkalosis will induce a constriction of the arterioles in the brain, consequently reducing blood flow, thus leading to dizziness (21). In regard of this causality, it can be assumed that hyperventilation is present at first and, depending on its severity, dizziness occurs in a second time. In our group of patients, dizziness was the third most frequently met symptom (26.3%) and hyperventilation only the fifth (15.8%), which was not expected, in regard of the latter described mechanism. In one case there was an association between both symptom-entities, but two other cases of hyperventilation did not present dizziness, which can be normal if the respiratory alkalosis is not strong enough to cause a cerebral vasoconstriction. Surprisingly, in five out of six cases, dizziness was reported by patients, even though hyperventilation as trigger element was not evident.

The other symptoms described in figure 3 and found in our sample (tiredness, paraesthesia, thoracic pain and nocturnal cough) were only present in one case out of 19. Therefore it is impossible to draw any conclusions for these manifestations. One particularity that should be briefly mentioned for these symptoms is the nocturnal cough. According to the literature, cough might suggesting asthma, with nocturnal cough being no exception (22). The patient with nocturnal and daytime cough, also showed exercise related breathlessness, evoking an asthma, but the exercise testing for asthma was negative. It is however not excluded that this was a false negative exercise test.

The group DB associated to EIA presented slightly more symptoms than the DB only group, but the difference is not significant, since each group presented a high variability in the number of symptoms. Also, no difference between the weight based categories in the sample could be observed. Each group had a mean number of 2 or 3 symptoms, with a high variation in absolute numbers of symptoms. This relative small difference between weight groups is probably due to the small number of patients in most of the groups. Generally, it was expected that the overweight and obese group would present more symptoms, due to deconditioning or higher exercise levels. The BMI e.g. has been described to have an influence on the risk for asthma. A study by Lau S. and Wahn U. (5), found that both extremes of BMI are putting the person/patient at risk for developing asthma. Underweight is a risk factor for early wheeze and lower lung functions and obesity in particular is associated with asthma and a risk factor for more severe forms. The analysis of the exercise tests is based essentially on the FEV1 values. We used as definition a fall of ≥ 10% in FEV1 (5,7). This threshold is however not yet clearly defined due to the fact that others propose a fall of ≥ 15% (7), respectively to apply a sport specific fall of FEV1 in % predicted.

The baseline data of patients with an association of EIA and DB are similar to the overall sample in respect to its general features, i.e. age, gender, BMI, familial history.

Within the sample of these five cases some common points can be highlighted. The personal history is complex with overlapping symptoms. Each patient at some point of his medical history shows non-specific respiratory symptoms happening during exercise (mainly endurance sports), in the majority with improvement at rest. However, these symptoms lead to different investigations. Mainly, a respiratory aetiology was rapidly suspected and investigated; in some cases multiple cardiologic investigations have been performed to exclude exercise related cardiac disease. Another common point in 4 patient histories was a positive family history of asthma either alone or combined with allergies, which however, did not mean that the patient suffered from allergies himself.

In most cases, DB has been diagnosed after EIA. After positive effort testing, patients were prescribed a standard combination of anti-asthmatic treatment of inhaled corticosteroids (ICS) and bronchodilators. This treatment led to a relative improvement of the symptoms, but not to a complete disappearance. Even higher doses of ICS and bronchodilators or other treatment trials were inefficient and didn't resolve the situation. Sometimes the patients had follow-up spirometries performed, with an improvement of lung functions, but with a clear persistent attenuated form of symptoms. These symptoms remained the same as those experienced before during exercise, prior to the introduction of anti-asthmatic treatment. These symptoms and their resistance to asthmatic treatment with ICS or beta-agonists were evocative for DB (Table 2). Follow-up exercise-tests were however not systematically performed. This kind of follow-up could have brought an objective way to monitor improvement during exercise respectively the efficiency of EIA management in these patients, to better discriminate between EIA and DB. After the diagnosis of DB was retained, physiotherapy treatment was prescribed. The respiratory physiotherapy was adapted from patient to patient with a highly variable number of sessions. Even with this high variability of sessions and its repartition over time, these sessions helped to improve the remaining symptoms.

Another interesting point in some of these cases are the emergency department consultations, not related to asthma at all. The episodes leading to these consultations are more evoking a DB problematic, even though the patients had not a fully adapted anti-asthmatic treatment at this point. Such situations, with a patient suffering from asthma and no adequate treatment, are at risk for asthma exacerbations. But why did the patients not exacerbate in the same situation? Our hypothesis is that DB assumes a protective role in these patients. It is not possible to affirm this scientifically with this study, but there are some clues in favour of our hypothesis. The first one is the symptomatology. The most reported symptoms in the five cases are those which are typical for DB rather than asthma, confirmed by the not so good response to anti-asthmatic treatment, or not specific symptoms, like shortness of breath/dyspnea. The absence of asthma-like symptoms suggests that the patients are not able to fully develop an asthmatic response during exercise, because the exercise is interrupted prematurely, due to DB. When a proper exercise-test is performed and the patient is brought to the limits the spirometry can reveal an exercise-triggered bronchoconstriction. The second one is the low number of emergency consultations. None of them was asthma-related and even not exercise-related. Someone might now argue that if such a mechanism of DB exists, to protect the patient to experience an asthma exacerbation, it would be wrong to address therapeutically the DB as it would only put the patient on risk for such an exacerbation. This is somehow correct, however as patients were limited in quality of life in routine exercise as school sport, from our point of view DB and EIA should be treated accordingly. Our treatment suggestion for patients presenting with DB or EIA, at first, is to investigate if only one condition is present or if the patient presents an association of both and treat accordingly. A possible treatment algorithm is presented in Table 4.

The fifth case (see appendix) is more complicated to analyse, due to the patient's psychological condition. The origin of DB in this case might be as well as due to these psychological factors as a protection for EIA. Further, the symptomatology is nonspecific with hyperventilation and dyspnea and doesn't help to differentiate the origin of DB. However, this case raises the question to refer patients with DB, in addition to physiotherapy and respiratory consultation, also to a psychologist, which is suggested by Barker et al. for individual patients (12).

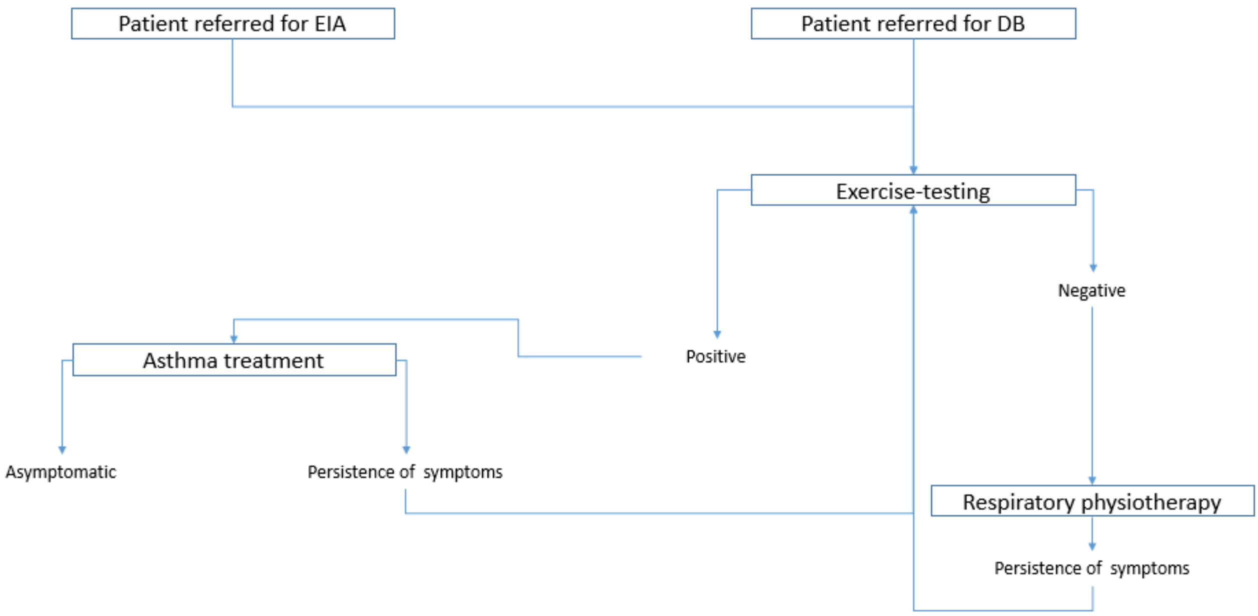
Even without a scientific proof of our hypothesis, there might be an implication of our hypothesis in regards of the respiratory physiotherapy. The explanation to the patient that DB has developed to prevent strenuous exercise and, by that, high risk of asthma exacerbation, facilitates probably the acceptance of the patient of having DB. This in return might facilitate the intervention by the physiotherapist. However, our collective was too small to have significant numbers for a scientific proof.

In regard of the exercise-related nature of these conditions and the mostly non-athletic population of our sample, it raises the question of exercise tolerance of our collective. Are the symptoms only related to EIA and DB, or are they partly due to a low exercise-tolerance? It is difficult to differentiate these two possibilities with our results. However, as it cannot be excluded, it is interesting to review the possibilities of intervention. Respiratory muscle training (RMT), although exact mechanism are still unknown, has been shown to increase exercise tolerance in athletic patients and is used in patients with obstructive lung disease (23). A Cochrane review of 2013 reviewed the potential use of RMT for asthmatic patients. There is today no clear evidence to support or refute the utility of RMT in an asthmatic population (24). However, it would be interesting to investigate such interventions in further studies.

The strengths of our study are that it is, to our knowledge, the first study to focus on the role of the association between DB and asthma. Most studies in the literature are focusing on the description of this association, but not on the impact of one condition on the other. Another strength point is the studied population. Studies on this subject in paediatrics are not frequent.

There are however many limitations with this study. It is a retrospective case series study with only 19 participants from one outpatient clinic. Therefore, the collected data-set was difficult to standardise and often relevant information was missing. To confirm our observations, a prospective study with a higher number of participants should be performed. This would allow standardising data collection and as well obtaining a stronger statistical evaluation. Secondly, the field exercise test in the respiratory consultation lacks precise standardisation as continuous heart rate monitoring. This is only somehow outweighed by the fact that during the free running test without technical equipment a real life situation was created, with most often appearance of the same symptoms which lead to a respiratory consultation. Thirdly, it lacks also a standardised questionnaire as the Nijmegen Questionnaire. Importantly, no registry exists in the respiratory consultation, in contrast to a basic registry in the physiotherapy unit, limiting the analysis to those cases referred to the in-house physiotherapy unit. Finally, patients were seen by different physiotherapists, with again a lack of standardisation in regards of the respiratory therapy. To improve further studies in this field, standardised information gathering should be a primary objective. The parameters in our study provided a basic information, but more specific information is needed as well. Therefore, we suggest to have a “respiratory check-list” to report precisely the symptoms and their timing (exercise-related or not). The symptoms presented by the patient should be completely investigated and specified). Other information such as socio-economic environment or training status also should be evaluated. Exercise-testing also should be consequently standardised with continuous heart rate monitoring, allowing to evaluate the exercise-intensity of the patient. If the patient’s symptomatology is only exercise-related, exercise-testing should be used as monitoring tool to evaluate the efficiency of anti-asthmatic treatment and to discriminate between EIA and DB symptoms. Another information which could have its importance in a sample like ours is the puberty staging, which has an impact on exercise tolerance and therefore influence the exercise-testing, due to higher respiratory muscle endurance in adolescent or preadult patients (25).

Table 4: management proposition for patient with EIA&DB association



Conclusion

DB is a frequent comorbidity in an asthmatic population, but also a frequent entity in the general population. The association of DB and asthma is described by multiple studies in the literature, but it is not completely understood and it is mostly studied in adult population. Our study suggests that DB might be playing instinctively a role in preventing EIA exacerbations. DB needs specific physiotherapy treatment particularly in those patients with EIA because treating only the EIA is not sufficient to resolve the exercise induced symptoms. Even though DB could be a protective factor for untreated asthmatic patients, the endpoint of patient follow-up should be aimed to allowing the patient to fully participate in every day's exercise-related activities without experiencing symptoms of these respiratory entities. Therefore, even though more studies are necessary, both entities, EIA and DB, should be treated to pursue this endpoint. The sequence of treatment, if our hypothesis is confirmed, should be focused in a first time on the potentially life-threatening condition, *i.e* EIA, and once this part of the treatment is efficient, basing on follow-up exercise-test results, the treatment should be focused on dysfunctional breathing.

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Annex

Table 5: Drug classes used in EIA treatment

	Short-acting β2 agonist	Long-acting β2 agonist	ICS	Lt-R antagonist
Salbutamol	✓			
Formoterol		✓		
Salmeterol		✓		
Budesonide			✓	
Fluticasone			✓	
Montelukast				✓

ICS: inhaled corticosteroids   Lt-R: leukotriene receptor

Case 1: Patient III (Table 3) Birth year: 1996 Gender: F

At age of 15, she presents with about one year exercise induced dyspnea, associated with thoracic pain, which causes dizziness and sometimes loss of consciousness, and in a second time a dry irritative cough associated to thoracic pain after 20 minutes of exercise. The patient is known to have allergies to bees, wasps and jellyfish, but not known for allergies to inhaled allergens. Family history is positive for allergies and asthma. The symptomatology presented during effort by the patient has led to multiple investigations in paediatric cardiology. During an ergospirometry, the patient developed a symptomatology similar to what she had previously experienced with breathing dependent thoracic pain, associated with nausea and important tiredness. The breathing during this episode was rapid and superficial, evoking a hyperventilation crisis. During a Tilt-test, to search for a vaso-vagal syncope after an episode of hypotension, she developed again hyperventilation symptoms.

After exclusion of a cardiac aetiology for the loss of consciousness, with normal resting electrocardiogram (ECG) and prolonged ECG monitoring, normal echocardiography and negative ergospiromtery, she was referred to the respiratory outpatient clinic.

During the first consultation, besides FeNO and a resting spirometry which were normal, an exercise test was performed. Free running test of 5 minutes 50 seconds with 5 minutes post effort, thoracic pain appeared with an associated hyperventilation crisis. Further 15 minutes post effort, the FEV1 fell 32%% with a positive broncho-reversibilitytest (FEV1 +19%), signing an EIA.

To note that the patient had also consulted two times the emergency department for hyperventilation crises without doing exercise. Due to the diagnosis of EIA associated with hyperventilation symptoms as DB, medical treatment and respiratory physiotherapy were prescribed.

The respiratory physiotherapy, 8 sessions in 3 months, focused on abdomino-diaphragmatic breathing, expirium prolongation and breathing management during effort as treatment points. She improved and could restart her dancing training. Physiotherapist reported however a dry, irritative cough appearing quickly during effort which hinders effort management.

Besides of bronchodilator inhalation (Salbutamol) just prior to exercise, change of fluticasone/salmeterol, for budenoside/formoterol 100/6 one inhalation in the morning. The concomitant adding of montelukast lead to a diminution of respiratory symptoms, but presented side effects (morning nausea and light headache). Finally, budenoside/formoterol was reset with the following dose: 100/6 2 inhalations 2x/day. The compliance to the treatment was not always optimal, due to other health problems as abdominal pain with diagnosis of nutcracker syndrome, which worried her a lot. But during time periods with a good compliance, the treatment has led to an improvement of the symptoms, including the dry irritative cough.

Case 2: patient XIV (Table 3) Birth date: 1997, Gender: F

At age of 14, this athletic patient was referred by the sport medicine consultation. She has five swimming trainings per week. She complains about exercise dyspnea for one year, principally in swimming, endurance sports and sports in cold air. She describes inspiratory difficulties with audible noise. She consulted therefore in sport medicine, where a spirometry has been performed which showed a FEV1/FVC of 64%, diminishing to 57% after exercise without bronchospasmolysis after inhalation of salbutamol.

Family history is negative for allergies.

At the respiratory outpatient clinic, pulmonary functions were tested, with normal results, and the free running test was performed outside with duration of 12 minutes (temperature of -6^{o}C and a humidity of 40%), heart rate measured at 170 bpm post exercise. Three minutes post exercise, a maximal diminution of 12% could be observed. The bronchospasmolysis test was also positive with a rise of 19% of the FEV1, leading to the diagnosis of EIA. The symptomatology reported by the patient after this effort test was the same as experienced before. The following treatment was prescribed: budenoside/formoterol (100/6 1 inhalation 1x/day) on days with sport, with salbutamol 1-2 inhalations just before physical activities, as well as montelukast if dyspnea persists under treatment.

Under this treatment, she presents a positive evolution. An improvement of dyspnea has been reported by the patient, but still repercussions on endurance activities like running and swimming. At this point, dysfunctional breathing is suspected and physiotherapy sessions are prescribed.

The physiotherapy (6 sessions in 5 months) focused on respiratory consciousness and learning of abdominal respiration. The patient remarked quickly changes and was able to do exercise without symptoms. For a total follow-up of three years, the patient could progressively diminish her medications, reaching a complete stop of it without recurrence of symptoms even during training and competitions.

Case 3: Patient VI (Table 3) Birth date: 1996 Gender: F

The patient was referred on the demand of her mother by her treating paediatrician. The medical history of this patient is loaded and she had already consulted an allergologist and a pulmonologist before. Her first known asthma exacerbation occurred at age 3 with associated signs of respiratory distress. Allergic tests were performed and were positive for dust, grass pollens and house dust mites. Since this first asthma exacerbation, the patient had 4 to 5 asthma exacerbations per year. The respiratory problems of the patient are manifest essentially by a cough with nocturnal predominance and wheezing. The asthma occurs during respiratory infections, can be triggered by emotions and is persistent during effort and cold air exposure. The family history is positive for allergies.

At age 16, she describes respiratory difficulties during sports, which hinders her to continue effort. These difficulties are not the same as experienced before during asthma crises. The symptoms vanish rapidly after interrupting sports and appear predominantly during endurance activities. A free running test and a spirometry have been performed. The baseline spirometry showed a normal FEV1 of 90% but a slightly decreased FEF 25-75 of 65% of predicted value. She stopped the free running test after 2' 20'' due to a hyperventilation crisis. She reported that she was at her maximum, but wanted to stop before because of the fear to trigger an asthma exacerbation. The maximal FEV1 decrease of 8% occurred 15 minutes after interrupting the test, reason why EIA could not be diagnosed at that point. The bronchoreversibility test was however positive with an increase of 16% of the FEV1. The follow-up has been lost for more than one year and a half, because of severe depression, without knowing if she was treated with medications. During this period of time, she began smoking 1 pack of cigarettes per day. She restarted sports at school, but develops rapidly symptoms which hinder her to continue effort. A second effort test has been performed. At rest, the FEV1 is of 86% and the FEF 25-75 of 65%. After the free running test of 2' 07'', the maximal FEV1 diminution of 34% occurred after 10 minutes, with a complete bronchoreversibility. During the free running, signs of hyperventilation could be observed, speaking for an underlying dysfunctional breathing. Heart rate was measured at 140 bpm.

The positive exercise-test and the clinical observation of hyperventilation speak for an association of EIA with concomitant dysfunctional breathing.

Physiotherapy sessions have been prescribed, with a local physiotherapist due to organisational reason. The physiotherapy sessions have been beneficial to the patient.

The respiratory treatment prescribed initially consisted of montelukast in addition to fluticasone/salmeterol. The respiratory symptoms are persistent under this type of treatment and the patient presented a single moderate asthma exacerbation, reason why the fluticasone/salmeterol treatment was increased to 250 mcg 2x/d and adding salbutamol, 2 pushes/4h by her treating physician. At her next respiratory outpatient clinic, this treatment has been replaced by budenoside/formoterol 400/12 one inhalation per day, and salbutamol inhalation again just prior to sports. Due to good evolution, the budenoside/formoterol dose has been reduced to 200/6 one inhalation prior sports, however follow-up was unfortunately lost since then.

Case 4: patient XVIII (Table 3) Birth date: 2001 Gender: M

Patient first consulted the respiratory outpatient clinic at age of 12 years. He reported for 3 years ongoing pain in the left hypochondrium, a buccal and wheezing breathing and also coughing 10 minutes after beginning sports (essentially running). These symptoms disappear after a few minutes of rest. No treatment has been tried.

He is also known for obesity and chronic nasal obstruction due to nasal septum and pyramid deviation. There is no notion of known allergy or eczema, with negative tests (IgE and prick-test) performed by an allergologist.

In his familial history there is no evidence of familial asthma. His elder brother is known for allergic rhino-conjunctivitis and obstructive bronchitis in early childhood.

Environmental history was positive for second hand smoke at home.

A free running test and spirometry has been performed. Normal baseline spirometry at rest. The patient interrupted effort after 4'30'', due to breathing difficulties. Heart rate was measured at 138 bpm. After 10 minutes post exercise, the spirometry showed a significant drop of 25%, speaking for EIA. The bronchoreversibility test was positive with an increase of FEV1 of +29%. A concomitant DB in form of respiratory dyscoordination is suspected due to the technique during pulmonary function tests, and respiratory physiotherapy sessions have been prescribed.

The physiotherapist noted difficulties in respiratory coordination and quick breathlessness in this obese patient during exercise including a test where he had also to sing. The therapy consisted in postural work and coordination of inspiration and expiration as well as using abdominal breathing during effort. Only little improvement during the first 6 sessions leading to a new series of 6 sessions, with finally clinical improvement of his respiratory technique.

Regarding medication, budenoside/formoterol, 100/6 1 inh 2x/d and salbutamol, prior to exercise have been prescribed, but the compliance to the treatment was unfortunately never optimal, including lack of trying to use Salbutamol before exercise. Finally, due to social family issues it was only possible that the patient was followed-up with the referring paediatrician, a previous registrar in the respiratory unit with knowledge about the problematic, with the advice to send him back to us in case of persistence of symptoms.

Case 5: Patient XIII (Table 3) Birth year: 1997 Gender: F

This patient was initially referred to the HEL for respiratory physiotherapy by her treating paediatrician, who reported that the patient had difficulties to breathe during endurance sports at school and at night, which caused the patient to wake up frequently.

In the medical history of the patient, there are two notable elements to mention. First, the patient had a psychological following for behavioural problems and hyperactivity, with parental problems and problems at school with her classmates, in form of mockery. The second element was an emergency consultation after an incident at school. Classmates had held her under water multiple times. The teacher reported a peribuccal cyanosis of unknown duration, but no loss of consciousness. The ambulance crew reported hyperventilation and a rapidly regressing Trousseau sign. The investigations at the hospital, limited to a blood gas analysis, and clinical examination, were all normal and the patient was discharged from the hospital. The major diagnosis retained for this episode was post stress hyperventilation.

The physiotherapy sessions focused on respiratory and body consciousness (open glottis, abdomino-diaphragmatic breathing), diaphragma relaxing and effort breathing rhythm. The evolution was positive, but not concluding, since the patient only showed up to the sessions three times before she stopped, due to a lack of time.

A few months later, the treating paediatrician referred the patient to the respiratory outpatient clinic for further investigations. The patient reported dyspnea and dizziness occurring during non-important exercise, like walking, and endurance and dyspnea also occasionally occurring at rest. A treatment of unknown dosage fluticasone/salmeterol, and salbutamol prior exercise, did not improve the symptoms.

Her family history is positive for allergic asthma. The physical examination was normal. Complementary IgE quantification showed an allergy to pollen. The resting spirometry and the FeNO were normal. A free running test was performed for duration of 6 minutes 18 seconds. The post effort spirometry showed a maximal fall of FEV1 of 16% after 10 minutes, speaking in favour of EIA. A bronchoreversibility test was performed and positive, with an increase of 13%. The main symptom reported after this test was hyperventilation.

After this consultation, a treatment of budenoside/formoterol 100/6 1 inh 1x/day and Salbutamol prior exercise was prescribed, however the efficiency could never be evaluated and follow-up was unfortunately lost due to multiple psychological issues.