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Parasympathetic activity in endurance athletes with and without asthma and healthy controls:

a cross-sectional study

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"Parasympathetic activity in endurance athletes with and without asthma and healthy controls: a cross-sectional study"

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Abstract

Background: Several studies have suggested that high intensive endurance training may promote the development of asthma and airway hyperresposiveness (AHR) through increased parasympathetic tone. There was association of parasympathetic parameters in elite swimmers with clinically relevant AHR. Increased parasympathetic activity in the airways of elite cross-country and biathlon skiers was also observed which contributed to asthma development. This further supports the role of autonomic nervous system in the development of airway responsiveness in elite endurance athletes.

Objective: The main objective was to compare parasympathetic activity between endurance athletes with self-reported asthma to endurance athletes without asthma. The second objective was to investigate possible associations between parasympathetic activity and training components in the same population.

Methodology: A cross-sectional study was conducted with 26 asthmatic endurance athletes, 27 healthy endurance athletes, and 28 healthy non-athlete controls. Pupillometry and four seconds exercise test (4sET) were used to measure parasympathetic activity.

Results: The present study found that asthmatic athletes had significantly lower value of minimum pupil diameter and pupil percent constriction than healthy athletes but not different with controls. No significant differences observed in cardiac vagal index resulted from 4sET. There were significant differences in training frequency and duration of the three groups. Daily training frequency and 2-3 hours duration of training had relationship with some pupillometry parameters in athletes.

Conclusion: The findings from the present study showed increased parasympathetic activity in asthmatic athletes compared to healthy athletes. Daily training frequency and 2-3 hours duration of training was related to parasympathetic activity changes in athletes.

Key words: asthma, endurance athletes, pupillometry, cardiac vagal index

Abbreviations		**Unit**
4sET	Four seconds exercise test	-
ACV	Average constriction velocity	mm/s
AHR	Airway hyperresponsiveness	-
ANS	Autonomic nervous system	-
CVI	Cardiac vagal index	-
ECG	Electrocardiography	-
EDA	Electrodermalactvity	-
EEG	Electroencelography	-
EGG	Electrogastrography	-
EOG	Electrooculography	-
EVH	Eucapnic voluntary hyperpnea	-
FEV_1	Forced expiratoryvolumein onesecond	$l \bullet min^{-1}$
FVC	Forced vital capacity	$l \bullet min^{-1}$
GI	Gastrointestinal	
HRV	Heart rate variability	-
IgE	Immunoglobuline E	-
MCV	Maximum constriction velocity	mm/s
%RRA	Reflex amplitude as percentage of initial	mm
RA	Reflex amplitude	mm
Resp	Respiration	-
SD	Standard deviation	-
TM75%	Time at which pupil redilated 75% reflex amplitude	s
V_E	Minute ventilation	$l \bullet min^{-1}$

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1.0 Introduction

1.1 Background

The asthma prevalence is reported high in elite athletes.[1,2] It has been reported in 2.7 to 22.8% of summer sports athletes and 2.8 to 54.8% of winter sports athletes.[1] In Norway around 10% athletes in junior and senior national teams had asthma in 1997, compared to 7% in the general population according to Norwegian study that was based on questionnaire.[2]

Several studies have suggested that high intensive endurance training may promote the development of asthma and airway hyperresposiveness (AHR).[3] Asthma was found to decrease in swimmers who had stopped high-level training.[4] Thus, it might indicate that for some athletes asthma is induced by training. Cross-country skiers and other endurance elite athletes who are for example exposed to cold air and chlorine have increased risk of developing asthma.[3,5]

The increased risk of asthma in elite athlete is related to repeated intensive endurance training with high minute ventilation (V_E) and delayed repair due to daily repetition of training. This is suggested to result in epithelial damage of airways and airway mucosal inflammation.[6] The autonomic nervous system mediates contraction and relaxation of bronchial smooth muscles. Intensive training can promote predominance of vagal activity as a compensatory response to sympathetic stimulation associated with frequent and intense training.[7, 8] Repeated intensive endurance training could lead to predisposition of increased bronchomotor tone and susceptibility to bronchospasm.[9] This imbalance is called *dysautonomia* and it has been shown using measurements of pupillometry in endurance runners. It reveals increased parasympathetic activity and reduced sympathetic activity.[10]

A previous study found no differences between asthmatic and non-asthmatic swimmers regarding parasympathetic parameters, but there was an association among those with clinically relevant AHR.[7] This further supports the role of autonomic nervous system in the development of airway responsiveness in elite swimmers.[7] There is also evidence that increased parasympathetic activity in the airways contributes to asthma development in elite cross-country and biathlon skiers.[11] Research related to the hypothesis of dysautonomia in the pathogenesis of asthma in athletes is needed to get definite answers which might allow for better targeted treatment of this specific asthmatic population.

The purpose of the present study is to investigate possible differences in parasympathetic activity between endurance athletes with and without asthma.

1.2 Objectives

The main objective is to compare parasympathetic activity between endurance athletes with self-reported asthma to endurance athletes without asthma.

The second objective is to investigate possible associations between parasympathetic activity and training components in the same population.

1.3 Research aims

1. To assess possible differences in parasympathetic activity between self-reported asthmatic endurance athletes, healthy endurance athletes, and healthy controls using pupillometry and the 4 seconds exercise test.
2. To investigate possible associations of training components (frequency and duration of training) and parasympathetic activity in self-reported asthmatic endurance athletes, healthy athletes, and healthy controls.

1.4 Study hypotheses

Based on the objectives and research aims, as well as review of previous literature, the hypotheses of the present study are:

1. $H0_1$= There is no difference in parasympathetic activity between the three groups.
   $H1_1$= There is a significant difference in parasympathetic activity between the three groups.
2. $H0_2$= There is no associations between training components and parasympathetic activity in the three groups.
   $H1_2$= There is associations between training components and parasympathetic activity in the three groups.

2.0 Theoretical Background

2.1 Asthma

Asthma is epidemiologically one of the most common chronic inflammatory disorder of the lungs which leads to widespread airflow limitation.[12] The development of asthma is determined by interaction between host susceptibility and environmental exposures that makes it a complex disease.[2] The pathogenesis of asthma is very complex and until today is not completely understood.[2,3,12] Majority of asthma has immunoglobuline E (IgE)-mediated background with sensitizations to inhaled allergen which is known as allergic asthma.[1,12]

2.2 Asthma in athletes

The prevalence of asthma varies worldwide with more than 5% of any population studied suffer from asthma.[12] Athletes have higher prevalence of asthma compared to general population.[2,5] However, overdiagnosis in this population is reported when asthma was diagnosed based on subjective findings, such as symptoms and history of diseases only.[3] Asthma was misdiagnosed in 21% of athletes in the 2004 British Summer Olympic team.[13] Asthma suspicion from clinical symptoms should be confirmed by objective tests, such as a 12% increase in forced expiratory volume in one second (FEV_1) from baseline or predicted value in response to a bronchodilator or AHR.[3]

There are strong evidences that the development of asthma and AHR in endurance athletes might be related to high-intensity repeated exercise, especially when athletes are exposed to allergens, pollutants, chlorine or cold air during training.[1,3,4,8,9] Extreme breathing during training may give mechanical stress on airway epithelial cells which release inflammatory mediators. The inflammatory mediators may contribute to increased inflammatory process which lead to airway remodeling, variable airway obstruction, and AHR.[3, 8]

Airway hyperresponsiveness is the increase above normal in the degree to which the airways will constrict upon exposure to non-sensitizing physical stimuli such as cold air, exercise, chemical substances such as metacholine and histamine or to sensitizing agents such as allergens in sensitized individuals.[14,15] Symptomatic asthma is typically associated with AHR but it may be observed without clinical manifestations as well.[16]

There had been reports on increased prevalence of asthma and AHR among elite swimmers and cross-country skiers.[16, 17, 18, 19, 20] Studies in competitive swimmers found a prevalence of AHR

ranging from 36-79% that was significantly higher than controls.[21,22, 23, 24, 25]. There was a correlation between AHR and exercise intensity (measured as blood lactate) in asthmatic and healthy swimmers.[17] In other studies swimmers had a higher prevalence of asthma and AHR than other athletes and it was suggested to be related with ambient swimming pool conditions.[22,24,25] Indoor air in swimming pool environments contains chemical compounds used for water treatment such as chlorine and its derivatives, chloramine, and chloroform, which could play role as irritants to the airways.[25] The theories however still need further studies to confirm the causality relationship between indoor pool air contaminants and AHR.[16]

Airway hyperresponsiveness was also reported to be significantly greater and asthma symptoms were more prevalent in cross-country skiers than controls.[26] Another study by Sue Chu et al observed signs of inflammation such as lymphoid follicles and deposition of tenascin in bronchial biopsies in during winter competition in adolescent cross-country skiers regardless their asthmatic status.[20] From few reports strenuous training at low temperatures seemed to be pathogenetic for asthma, possibly due to the repeated breathing of large amounts of cold air.[26] Environmental factors involving type and content of inhaled air could play an important role, considering most sports are practiced in various air conditions all year long and showed different prevalence of AHR between sport disciplines.[16, 26] The mechanisms involved in the development of AHR for each of air categories may be different.[26] Although exposure to cold air is certainly one of the most studied conditions which might influence development of asthma among athletes, it is uncertain whether AHR and bronchoconstrictive response to cold air is the effect of the low temperature itself or of the low water content of that inhaled air.[16]

Intensive training can also affect autonomic regulation by promoting the predominance of vagal activity as a compensatory response to the sympathetic stimulation associated with frequent and intense training.[7,11] Repeated intensive training could put on vagal predominance which induces not only the resting bradycardia of athletes but also to a susceptibility for increased bronchomotor tone and therefore susceptibility to bronchospasm.[3,7,8,9] Figure 1 shows factors involved in asthma development in elite athletes[8]:

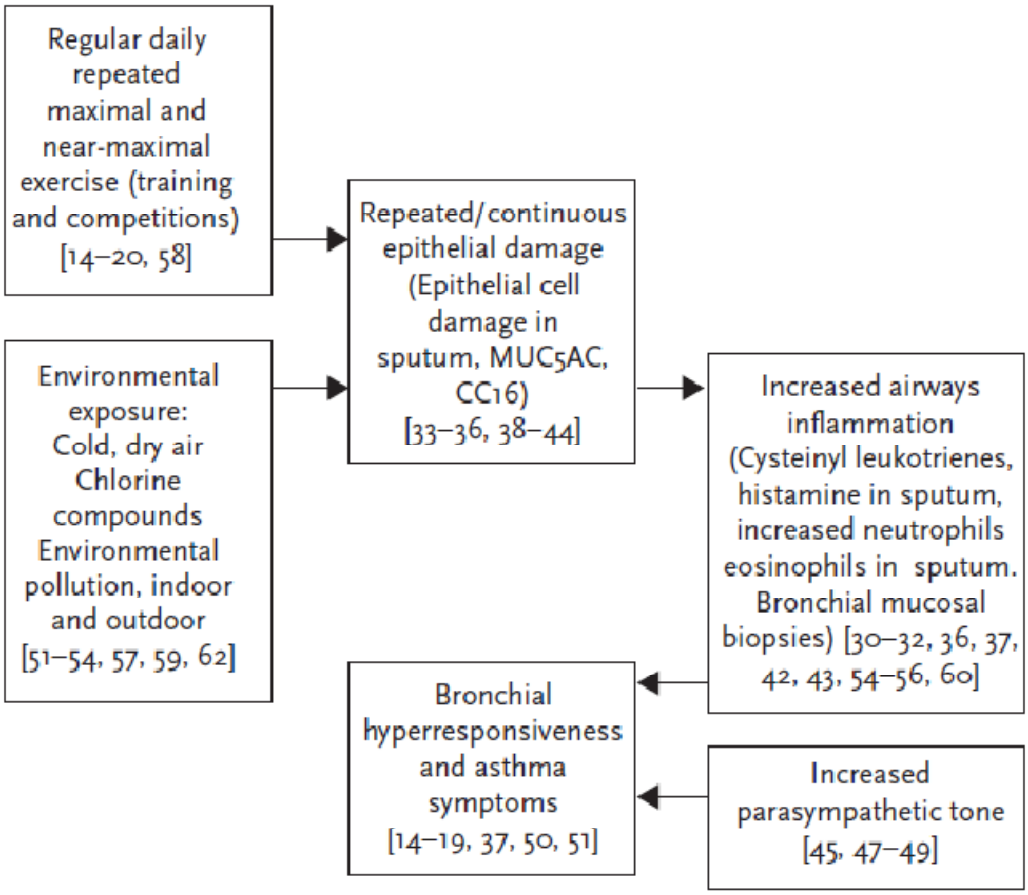

Figure 1. Factors involved in asthma development in elite athletes

Source: Carlsen K-H. Mechanisms of asthma developement in elite athletes. Breathe 2012; 8(4): 279-84.

A previous study found differences in parasympathetic parameters among swimmers with clinically relevant AHR.[7] Increased parasympathetic activity in the airways was also reported in elite cross-country and biathlon skiers[11] which was related to AHR and further supports the role of autonomic nervous system in airway responsiveness development in athletes.

2.3 Autonomic Nervous System

Most visceral functions of the body are controlled by autonomic nervous system (ANS). The system control arterial pressure, gastrointestinal motility and secretion, urinary bladder emptying, sweating, body temperature, and many other activities. There are two major subdivisions of autonomic nervous system which transmit efferent autonomic signals, they are sympathetic nervous system and parasympathetic nervous system. The next two figures show overview of sympathetic nervous system and parasympathetic nervous system.[27]

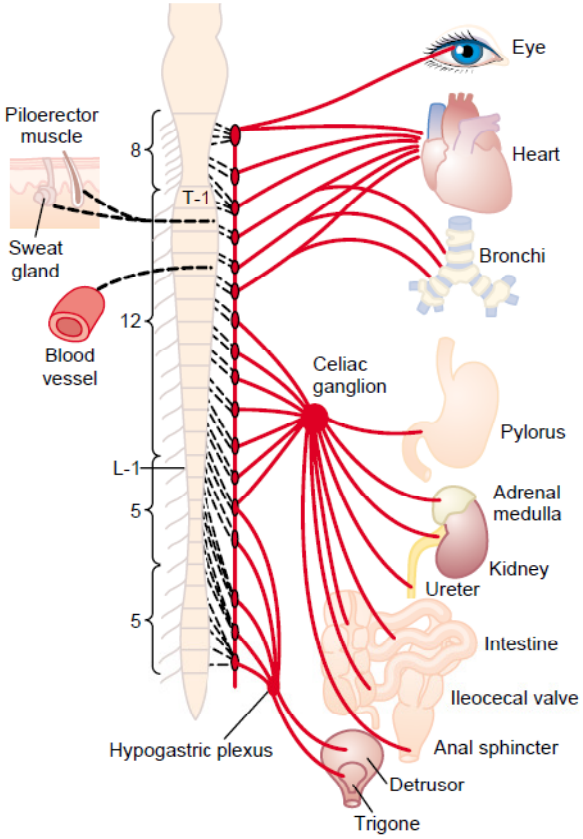

Figure 2. Sympathetic nervous system

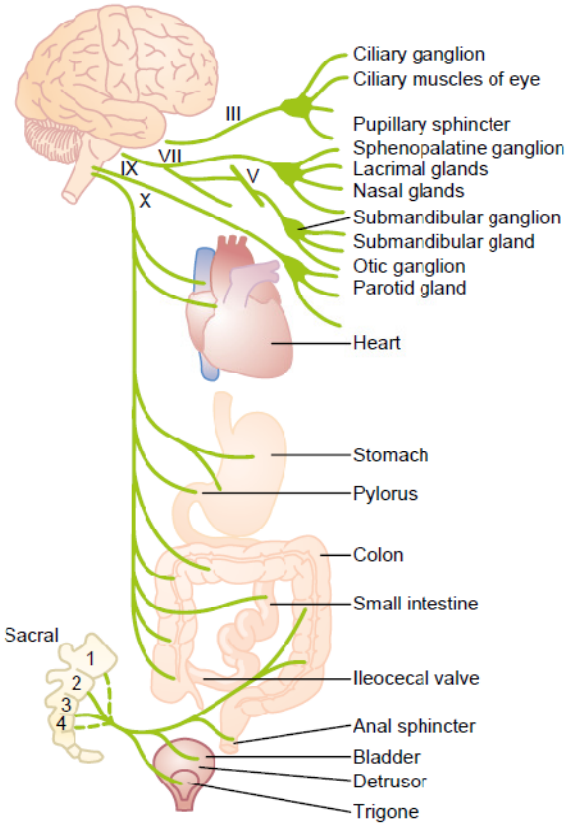

Figure 3. Parasympathetic nervous system

Source: Hall, JE, Guyton AC. Textbook of medical physiology: 2013. p.749-750.

The sympathetic nerve fibers originate in the spinal cord along with spinal nerves between cord segments T-1 and L-2 and pass first into the sympathetic chain and then to tissues and organs that are stimulated by the sympathetic nerves. The parasympathetic fibers leave the central nervous system through cranial nerves III, VII, IX, and X.[27]

2.4 Anatomy of parasympathetic nervous system

Parasympathetic nerves have preganglionic neurons where they supply the ganglia and postganglionic neurons which means they originate at the ganglia according to their anatomical location. Postganglionic nerves release neurotransmitter to end organs. They produce signal to effector organs such as glands, smooth muscle, and epithelial cells.[27,28]

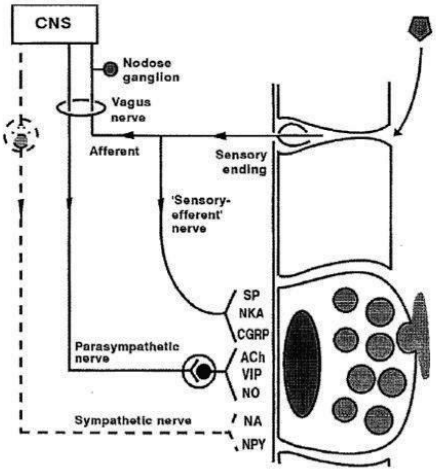

Figure 4. Innervation of airway-secreting cells (simplified model).

Source: Widdicombe, JH. Neuroanatomy of the airways. In: Pawankar, R.; Holgate, ST.; Rosenwasser, LJ., editors. Allergy Frontiers: Classification and Pathomechanisms. Springer; Tokyo: 2009. p. 459-468.

2.5 Parasympathetic nervous system control of various organs

2.5.1 Lungs

The parasympathetic nerves supply to the lungs travels through vagal nerve and is relayed via pulmonary plexus.[27,29] Pulmonary parasympathetic nervous system has both an afferent and an efferent division whose functions are to maintains airway tone, play a role in bronchoconstriction and mucus secretion.[27,30] Exposure of antigens to sensitized individuals has been reported to increase contraction of airway smooth muscles which is mediated by parasympathetic nerves.[31] Parasympathetic nervous system also controls excessive mucus secretion that leads to airway obstruction in asthmatics.[30] Increased mucus glands (hyperplasia), increased mucus gland size (hypertrophy), and increased mucus secretion are found in asthma and allergy.[27,28]

2.5.2 Heart

Parasympathetic nerves stimulation decreases heart rate and strength of heart contraction.[27]One of the function is to allow heart to rest between bouts of exercise.[27]

2.5.3 Eyes

Roles of parasympathetic nervous system in the eye includes lens accommodation (focusing), pupil contraction, and production of the protective mucus layer of tear film.[33,34,35] Stimulation of parasympathetic contracts the ciliary muscle that releases the tension on the ligaments and allows the lens to become more convex which results in the eye to focus on objects that are near.[27] The rest of the roles of parasympathetic nervous system on various organs are shown in the next figure.[27]

Autonomic Effects on Various Organs of the Body

Organ	Effect of Sympathetic Stimulation	Effect of Parasympathetic Stimulation
Eye		
Pupil	Dilated	Constricted
Ciliary muscle	Slight relaxation (far vision)	Constricted (near vision)
Glands	Vasoconstriction and slight secretion	Stimulation of copious secretion (containing many enzymes for enzyme-secreting glands)
Nasal		
Lacrimal		
Parotid		
Submandibular		
Gastric		
Pancreatic		
Sweat glands	Copious sweating (cholinergic)	Sweating on palms of hands
Apocrine glands	Thick, odoriferous secretion	None
Blood vessels	Most often constricted	Most often little or no effect
Heart		
Muscle	Increased rate Increased force of contraction	Slowed rate Decreased force of contraction (especially of atria)
Coronaries	Dilated (β_2); constricted (α)	Dilated
Lungs		
Bronchi	Dilated	Constricted
Blood vessels	Mildly constricted	? Dilated
Gut		
Lumen	Decreased peristalsis and tone	Increased peristalsis and tone
Sphincter	Increased tone (most times)	Relaxed (most times)
Liver	Glucose released	Slight glycogen synthesis
Gallbladder and bile ducts	Relaxed	Contracted
Kidney	Decreased output and renin secretion	None
Bladder		
Detrusor	Relaxed (slight)	Contracted
Trigone	Contracted	Relaxed
Penis	Ejaculation	Erection
Systemic arterioles		
Abdominal viscera	Constricted	None
Muscle	Constricted (adrenergic α) Dilated (adrenergic β_2) Dilated (cholinergic)	None
Skin	Constricted	None
Blood		
Coagulation	Increased	None
Glucose	Increased	None
Lipids	Increased	None
Basal metabolism	Increased up to 100%	None
Adrenal medullary secretion	Increased	None
Mental activity	Increased	None
Piloerector muscles	Contracted	None
Skeletal muscle	Increased glycogenolysis Increased strength	None
Fat cells	Lipolysis	None

Figure 5. Autonomic effects on various organs of the body

Source: Hall, JE, Guyton AC. Textbook of medical physiology: 2013. p.754

2.6 Measurement of parasympathetic activity

The autonomic nervous system extends to almost every organ system in the body.[27,36] There are so many organ-specific-tests for autonomic function such as urodynamic studies, gastric motility testing, pupillometry, tests of lacrimal and salivary gland production.[36] The next figure shows an overview of nervous system measurements including the parasympathetic nervous system:[37]

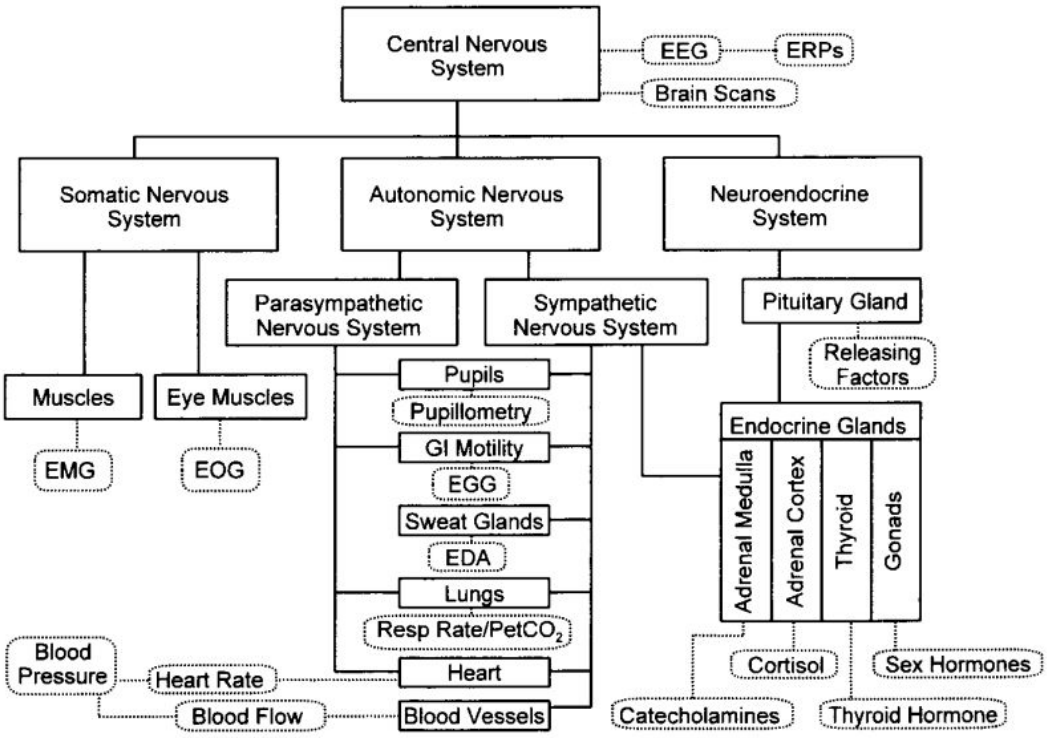

Figure 6. Organ systems and associated physiological measurement parameters. Key: EEG = electroencelography; ERPs = event related potentials; EMG = electromyography; EOG = electrooculography; GI = gastrointestinal; EGG = electrogastrography; EDA = electrodermal activity; Resp = respiration; $PetCO_2$ = pulmonary end tidal carbon dioxide.

Source: Larkin KT. Psychophysiological assessment. In: Hersen, M, editor. Clinician's handbook of adult behavioral assessment. Elsevier Inc: 2006. p.167

2.6.1 Heart rate variability

Heart rate variability (HRV) describes variations of both instantaneous heart rate and R-R intervals.[38] Heart rate variability is influenced significantly by age, race, sex, exercise, physical fitness, clinical conditions, and drug treatment, but most 24-hour HRV appears to be stable when measured on a day-to-day basis and over periods of days to weeks when there are no major intervening clinical events.[38,39] The laboratory evaluation of the parasympathetic nervous system activity includes measures of HRV at rest and in response to deep respiration, Valsalva

maneuver, postural changes, and apneic facial immersion. These tests primarily provide an index of vagal cardiac function.[39]

Heart rate variability can also be observed during cardiac activity at the onset of exercise such as by the 4 seconds exercise test (4sET) developed by Araujo et al.[40,41] The test indirectly measure cardiac vagal tone through initial heart rate transient of dynamic short term exercise performed during apnea.[41] The utility of 4sET measurement is to assess integrity of parasympathetic branch of autonomic nervous system.[40]

Araujo et al had demonstrated fast rest-exercise-rest heart rate transitions were strongly dependent on vagal activity.[40] Later studies found that in the first 4 seconds of a rapid exercise involving large muscle groups, the increase in heart rate was blocked by atropine but not influenced by propranolol and indicated vagal deactivation that is predominant at rest as the mechanism involved in this physiological response to exercise.[40,42,42] These studies validated the 4-s exercise test (4sET) as a simple and non-invasive technique for assessing vagal modulation of chronotropism in the rest-exercise transition, and it has been routinely applied in clinical practice since then.[42,43,44]

2.6.2 Pupillometry

Dilation and constriction of pupil represent both sympathetic and parasympathetic nervous system activation.[37] Pupil is controlled by two kinds of muscles whose innervations are different. The iris sphincter is innervated by the parasympathetic nervous system while the dilator by the sympathetic nervous system.[27,45]

The size and pupil's response are regulated by the opposite actions of the sphincter and dilator muscles in the iris.[46] The constrictive phases are due to a parasympathetic activation reduced at its ending, first by a superimposed central sympathetic inhibition of the Edinger-Westphal nucleus then by peripheral sympathetic activation of the iris dilator.[47] The pupillary light reflex amplitude is a measure of the parasympathetic response, equivalent to the pupillary parameters reflex amplitude (RA) and reflex amplitude as percentage of initial (%RRA).[10,46,47]

The redilation phases are caused by parasympathetic relaxation, facilitated by cholinergic inhibition of the dilator muscle, central sympathetic inhibition of the pupillomotor nucleus and/or an increase in peripheral sympathetic activity.[46] Initially, the pupil dilates rapidly as the parasympathetic energy finishes (during this phase, the pupil reaches its maximum dilatation

velocity) and thereafter, the peripheral sympathetic enlarges the pupil more slowly.[10,47] It has been shown that time to three-quarter dilatation (the pupillary parameter TM 75%) precisely represents this peripheral sympathetic activity.[10,46]

From pupillometry parasympathetic parameters can be assessed with these measurement: maximum pupil diameter, minimum pupil diameter, pupil percent constriction, latency, average constriction velocity (ACV), and maximum constriction velocity (MCV) which had been demonstrated in previous studies.[7,10] Maximum pupil diameter is initial resting pupil size and minimum pupil diameter is pupil size at peak of the constriction. Latency shows time difference between initiation of retinal light stimulation and onset of pupillary constriction. Average constriction velocity is amount of the constriction divided by duration of constriction and MCV is peak value of velocity during constriction.[48]

3.0 Methodology

3.1 Study design

This study is part of the PhD-project "Mechanism for asthma in athletes" (the MASI-study). The present study is an individual study using data collected in the main study regardless that the population and the test procedures are somewhat similar. Only those test results that are needed to answer the present hypotheses are included in this thesis. This is a cross-sectional study with three groups, consisting of asthmatic athletes (group 1), healthy athletes (group 2) and healthy, non-athlete (controls) subjects (group 3). The three groups were compared in relation to current aims and hypotheses. Parasympathetic activity measurements included in the present study are the four seconds exercise test and pupillometry. The subjects attended the laboratory two times, separated by more than 24 hours but no more than 3 weeks and all the three groups conducted the same test procedures.

3.2 Literature research

A relevant literature search was conducted through PubMed, Medline and Limo. Search words were asthma, asthma in athletes, asthma and cross-country, asthma and swimming, parasympathetic activity, parasympathetic nervous system in athletes and non-athletes, allergy, training, exercise. Relevant papers in English which included either/both athletes or non-athletes were then encompassed, and are discussed and compared with findings reported in this study.

3.3 Recruitment

The first 30 consecutive competitive athletes with asthma and 30 healthy athletes, as well as healthy subjects who agreed to participate in the study were included. Athletes were recruited from sport clubs in the south-eastern part of Norway, as well as from the national teams (junior, recruit and senior) through Olympiatoppen in Oslo, Norway. Control subjects were recruited through the Norwegian School of Sport Sciences and the University of Oslo, as well as local high schools. Participants were informed both orally and written upon volunteering to the project and signed a written consent. A written consent was submitted from parent/guardian if the participant was less than 18 years of age.

3.4 Subjects

The study population included endurance athletes at national and international level (cross-country skiers and swimmers) with and without self-reported asthma as well as control subjects (non-athletes) who were 16-35 years old, both males and females. The category of asthma in athletes is

self-reported based on clinical and history of symptoms, physical examination of signs indicating the presence of bronchial obstruction.[49] The main symptoms of asthma are recurring episodes of bronchial obstruction and the term current asthma is used when at least one episode of asthma has occurred during the last year. Subjects were placed in the three different groups after filling out a questionnaire about asthma and allergy (see Appendix).

3.5 Inclusion and exclusion criteria

If the subject reported having asthma and/or asthma symptoms and/or use of anti-asthmatic medication as well as training ≥10 hours/week, they were placed in the asthmatic group. Athletes who trained ≥10 hours/week, not reporting asthma were placed in the healthy athlete group. Healthy subjects training ≤5 hours were placed in the control group. Subject was excluded when he/she had diseases or conditions that interfered or affected the results of the tests and/or if there was anything in the opinion of the investigator had placed the subject at increased risk or precluded the subject's full compliance in the study.

3.6 Measurement

3.6.1 Test Protocol

Test protocol is described in the next table and figure.

Table 1. Test protocol

Test day	Day 1		Day 2
Test procedures	1. Spirometry 2. Pupillometry 3. The 4sET 4. Questionnaire $AQUA_{2008}$	Minimum 24 hours	1. Spirometry 2. Pupillometry 3. The 4sET 4. Questionnaire $AQUA_{2008}$ Day 2 measurement(s) were done when was not conducted at day 1

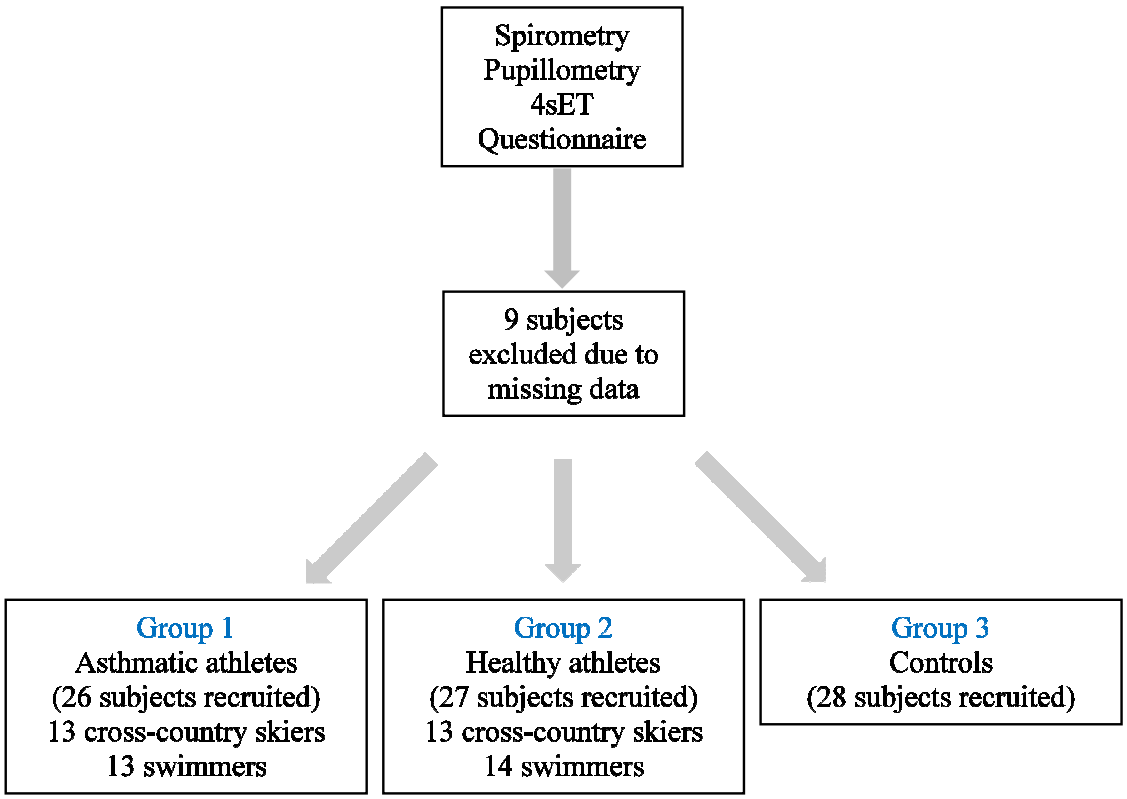

Figure 7. Research test protocol

3.6.2 Spirometry

Baseline lung function was measured by spirometry using maximum expiratory flow volume loops according to European standard[50] and recorded as forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC). Spirometry was measured using MasterScreen Pneumo Jeager® (Würzburg, Germany) and reference values by Stanojevic et al.[51]

3.6.3 The 4 second exercise test

This 4sET is one of physiological and clinical procedures to assess autonomic condition which was initially proposed by Araújo et al.[40,41] In the present study subjects were instructed to pedal as fast as possible on a cycle ergometer with no load, from the fourth to the eight second of a maximal inspiratory apnea.[40] After RR interval stabilization at rest, four verbal commands were given, in the following sequence: (0 s) take a deep inspiration, (4 s) cycle as fast as possible, (8 s) suddenly stop cycling, and (12 s) perform expiration. The R-R intervals were recorded using heart rate monitors from Polar Electro® (OY, Kempele, Finland). No differences were found in assessing HRV when comparing the Polar® heart rate monitor with echocardiogram (ECG).[52] To quantify the cardiac vagal modulation, the ratio between the longest RR interval before exercise and the shortest RR interval during the exercise were identified and called the cardiac vagal index

(CVI). The test maneuvers were performed in duplicates and the one with the highest CVI was used for analysis.

3.6.4 Pupillometry

For the present study, pupillometry was performed according to Felipe et al.[10] Pupillary measurements were assessed with the portable infrared PLR-200™ Pupillometer (NeurOptics Inc, CA, USA), which stimulated the eye with a light flash (180 nm peak wave light) and then captured and analyzed a rapid sequence of digital images to obtain a temporal measurement of the diameter of a human pupil. The subjects spent 15 minutes in a semi-dark room to allow their eyes to adjust to low lighting levels before measurement. Subjects were then instructed to focus with the eye that is not being tested on a small target object, keeping head straight and both eyes wide open during measurement. One pupil light response curve to each eye was recorded for each subject and the mean values were used for analyses. Each recording will last for approximately 3 seconds. The following parameters were collected: the diameter of the pupil before and just at the peak of the constriction (given in millimeters); the percent of the constriction; the time of the onset of the constriction (given in seconds); as well as the average and the maximum constriction velocity (given in millimeters/second).

3.7 Questionnaire

The questionnaire used in the present study was the modified $AQUA_{2008}$, developed for the assessment of asthma, allergy and other respiratory symptoms (see Appendix).[53] The questionnaire was used to assess training components of the subjects and to evaluate if the subject were to be placed in the asthmatic group 1, in the healthy group 2, in the control group 3 or to be excluded from the study.

3.8 Data collection

All results were continuously listed on result sheets while each test was conducted. The result was then later listed on a computer. Data registrations and the result sheets were anonymized and made inaccessible to all persons other than those responsible for the project. Data for this study includes age, gender, height, body mass, parasympathetic activity. Clinical data were entered into a data capture system. The data system includes password protection and internal quality checks.

3.9 Statistical methods

Statistical analyses were performed with Statistical Package of Social Sciences (SPSS) version 15.0 and Microsoft Excel 2010. Microsoft Excel 2010 was used to make figures, and Microsoft Word 2010 to make tables. Demographic data were given as mean with standard deviation (±SD) in parentheses if normal distributed, or median with percentiles if not normally distributed. If satisfying normal distribution, differences between two measurements were analyzed by the Student's t-tests otherwise Mann-Whitney test was used. Analysis of Variance (ANOVA) was used to assess differences between three or more groups if the data were normally distributed otherwise Kruskal-Wallis test was done. Chi-square (x^2) test was used to assess differences between categorical data if the conditions were fulfilled, otherwise Fisher's exact test was used.

3.10 Ethical considerations

The present study was carried out according to scientific standards and provided more information and intentionally contributed to increase knowledge about parasympathetic activity and development of asthma in healthy and asthmatic athletes. The investigator ensured that this study is conducted in full conformity with the principles set forth in the Declaration of Helsinki. The Regional Medical Ethics committee (REK) and the Norwegian data inspectorate had approved the study (Appendix in Norwegian).

The study protocol, documentation, data, and all other information generated were held in strict confidence. No information concerning the study or the data was released to any unauthorized third part. None of the parasympathetic activity measurements was considered to carry any element of risk. As subjects must refrain from any drugs before testing, the study might interfere with well-regulated anti-asthmatic treatment in some athletes. However, test days were facilitated to each subject's time schedule so that any competitions or training programs was not influenced by participation in the study and that there was no danger to the subject. Experienced test personnel were present during testing.

4.0 Results

4.1 Subject Characteristics

Table 2. Subject characteristics with baseline lung function for asthmatic athletes, healthy athletes, and controls

Measurement	Asthmatic athletes (n=26)	Healthy athletes (n=27)	Controls (n=28)
Age(year)	19 (16-32)	18 (16-23)	26.50(±4.86)#*
Height (cm)	179.03(±8.79)	179.24(±9.11)	175.02(±9.30)
Weight(kg)	73.26(±12.16)	73.11(±9.27)	73.30(±11.99)
Sex (M/F)	16/10 (61.5%/38.5%)	19/8 (70.4%/29.6%)	12/16 (58%/42%)
FEV_1	4.64(±0.83)	4.80(±0.92)	3.89 (3.03-5.93)#*
FEV_1 (%predicted)	112.74(±14.32)	115.76(±13.01)	103.45 (91.5-132.4)#*
FVC	5.93(±1.19)	5.81(±1.13)	5.10(±1,08)#*
FVC (%predicted)	120.81(±11,65)	113.4 (92.6-146.2)	109.1 (97.4-138)#*

Values are means ±SD except age in asthmatic athletes and healthy athletes (median and range) and FEV_1, FEV_1 (%predicted) in controls, and FVC (%predicted) in healthy athletes and controls (median and range).
= significant compared to healthy athletes ($p< 0.05$).
*= significant compared to asthmatic athletes ($p< 0.05$).
M = males, F = females, FEV_1= forced expiratory volume in the first second, FVC = forced vital capacity

Age was not normally distributed in asthmatic athletes and healthy athletes. The three groups had significant differences ($p<0.001$). The controls were older than the asthmatic athletes and the healthy athletes. There were no differences in height and weight among the three groups. Asthmatic athletes and healthy athletes had more males than females.

FEV_1 and FEV_1 (%predicted) were not normally distributed in controls and the three groups had differed significantly ($p=0.011$ and $p=0.017$), the healthy athletes had the highest FEV_1 and FEV_1 (%predicted). Asthmatic athletes had the significantly highest FVC ($p=0.018$). FVC(%predicted) was not normally distributed and the three groups differed significantly ($p=0.048$), with the highest FVC(%predicted) in the asthmatic athletes.

4.2 Parasympathetic activity parameters

Table 3. Measurement of parasympathetic activity using pupillometry and four seconds exercise test (4sET) for asthmatic athletes, healthy athletes, and controls

Measurement	Asthmatic athletes (n=26)	Healthy athletes (n=27)	Controls (n=28)
Pupillometry			
Max diameter (mm)	6.50(±0.59)	6.89(±0.48)	6.37(±0.97)#
Min diameter (mm)	4.45 (±0.61)	4.97(±0.53)*	4.35(±0.87)#
Percent constriction (%)	-31.54 (±4.84)	-27.96 (±3.39)*	-32.28 (±5.03)#
Latency (s)	0.21(±0.02)	0.22(±0.02)	0.22(±0.02)
ACV (mm/s)	**-**4.18(±0.59)	**-**4.02(±0.31)	**-**4.16(±0.51)
MCV (mm/s)	**-**5.59(±0.74)	**-**5.23(±1.21)	**-**5.67(±0.79)
Measurement of 4sET			
Cardiac Vagal Index	1.44(±0.17)	1.42(±0.17)	1.38(±0.19)

= pupillometry values are taken from average value of right and left eye.
Values are means ±SD.
Max diameter = maximum pupil diameter, Min diameter = minimum pupil diameter, ACV = average constriction velocity; MCV = maximal constriction velocity, 4sET = 4 seconds exercise test
= significant compared to healthy athletes ($p<0.05$)
* = significant compared to asthmatic athletes ($p<0.05$)

There were significant differences in maximum pupil diameter, minimum pupil diameter, and percent constriction of the pupil between the healthy athletes and the controls. The healthy athletes had the highest value of maximum and minimum pupil diameter and percent constriction. There were significant differences in minimum pupil diameter and percent constriction of pupil between asthmatic athletes and healthy athletes. There were no significant differences in cardiac vagal index among the three groups. The next figures show differences of means between asthmatic athletes, healthy athletes, and controls.

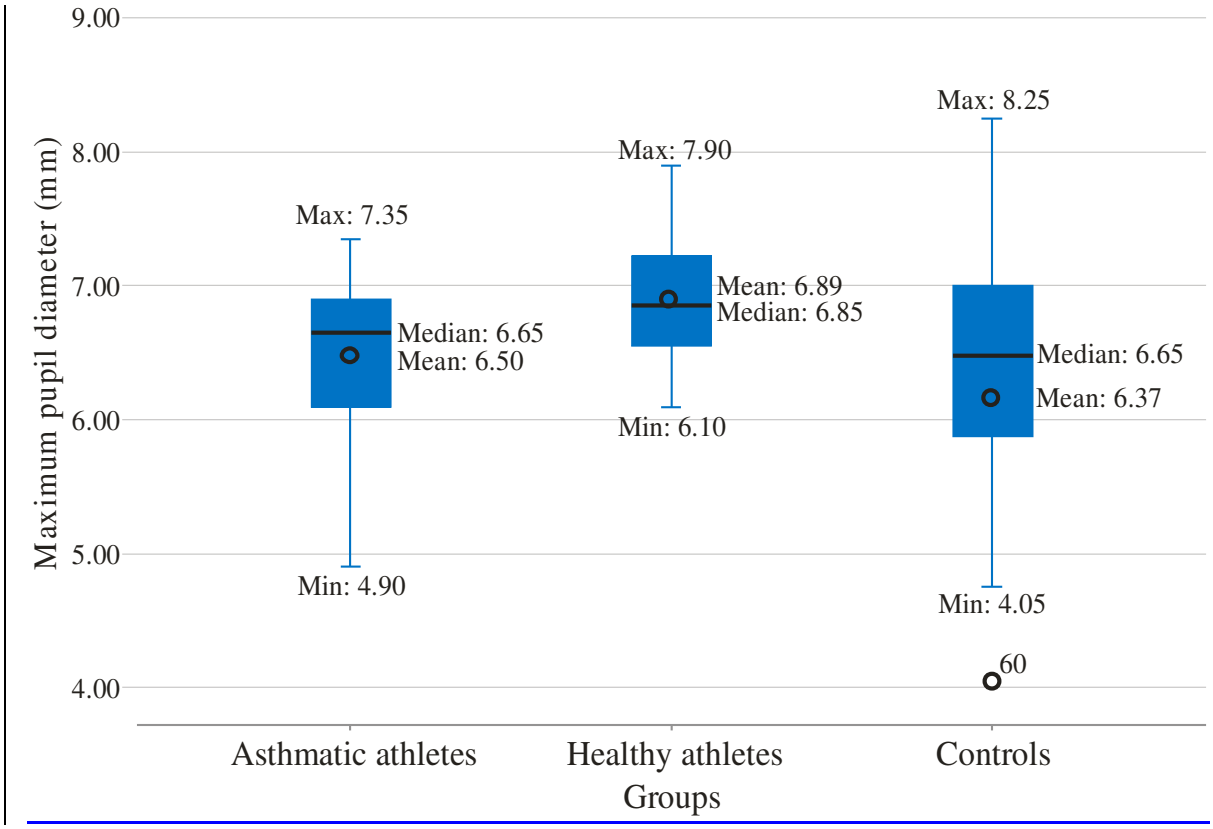

Figure 8. Maximum pupil diameter for asthmatic athletes, healthy athletes, and controls
O = mean
ANOVA test result p=0.025

There was a significant difference between groups as determined by one-way ANOVA ($F(2.78)=3.87$). A Tukey post-hoc test revealed that maximum pupil diameter was significantly higher (6.89±0.48) (p=0.024) in healthy athletes as compared to controls (6.37±0.97). There were no significant differences between asthmatic athletes and both healthy athletes and controls.

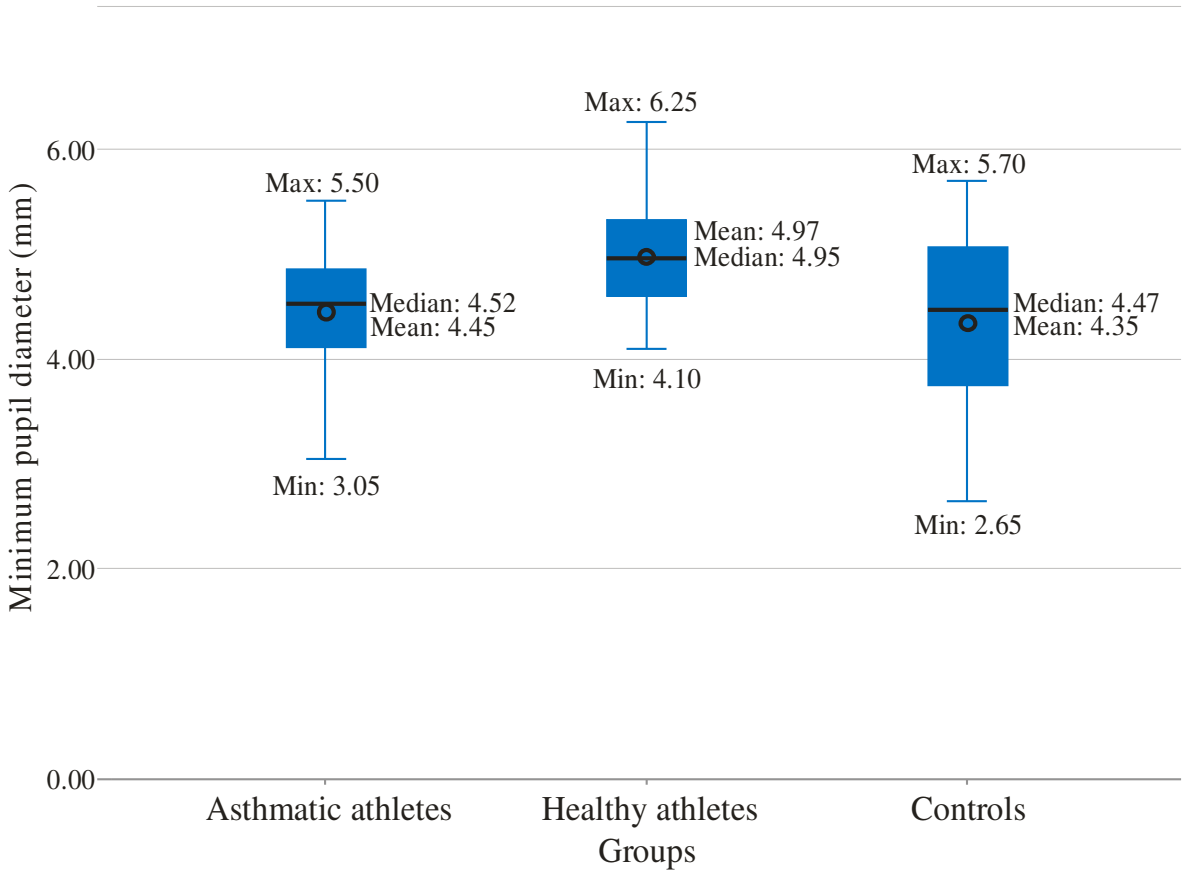

Figure 9. Minimum pupil diameter for asthmatic athletes, healthy athletes, and controls
O = mean
ANOVA test result p=0.003

There was a significant difference between groups as determined by one-way ANOVA ($F(2.78)=6.46$). A Tukey post-hoc test revealed that the minimum pupil diameter was significantly higher (4.97±0.53) (p=0.003) in healthy athletes as compared to controls (4.35±0.87) and compared to asthmatic athletes (4.45±0.61) (p=0.019). There was no significant difference between the asthmatic athletes and controls.

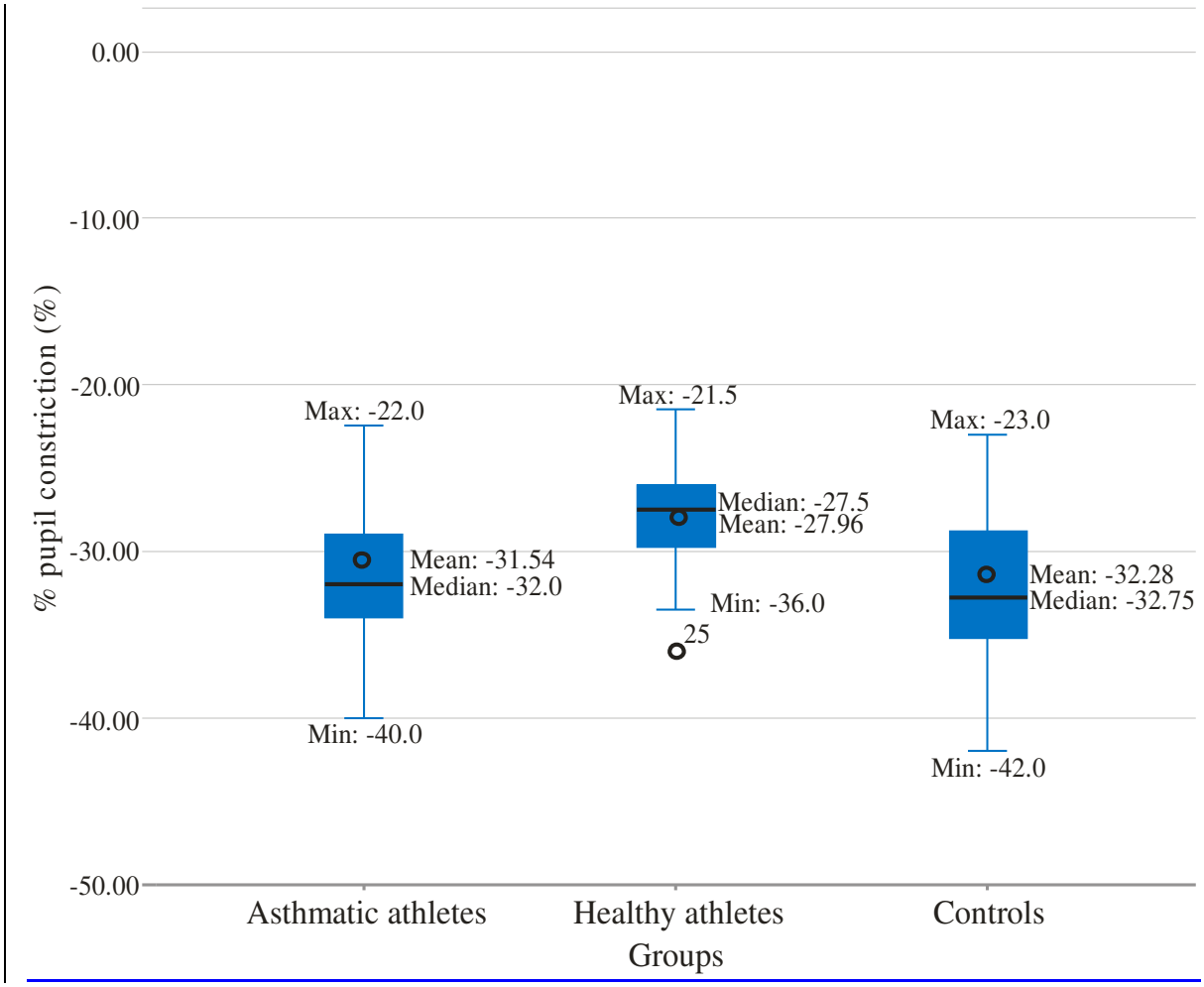

Figure 10. Percent pupil constriction for asthmatic athletes, healthy athletes, and controls
O = mean
ANOVA test result p=0.001

There was a significant difference between groups as determined by one-way ANOVA ($F(2.78)=7.22$). A Tukey post-hoc test revealed that the percent pupil constriction was significantly higher (-27.96 ±3.39) (p=0.002) in the healthy athletes as compared to the controls (-32,28±5,03) and as compared to the asthmatic athletes (-31.54±4.84) (p=0.013). There was no significant difference between asthmatic athletes and controls.

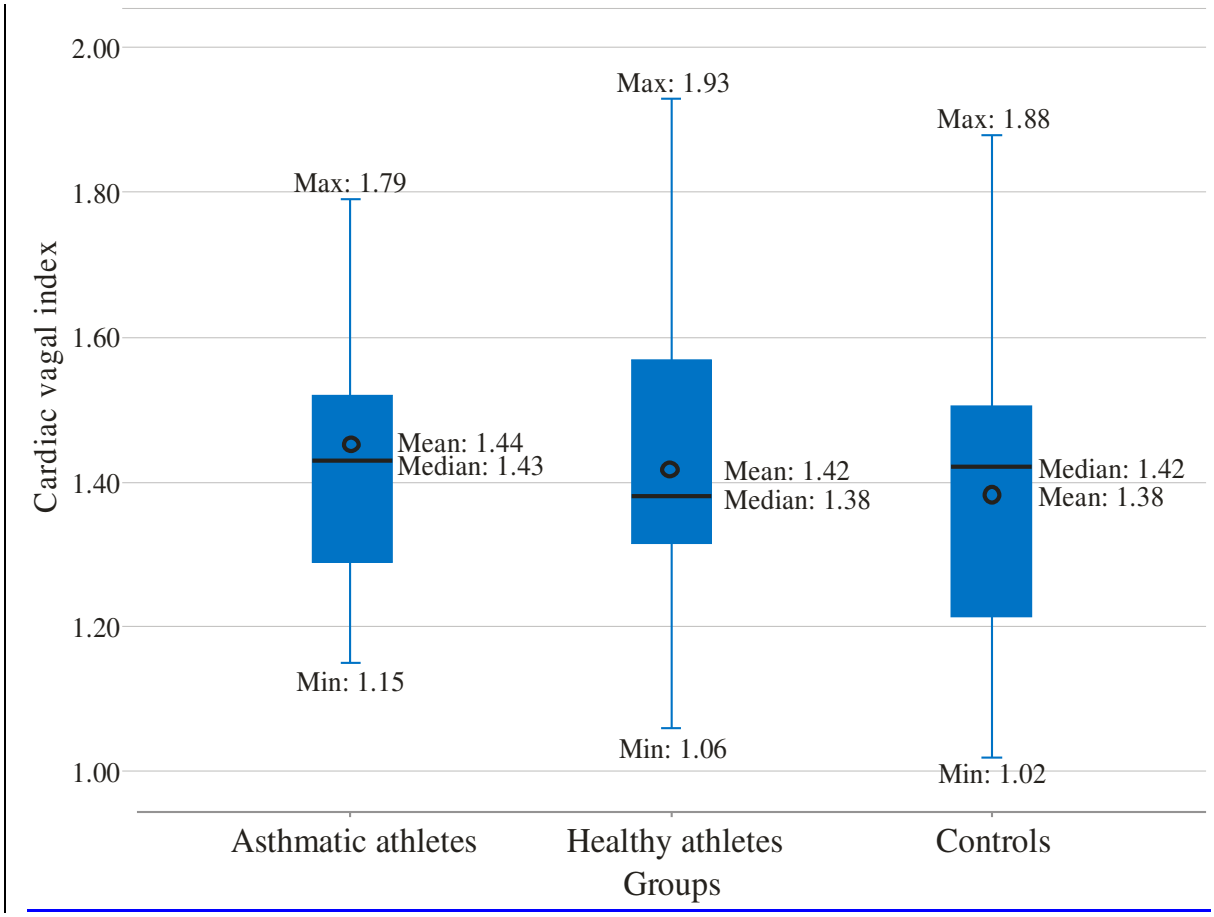

Figure 11. Cardiac vagal index for asthmatic athletes, healthy athletes, and controls
O = mean

There were no significant differences found in cardiac vagal index among three groups.

4.3 Training components

4.3.1 Training frequency

The next figure shows an overview of training frequency. Healthy athletes had the highest number of subjects who trained daily per week (Fisher's exact test p<0.001).

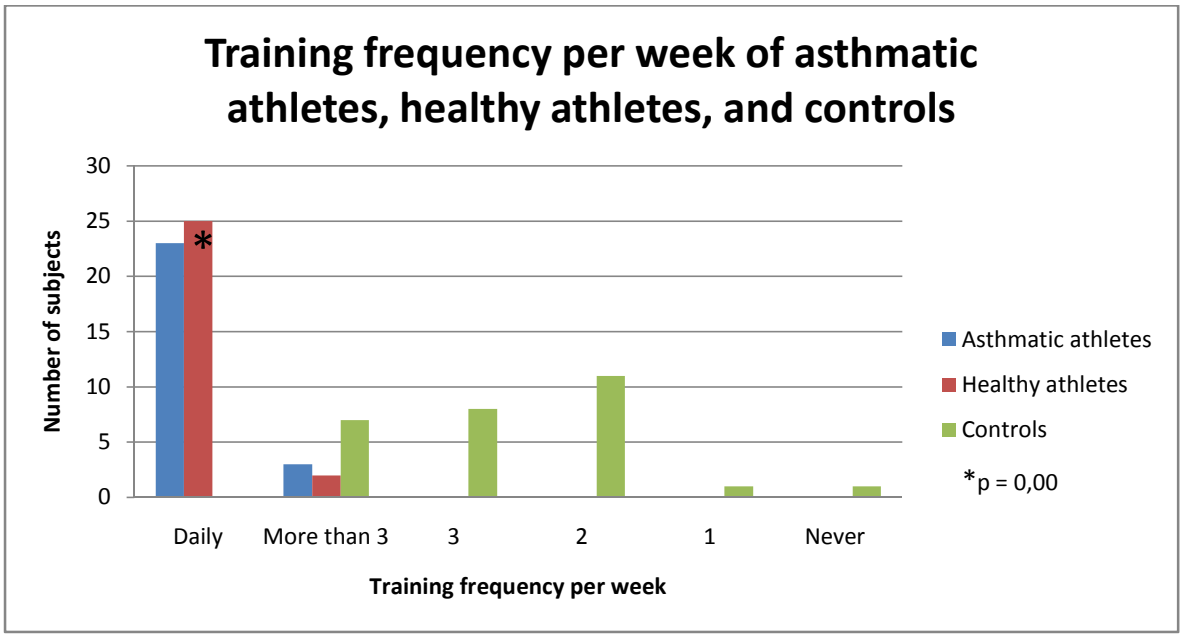

Figure 12. Training frequency per week of asthmatic athletes, healthy athletes, and controls

4.3.1.1 Pupillometry

All values of pupillometry parameters were divided into three equal categories (low, middle, and high values) to assess the relationship with training frequency divided into 6 categories (never, 1, 2, 3, more than 3 times per week, and daily training per week). There was only minimum pupil diameter (p = 0.036) which was related to training frequency in asthmatic athletes. There were more than half of the asthmatic athletes (12 out of 23 athletes) with daily training frequency (highest training frequency) who had the low value of minimum pupil diameter.

There were significant differences observed in maximum pupil diameter, minimum pupil diameter, percent constriction of pupil regardless of high, middle, low categories between asthmatic athletes and healthy athletes who trained daily per week. Asthmatic athletes had lower values than healthy athletes. Table 4 shows pupillometry measurements in the two groups who trained daily.

Table 4. Pupillometry measurements of athletes who trained daily

Pupillometry measurements	Groups	N	Value (mean ± SD)
maximum pupil diameter (mm)	Asthmatic athletes	23	6.44±0.59)
p=0.004	Healthy athletes	25	6.92 ±0.47
minimum pupil diameter (mm)	Asthmatic athletes	23	4.41 ±0.64
p=0.004	Healthy athletes	25	5.00 ±0.54
% pupil constriction (%)	Asthmatic athletes	23	-31.74 ±0.51
p = 0.001	Healthy athletes	25	-27.86 ±0.35

N = number of subjects

4.3.1.2 Four seconds Exercise Test (4sET)

There was no relationship between training frequency and cardiac vagal index in the three groups. There was no relationship between daily training frequency in regards of CVI category in all groups and there were either no differences observed in CVI regardless of high, middle, and low category between asthmatic athletes and healthy athletes who trained daily per week.

4.3.2 Training duration

The next figure shows an overview of training duration of the 3 groups. There were more asthmatic athletes who trained 2-3 hours compared to other groups per session, but two healthy athletes had the longest training duration per session which was more than 3 hours per session (Fisher's exact test p value <0.001).

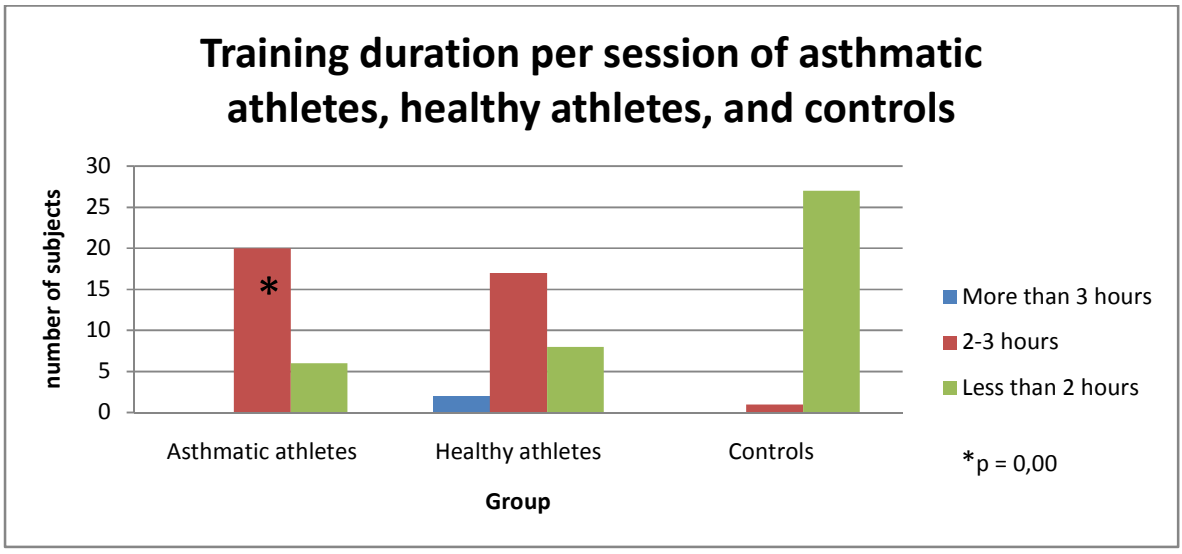

Figure 13. Training duration per session of asthmatic athletes, healthy athletes, and controls

4.3.2.1 Pupillometry

All values of pupillometry parameters were divided into three equal categories (low, middle, and high values) to assess the relationship with training duration divided into 3 categories (less than 2 hours, 2-3 hours, and more than 3 hours). Training duration was related to maximum pupil diameter (p=0.039), minimum pupil diameter (p=0.02), and pupil average constriction velocity categories in healthy athletes (p=0.013). More healthy athletes who trained 2-3 hours per session had high maximum pupil diameter (>6.93 mm), high minimum pupil diameter (>4.93 mm) and high pupil average constriction velocity (>3.92 mm/s) than the other two groups.

There were significant differences observed in maximum pupil diameter, minimum pupil diameter, percent constriction of pupil regardless of high, middle, low categories between asthmatic athletes and healthy athletes who trained 2-3 hours per session. Asthmatic athletes had lower values than healthy athletes. Table 5 shows pupillometry measurements in asthmatic and healthy athletes who trained 2-3 hours per session.

Table 5. Pupillometry measurements in asthmatic and healthy athletes who trained 2-3 hours per session

Pupillometry measurement	Group	N	Value (Mean ± SD)
maximum pupil diameter (mm)	Asthma athlete	20	6.40 ± 0,60
p=0.004	Healthy athlete	17	6.95 ± 0.47
minimum pupil diameter (mm)	Asthma athlete	20	4.38 ± 0.65
p=0.001	Healthy athlete	17	5.06 ± 0.54
% pupil constriction (%)	Asthma athlete	20	-31.75 ± 5.41
p=0.004	Healthy athlete	17	-27.20 ± 3.22

N = number of subjects

4.3.2.2 Four seconds Exercise Test (4sET)

There was no relationship observed between training duration with cardiac vagal index as result from 4sET in the three groups. There was no relationship between 2-3 hours training duration per session in regards of CVI category in all groups and there were also no differences observed in CVI between asthmatic athletes and healthy athletes who trained 2-3 hours per session.

5.0 Discussions

In the present study parasympathetic activity is presented as results of two tests, pupillometry and 4sET. There were significant differences in some parasympathetic activity parameters measured by pupillometry between the three groups. Healthy athletes had significantly higher value of maximum pupil diameter, minimum pupil diameter, and percent pupil constriction than controls and was significantly higher in minimum pupil diameter and percent pupil constriction than asthmatic athletes. Pupillometry measurements were differed between asthmatic athletes and healthy athletes and between healthy athletes and controls, but not between the asthmatic athletes and controls (Table 3, Figure 7, Figure 8, Figure 9). Cardiac vagal index showed a tendency that asthmatic athletes had the highest cardiac vagal index, but was not significant (Table 2).

The results in the present study are in agreement with previous studies investigating increased parasympathetic activity in endurance athletes.[7,10,11] There were no differences observed in latency, average constriction velocity, and maximum constriction velocity in the pupillometry among the three groups. Latency is the time from stimulus to onset of response and it relates to contriction velocity (average and maximum constriction velocity).[48,54] None studies to our knowledge have observed differences of latency between asthmatic athletes and healthy athletes or to controls. One study reported significant difference when asthmatic athletes were stratified based on the severity of AHR.[7] Most of the latency were due to slow iris muscle constriction in a study of healthy subjects.[54] Animal studies implied that majority of the latency in normal subjects was due to delay in iris smooth muscle contraction and only a relatively small part was due to conduction along the pupillary reflex pathway.[54,55]

Based on previous studies, it might be suggested that the three groups had possibly similar characteristics of delay in iris muscle contraction which resulted in the similar results for latency and related constriction velocity. More studies are needed to determine factors affecting latency and constriction velocity in asthmatic subjects and athletes.

Cross-sectional studies have reported that trained subjects had higher HRV than untrained/sedentary subjects.[56,57,58] However other studies did not find the same results, which might be related to non-existent of training bradycardia after exercise program.[59,60,61] The present study showed a tendency that asthmatic athletes had the highest HRV presented in cardiac vagal index, but not significant. This could partly be affected by the wide range of cardiac vagal index results (Figure 10) in the controls (1.02-1.88) which was almost similar to asthmatic athletes

(1.15-1.79) and healthy athletes (1.06-1.93). The fact that the controls were recruited from students at universities and colleges in Oslo might affect the results as well. According to the Norwegian Public Health, college and university-educated people are more likely to exercise in their leisure time which resulted in better physical fitness and may be affecting cardiac vagal index.[56,57,62]

The present study observed that healthy athletes group had the highest number of subjects who trained daily per week and that differed significantly from asthmatic athletes and controls (Figure 11). Although most healthy athletes trained daily, there was no relationship with pupillometry variables. Only minimum pupil diameter was related to training frequency in asthmatic athletes. Asthmatic athletes who trained daily had a low minimum pupil diameter.

Significant differences of minimum pupil diameter, maximum pupil diameter, and percent constriction were observed in athletes who trained daily, giving asthmatic athletes lower value of maximum, minimum pupil diameter, and lower percent constriction than healthy athletes. Minimum pupil diameter defined as pupil size of the peak of constriction which the constrictive phase was performed by parasympathetic activation and supplied iris sphincter.[46,47,48] The lower size of minimum pupil diameter suggests the higher parasympathetic activity.[7,48]

In the present study, daily training resulted in lower minimum pupil diameter size in asthmatic athletes. This result was in agreement with Couto et al which observed the smaller pupil diameter in athletes showing severe AHR compared to less severe AHR swimmers although the study did not analyze frequency of training.[7] The previous study also observed lower value of maximum pupil diameter as a consequent of higher percent constriction and lower latency in athletes with severe AHR.[7] Further research are still needed to confirm the relationship of daily training to increased parasympathetic activity.

The present study observed that daily training frequency was related to higher parasympathetic activity in asthmatic athletes. Although more healthy athletes had daily training frequency than the other two groups, parasympathetic activity was observed higher in asthmatic athletes. This finding suggests that asthmatic athletes might either already have higher parasympathetic activity regardless of the training frequency or that higher parasympathetic activity is developed during years of training.

There were significant differences in duration of training sessions in the healthy athletes group with more asthmatic athletes training 2-3 hours per session. There was a relationship between training duration and maximum pupil diameter, minimum pupil diameter, and pupil average constriction range in healthy athletes. Most healthy athletes trained 2-3 hours per session and had a high value of all the respective pupillometry variables. This suggested that 2-3 hours training duration in healthy athletes do not increase parasympathetic activity.

Significant differences in maximum pupil diameter, minimum pupil diameter, and percent constriction were observed between asthmatic and healthy athletes who trained 2-3 hours per session, giving asthmatic athletes lower value of the respective pupillometry variables. This findings suggest that 2-3 hours per training session was related to higher parasympathetic activity in asthmatic athletes but not in the healthy athletes.

In general elite endurance athletes had twice sessions per day for average 2 hours per session.[63,64] Elite Norwegian swimmers are reported to have minimum training duration of 2-3 hours daily[64] in the same study, 62.5% of the swimmers were positively tested for AHR by either methacoline challenge and/or eucapnic voluntary hyperpnea (EVH).[64] Another study reported that competitive swimmers had average 21 hours training per week and cold air athletes (speed-skaters, cross-country skiers and biathletes) had average 16 hours training per week[65]. Sixty nine percent of the swimmers had AHR and 28% of the cold-air athletes, respectively.[65] In the present study most athletes trained 2-3 hours per session resulting in 14-21 hours training per week and differences in parasympathetic activity were observed between the two athletes groups. The 2-3 hours duration per session was in fact the common training duration for elite endurance athletes and interestingly this present study showed that there was an increased parasympathetic activity in asthmatic athletes but not in healthy athletes. This finding also suggests that asthmatic athletes might either already have higher parasympathetic activity regardless of the training duration or that the higher parasympathetic activity was developed during the training.

There were no differences observed in cardiac vagal index regarding training frequency and duration in all groups, and cardiac vagal index was not significantly different in athletes who trained daily and did 2-3 hours training per session. Interestingly the values showed the same trend with pupillometry measurement, with higher values found in asthmatic athletes compared to healthy athletes showing increased parasympathetic activity in asthmatic athletes. However the values were not significantly different.

Cardiac vagal index shows cardiac vagal modulation. The present study observed that means of CVI in all groups were lower than average CVI reference values in healthy non-athletes subjects in relatively same age range category (18-31 years old).[44] Previous studies observed that decreased cardiac vagal modulation was one of the characteristics of autonomic dysfunction.[66,67,68,69] The present study suggests that there is autonomic dysfunction in asthmatic athletes based on the pupillometry measurement. However, considering minimum and maximum value of all groups (Figure 11) are still in the range of reference value,[44] autonomic dysfunction in the subjects of the present study that indicate pathology in cardiovascular system is not conclusive.[44] Moreover, the reference value was made based on healthy non-athletes subjects and the results of CVI were not significantly different as observed in pupillometry (Table 3 and Figure 11).

The results in the present study are not in agreement with Kaltsatou and colleagues who found correlations between parasympathetic indices of HRV assessed in time and frequency domain and pupillometry measurements in athletes and sedentary subjects.[70] Different target organs of parasympathetic nervous system might affect the results of these two measurements as observed in a study by Stang et al.[71] It was observed poor agreement between parasympathetic activity levels measured in two different target organs of athletic subjects; the heart and the pupil.[71] Pupillometry showed better repeatability compared with the 4sET.[71] HRV might be influenced significantly by age, race, sex, exercise, physical fitness, clinical conditions, and drug treatment, although most 24-hour HRV appears to be stable when measured on a day-to-day basis and over periods of days to weeks when there are no major intervening clinical events.[38,39,70]

Recent studies have found that parasympathetic nervous system regulates common characteristics of allergic diseases and asthma such as increased smooth muscle contraction, hypersecretion, and inflammation.[28,30] Evidence has shown a role of the parasympathetic nervous system in allergic diseases for example by surgical and pharmacologic cutting and blocking of parasympathetic nerves which prevented allergic diseases progression and symptom manifestation.[30,32] In the present study no differences in parasympathetic activity variables were found between asthmatic athletes and controls and therefore the current asthmatic condition was still not conclusive to have a role in the parasympathetic activity changes in athletes although there were differences and relationship between pupillometry measurements and training components in asthmatic athletes when compared to healthy athletes. The present study suggests that the duration of training bouts might contribute to changes in parasympathetic activity in non-asthmatic athletes.

Previous studies have reported increased parasympathetic activity resulted from pupillometry and HRV using ECG in sitting and supine position in non-athletes subjects with rhinitis allergy.[72,73] The same increased parasympathetic activity and HRV were observed in endurance athletes.[56,57,58,68,74] This suggested training affect the increase in parasympathetic activity.[56,57,58,68,74] Other studies in asthmatic endurance athletes including the present study, have also reported an increase in parasympathetic activity.[7,11] These findings lead to the question whether increased parasympathetic activity might be hazardous in the future to human autonomic nervous system especially in asthmatic subjects.[10] Physical activity and regular exercise training in moderation have been reported to have beneficial effects in asthma control, despite asthmatic athletes were reported to have increase in parasympathetic activity.[75,76] Continuing some training throughout life seems worthy considering all heart rate variability parameters were superior in the senior athletes.[77] Further studies are needed to confirm and monitor training volume in asthmatic subjects that might relate to parasympathetic activity changes. Such changes could lead to pathological autonomic dysfunction.[66,67,68,69]

Based on a pilot project of MASI study the power calculation was made based on pupillometry and cardiac vagal index as main outcome. Thirty subjects in each three groups were found to achieve 80% power to detect differences between groups with a 0.05 significance level. This supports the power of the present study's findings.

The characteristic of lung function by baseline spirometry in the three groups were significantly different. Healthy athletes had the highest value as compared to asthmatic athletes and controls. Higher predicted values of pulmonary function in athletes are also reported in previous studies.[78,79,80,81]

Respiratory symptoms are reported in people doing sport activities especially at elite level and they are therefore suspected to have asthma and/or exercise-induced asthma.[3] However, many respiratory symptoms are actually common physiological symptoms or results of intensive training especially in a cold air environment or polluted environment.[82,83] Moreover, other airways problems, for example vocal cord dysfunction, might also have been misdiagnosed as exercise-induced asthma.[83] The controls who possibly had an active lifestyle might have been motivated to voluntary joining the present study to check if he/she had asthma due to their experiences of having respiratory symptoms during exercise. There are still possible that the controls have an under-diagnosed asthma or exercise-induced asthma, which have not been objectively proven. Considering the active lifestyle of college students, asthma and other

respiratory symptoms might had been overlooked by controls as they had good physical fitness level.[62,82,83]

6.0 Study limitation and suggestion

The limitations of the study are the self-reported asthma by questionnaire and the cross-sectional design. As self-reported asthma symptoms are not reliable to be taken as diagnosis, there might be different findings found regarding the three group categories. For future studies more objective measurements as bronchial provocation tests or reversibility tests are needed to confirm the diagnosis of asthma and/or exercise-induced asthma.[3,11,82,83]

Data of training frequency and duration were self-reported by questionnaire, which might be biased by subjects' memory. It would give more reliable results if the data was supported by actual training logs. The issues of not having completely sedentary subjects in the control group might also contribute to similar physical fitness between the controls and the other groups that resulted in similar CVI. Physical fitness was not analyzed in the present study but generally indicated in the height and weight which was not differed significantly in all groups (Table 2).

Consecutive recruitment of the subjects for the present study had disadvantages as it was a non-probability sampling which could make the sample to be actually representative of the population. However it was still done due to adjustment with training schedule of athletes and feasibility of the study.

The present study design was cross-sectional and cannot draw a cause-and-effect relationship as to determine which condition(s) came first, whether endurance training caused increased parasympathetic activity and asthma development, or difference in parasympathetic activity was the predisposition to develop asthma in endurance elite athletes.

Pupillometry measures parasympathetic activity in cranial level and that might not be completely suitable for assessing parasympathetic activity in the lungs.[10] Assessment using metacholine provocation gives reflection to sensitivity to cholinergic stimulation on bronchial smooth muscle and mucous glands might be a better measurement of the parasympathetic nervous system in relation to asthma and AHR as found in a study by Stang et al.[11]

The use of questionnaire to group subjects as asthmatics and non-asthmatics could not be relied as true diagnosis, however, the use of questionnaire to select each group is practical and feasible in field and will be convenient in larger studies such as observed in marathon runners.[84] The AQUA© itself is originally a standardized validated questionnaire although the subjects participated in the validation were soccer players.[53]

7.0 Conclusion

1. The present study found that asthmatic athletes had significantly lower value of minimum pupil diameter and pupil percent constriction compared to healthy athletes which indicated an increase in parasympathetic activity.
2. Heart rate variability assessed by cardiac vagal index showed a tendency, but not significant, that the asthmatic athletes had the highest cardiac vagal tone.
3. The present study suggests that daily training frequency and 2-3 hours per session has contribution in parasympathetic activity changes in athletes.

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Appendix

Written informed consent (in Norwegian)

Jeg har lest informasjonsskrivet om Forespørsel om å delta i en forskningsstudie:
«Er toppidrett skadelig for luftveiene?».

Jeg gir min tilslutning til deltagelse i undersøkelsen. Jeg er kjent med at jeg når som helst kan trekke meg fra prosjektet uten å måtte oppgi grunn for det. Jeg er klar over at de innsamlede data utelukkende brukes til forskning.

Forsøkspersonens navn: _____

Jeg nåes på telefon (dagtid): _____

Epostadresse: _____

Dato: _____ Underskrift: _____

<u>For foresatte dersom forsøkspersonen er under 18 år:</u>

Foresatte skriver under <u>i tillegg til</u> forsøkspersonen.

Dato: _____ Underskrift foresatte: _____

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Tor Even Svanes	22845521	07.03.2013	2013/167/REK sør-øst C
			Deres dato:	Deres referanse:
			22.01.2013	

Vår referanse må oppgis ved all henvendelser

Kai-Håkon Carlsen
Oslo Universitetssykehus

2013/167 Er toppidrett skadelig for luftvegene?

Forskningsansvarlig: Oslo Universitetssykehus
Prosjektleder: Kai-Håkon Carlsen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 14.02.2013. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf forskningsetikkloven § 4.

Prosjektomtale
Forekomst av astma og bronkial hyperreaktivitet (BHR) er svært høy i kondisjonsidrett, særlig vinteridrett (langrenn, skiskyting) og svømming (>50% på landslagsnivå). Årsaken er ukjent. Hensikten med studien er å klarlegge mekanismer for bedret forståelse som kan forebygge astma. Det vil være en case-kontroll studie der 30 toppidrettsutøvere med astma, 30 uten astma og 30 friske kontroller, i alderen 16-40 år, skal inkluderes. Man vil registrere lungefunksjon, BHR (metakolinprovokasjon)luftvegs-inflammasjon og -epitelskade (indusert sputum, ekshalert pustekondensat), prikktest, parasympatisk aktivitet (pupillometri og variasjon i cardial aktivitet)spyttkortisol, xenobiotic eksponering. Deretter skal man analysere sammenheng mellom faktorer og utvikling av astma og BHR. Studien er samtykkebasert, og det vil opprettes en spesifikk forskningsbiobank.

Vurdering
Komiteen har ingen innvendinger til designet i studien.

Forskningsbiobank
Det søkes om å opprette en spesifikk forskningsbiobank med navn Er toppidrett skadelig for luftvegene? i prosjektet.

Ansvarshavende for forskningsbiobanken er Wenche Reed. Forskningsansvarlig er Oslo Universitetssykehus.

Biobanken vil bestå av blodprøver, urinprøver, spyttprøver, indusert sputum og luftveiskondensat.

Biobanken planlegges å vare til 2028. Deretter skal materialet behandles i henhold til helseforskningslovens § 30.

Biologisk materiale vil potensielt utføres til utlandet i henhold til helseforskningslovens § 37. Deltakerne er orientert om dette i informasjonsskriv.

Besøksadresse:
Nydalen allé 37 B, 0484 Oslo

Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskningsetikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK sør-øst og ikke til enkelte personer.

Kindly address all mail and e-mails to the Regional Ethics Committee, REK sør-øst, not to individual staff.

Informasjonsskriv og samtykkeerklæring
Informasjonsskrivet er sterkt preget av fagterminologi og medisinske begreper. Skrivet er dessuten langt. Begge deler gjør informasjonen til deltakerne mindre tilgjengelig enn den ladde trenger å være. Det bes om at prosjektleder gjennomgår skrivet med tanke på å gjøre det mer allmenngyldig

Det bes videre om at selve samtykkeerklæringen flyttes til etter kapittel A og B av skrivet. Samtykkeerklæringen skal komme etter at all relevant informasjon er gitt.

Endelig bes det om at det anføres at REK sør-øst har godkjent studien. I det foreliggende skrivet står det at REK har vurdert studien og ikke har innvendinger.

Ut fra dette setter komiteen følgende vilkår for prosjektet:

1. Informasjonsskriv skal revideres i tråd med det overnevnte, og sendes komiteen til orientering.

Vedtak
Prosjektet godkjennes under forutsetning av at overnevnte vilkår oppfylles, jf. helseforskningslovens §§ 9 og 33.

I tillegg til vilkår som fremgår av dette vedtaket, er tillatelsen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 31.12.2018. Av dokumentasjons- og oppfølgingshensyn skal opplysningene likevel bevares inntil 31.12.2023. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen ett halvt år fra denne dato.

Komiteens avgjørelse var enstemmig.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema senest 15.08.2016, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klagerådgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK sør-øst. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst, sender klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren.

Vi ber om at alle henvendelser sendes inn med korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskningetikkom.no.

Med vennlig hilsen

Arvid Heiberg
prof. dr.med
leder REK sør-øst C

Tor Evan Svanes
seniorrådgiver

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Patient ID ☐☐ - ☐☐☐

6. Do you suspect that you suffer from allergy, independently of any medical diagnosis ? ☐ Yes ☐ No

7. Have you ever used anti-allergic or anti-asthma drugs ? ☐ Yes ☐ No

7b. If yes, which?
- ☐ Antihistamins
- ☐ Corticosteroids
- ☐ Bronchodilators
- ☐ Laukotrien antagonists (singulair)
- ☐ Allergy vaccines

8. Is there any allergic subject in your family? ☐ Yes ☐ No

8b. If yes, who?
- ☐ Mother
- ☐ Father
- ☐ Sibling(s) including half siblings
- ☐ Other relatives
- ☐ Children

9. Do you often have red eyes with tears and itching? ☐ Yes ☐ No

10. Do you often have runny, itchy nose (apart from colds): ☐ Yes ☐ No

11. Have you ever felt tightness in your chest and/or wheeze? ☐ Yes ☐ No

12. Have you ever had itchy skin eruptions? ☐ Yes ☐ No

13. Have you ever had severe allergic or anaphylactic reactions? ☐ Yes ☐ No

14. Have you ever had shortness of breath, cough and/or itching of the throat during or following exercise? ☐ Yes ☐ No

14b. If yes, you have more difficulties:
- ☐ At the beginning of the training session
- ☐ At the end of the training session
- ☐ During the whole training session

15. If you have suffered from any of the above, did these symptoms occur:
- ☐ Mainly outdoor
- ☐ Mainly indoor
- ☐ Indoor and outdoor equally
- ☐ Mainly in spring
- ☐ Mainly in cold or humid conditions
- ☐ All year around
- ☐ Independently of any environmental conditions

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Patient ID ☐☐ - ☐☐☐

16. Have you ever had allergic reactions to foods? ☐ Yes ☐ No

16b. If yes, do you remember to which food? _____

17. Have you ever had allergic reactions to drugs? ☐ Yes ☐ No

17b. If yes, do you remember to which drug? _____

18. Do you know that some drugs for allergic and respiratory diseases are prohibited or under restrictions by the World Anti-Doping Agency (WADA)? ☐ Yes ☐ No

18b. If yes, tick which substances, you think are included in this category:

- ☐ Antihistamines
- ☐ Bronchodilators
- ☐ Vasoconstrictors
- ☐ Topical corticosteroids (Nasal inhalers, eye droplets, dermatological preparations)
- ☐ Inhaled corticosteroids
- ☐ Injected or oral corticosteroids

19a. Do you think that anti-allergic and/or respiratory drugs may:

☐ Reduce performance ☐ Improve performance ☐ Don't affect performance

19b. Do you think that anti-allergic and/or respiratory drugs may be in conflict with anti-doping regulations? ☐ Yes ☐ No

20. Have you used more than three courses of any of these drugs during the last year? ☐ Yes ☐ No

20.b.. If yes, tick which category of drugs you did use:

- ☐ Antibiotics
- ☐ Anti inflammatory drugs
- ☐ Pain reducing drugs
- ☐ Drugs for reducing fever
- ☐ Others, which....

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Patient ID ☐☐ - ☐☐☐

21. Have you used any other (except anti-asthma/anti-allergic) drug during the last week?

☐ Yes ☐ No

21 b. If yes, which drug? _____

22. Do you frequently suffer from upper respiratory infections (pharyngitis, colds, otitis media, tonsillitis, laryngitis) or fever?

☐ Yes ☐ No

22 b. If yes, are these infections more frequent during periods when you train more often than usual or during overtraining periods?

☐ Yes ☐ No

23. Have you suffered from recurrent labial herpes?

☐ Never
☐ 1-3 times
☐ More than 3 times

24. How many times during the last year were you unable to train because of infections?

☐ Never
☐ 1-3 times
☐ More than 3 times

25. If you have respiratory symptoms, which?

☐ Episodes of heavy breathing
☐ Wheeze
☐ Cough
☐ Phlegm, expectorate

26.Does this occur?

a. During exercise / training / competition: ☐ Yes ☐ No

b. During colds ☐ Yes ☐ No

c, After contact with animals, pollens, others: ☐ Yes ☐ No

27. With respiratory symptoms and dyspnoea related to exercise, when and how?

a. During maximum exercise ☐ Yes ☐ No

b. After the exercise: ☐ Yes ☐ No

c. In the afternoon, after training and/or competition: ☐ Yes ☐ No

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Patient ID ☐☐ - ☐☐☐

28. When you have these respiratory symptoms?

a. Is it difficult to inhale ☐ Yes ☐ No

b. Is it difficult to exhale ☐ Yes ☐ No

c. Both: ☐ Yes ☐ No

29. Do the respiratory symptoms / dyspnoea occur?

☐ Outdoors
☐ Indoors
☐ Both outdoors and indoors

30. How often do you have heavy breathing?

☐ Daily
☐ Several times a week
☐ Weekly
☐ Monthly
☐ More rarely

31. Does your respiratory symptoms increase with simultaneously?

☐ Low temperatures, cold air inhaled
☐ Fog

32. Do the respiratory symptoms have impact on your sports performance? ☐ Yes ☐ No

33. Do you have symptoms from eyes or nose? ☐ Yes ☐ No

34 a. Do you smoke? ☐ Yes ☐ No

34 b. If yes, how many cigarettes a day?

☐ Less than 5
☐ 5-20
☐ More than 20

35. Do you use snus? ☐ Yes ☐ No

36. Do you use any foods supplements (vitamins, amino acids, creatine)? ☐ Yes ☐ No