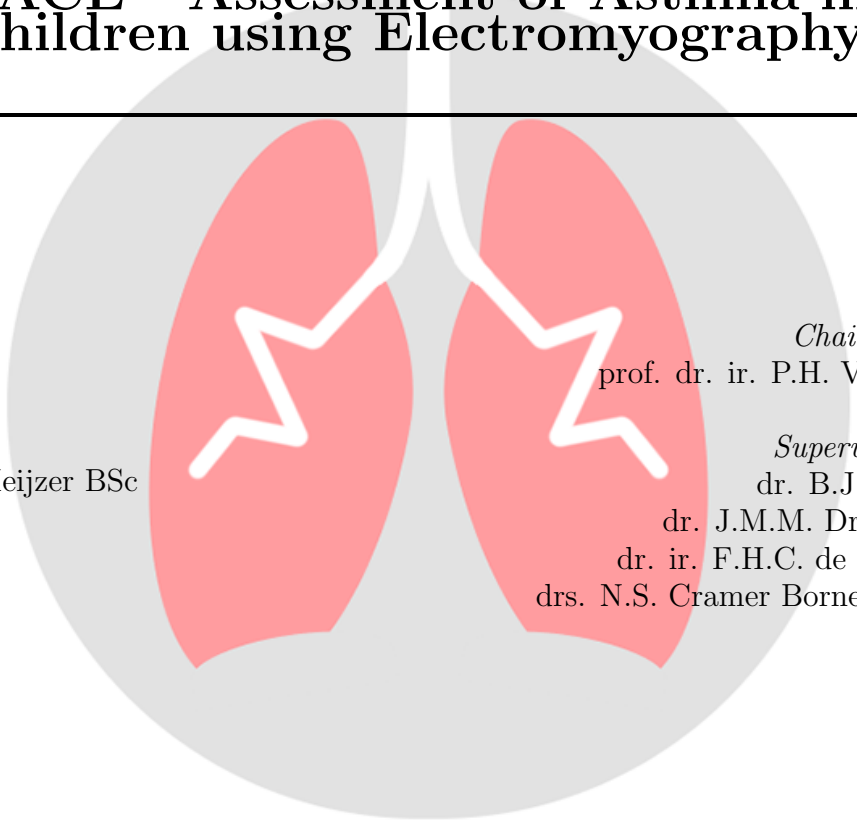
University of Twente

Masters Thesis

Department of pediatrics MST Enschede

AACE - Assessment of Asthma in Children using Electromyography



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Abstract

Rationale Asthma is one of the most common chronic diseases in childhood, occurring in up to 10% of all children. Exercise induced bronchoconstriction (EIB) is indicative of uncontrolled asthma and can be assessed by means of an exercise challenge test (ECT). These tests however draw heavily on healthcare resources and require demanding repetitive forced breathing manoeuvres of children. In this study the electric activity of the respiratory muscles was measured as a tool to assess EIB.

Methods Children suspected of exercise induced respiratory symptoms performed an ECT wearing a portable EMG amplifier (Dipha-16, Demcon Macawi respiratory systems, Enschede, the Netherlands). EIB was defined as a fall in FEV1 of greater than 13%. Electrodes were placed bilaterally at the diaphragm and accessory breathing (intercostal-, sternocleidomastoid- and trapezoid) muscles. A single reference electrode was placed at the sternum. Children were asked to sit still for 30 seconds after each spirometry measurement to obtain EMG measurements. Data was pre-processed and analyzed in Matlab.

Results 20 Out of 43 children were diagnosed with EIB. Peak amplitude measured at the diaphragm increased significantly more in children with EIB than in children without EIB; $4.85\mu V(1.82 - 7.84)$, compared to $0.20\mu V\,(-0.10 - 0.54)$, ($P < 0.001$) at the point of maximal bronchoconstriction. Increases in EMG peak heights at the diaphragm can accurately distinguish between EIB and non-EIB (Sensitivity 95%, Specificity 91%, AUC 0.973). Increase in activity at the diaphragm is related to the decrease in pulmonary function ($Pearson's\, R : 0.77$, $R^2 = 0.58$, $P < 0.001$). Accessory breathing muscles were often not measurable at baseline, therefore accurate assessment of the changes in activity in response to exercise could not be attained.

Conclusion These results imply that EMG measurements of the diaphragm can be used to accurately distinguish between EIB and non-EIB in children in response to exercise. Larger increases in peak amplitude suggest an increased work of breathing as is expected in children with EIB. Moreover, we found a relation between the decrease in pulmonary function and the increase of EMG peak activity. This technique provides opportunities to non-obtrusively measure bronchoconstriction when spirometry is not feasible or available and may be applied in the clinical setting, such as emergency medicine or in hospital- or home monitoring.

Preface

Before you lies my thesis, written to obtain the degree of Master of Science at the University of Twente in Technical Medicine and is the result of my work conducted between November 2017 and November 2018.

The initial idea of this work came from dr. Jean Driessen, who handed me two articles back in the summer of 2017 regarding EMG measurements of the breathing muscles and a histamine provocation test. His question was plain and simple; Do you think that we can do this with asthma? After having read some additional literature and an extensive conversation with dr. ir. Frans de Jongh, the three of us came to the conclusion that this subject would be perfect to complete my masters degree with.

In November 2017 I started writing my plan of action and a measurement protocol for the medical ethics committee. Approval of the medical ethics committee was fortunately obtained not long after submitting the protocol, so I could quickly start making sure all measurement equipment was ready for use.

What followed was a period of many self-measurements and programming, trying to understand what the obtained signals mean. After all, for me this was the first time I actually looked at measurement data. I wrote the application I used for analysis during this period, often reminded of the single most important lesson in programming I ever had; If you have written a piece of code, do not **EVER** expect it to work.

Between April 2018 and September 2018 I included 50 patients into my study at OCON, which is when I started getting more and more enthusiastic about conducting this research. Being able to see and measure from the beginning, following the data until the end of analysis and trying to understand what my findings mean greatly motivated me.

I've learned a lot about asthma care, and being able to see what adequate care means to these children boosted my motivation even more. Moreover I hope that my work can further contribute into the care for these children and I hope to personally be able to contribute to that cause in the future as well.

I hope you will enjoy reading my thesis as much as I did writing it.

Pascal Keijzer

Acknowledgements

The work that lies before you could not have been established without the help of many others, for which I am incredibly grateful.

To all the children that participated in my study and their parents. Thank you! Without you this work would not have been possible. Despite that fact that you personally may not have benefited from these measurements, many others in the future may!

Dr. Boony Thio, starting from my final M2 internship you have been the most accessible medical supervisor I have had in the past two years. Accessible however did not always mean that it was easy talking about the serious stuff. Because the important stuff had to be dealt with first, and we've had some great discussions about every game Ajax has played over the past one and a half year. When it came to the serious stuff however you taught me to always keep thinking about what my findings imply and you always thought along with me when I did not see the answer.

Dr. Jean Driessen, your enthusiasm working with children was one of the first reasons for me to think about doing my graduation internship in this field, even before we thought of my subject. You taught and showed me that working with children in a hospital requires you to improvise, and that talking to a 4 or 14 year old requires much more adaptation than talking to a 24 or 34 year old. Furthermore it gives me hope for the future to see that even a medical professional with a PhD in pediatric asthma can still be an active gamer.

Dr. ir. Frans de Jongh, at first you were a bit skeptical whether we could even obtain valid measurements from children, but luckily you gave me the benefit of the doubt to start my graduation internship. Throughout the year you've been very supportive and often aided me in my analysis procedure. Furthermore I much enjoyed our conversations about traveling and I will gladly make use of your advice in that field as well.

Drs. Nicole Cramer Bornemann, over the past year you've helped me learn a lot about myself, what drives me and what my talents are. I often found it difficult to quite get to the bottom of these questions, but through our discussions it taught me a lot more about myself than I could have anticipated.

Prof. dr. ir. Peter Veltink, I would like to thank you for fulfilling the role of chairman on such short notice and for being the external supervisor for my committee.

My technical medicine colleagues, you guys always made sure that our working atmosphere was great. You guys helped my with my research and supplied me with plenty of corny jokes. Fortunately you all valued food as much as I do, and our weekly trips to the

market were much appreciated. As well as our daily ice cream during the summer, we agreed that was simply a necessity. I'm sorry for the mess, and I believe I still owe you guys a sushi lunch. Don't worry, it'll be there, one day.

Femke, you have always supported me throughout the year even when I was incredibly moody. Your unwavering support always keeps me going and I am sure that this work would not have been possible without you backing me.

Finally, mom, dad, I think that I understate this quite a bit when I say that everything took a bit longer than we had anticipated. Nevertheless I always knew that despite that fact that I wasn't home as much anymore, you guys were always there for me. I am proud of the work that lies before you and I hope to make you proud when I do finally graduate.

List of abbreviations

Abbreviation	**Meaning**
AACE	Assessment of Asthma in Children using Electromyography
ATP	Adenosine triphosphate
ATS	American Thoracic Society
AUC	Area under curve
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CVC	Cardiovascular condition
ECT	Exercise challenge test
EIA	Exercise induced asthma
EIB	Exercise induced bronchoconstriction
EMG	Electromyography
$FEV_{0.5}$	Forced expiratory volume in 0.5 seconds
FEV_1	Forced expiratory volume in 1 second
FOT	Forced oscillation technique
FRC	Functional residual capacity
HR	Heartrate
ICD	Internal cardioverter defibrillator
ICs	Inhaled corticosteroids
IgE	Immunoglobulin E
MNT	Mouth nose throat
MST	Medisch Spectrum Twente
O_2	Oxygen
OCON	Orthopedisch Centrum Oost-Nederland
$P_{A_{O_2}}$	Partial pressure of oxygen in alveolar air
$P_{C_{O_2}}$	Partial pressure of oxygen in capillary blood
P_{IP}	Intrapleural pressure
R_{AW}	Airway resistance
R_{Br_n}	Resistance of bronchus branch of the n^{th} generation
RMS	Root mean square
ROC	Receiver operator characteristic
SABA	Short acting beta adrenoceptor agonist
ZGT	Ziekenhuisgroep Twente

Contents

1 Introduction

Asthma is one of the most common chronic inflammatory diseases in children, and is charactarised by bronchial hyper responsiveness to various stimuli, such as cold and dry air, pollen, dust mites and exercise [1]. Children may be afraid that activity will provoke their asthma, or simply become less interested in physical activity altogether [2, 3]. This can lead to a sedentary lifestyle, and possibly obesity [4]. The relationship between asthma and obesity works both ways, children who are obese are more likely to experience asthma exacerbations. On the other hand a lack of physical activity is a known risk factor for developing obesity [5, 6]. Children are often no longer capable of competing and come along with their peers, necessitating treatment. The most common symptoms in asthma involve coughing, wheezing, shortness of breath and chest tightness.

1.1 Prevalence of asthma

The occurrence of asthma is on the rise in the Netherlands, with a current year prevalence of over 610.000 in 2015, children and adults [7]. Children between the ages of zero and fourteen in the Netherlands display a prevalence of 7-10%, with a higher incidence in boys [8, 9].

1.2 Triggers of asthma

The division in asthma types is made based upon the inflammatory response, being either T-helper-2-associated or non-T-helper-2-associated [10, 11]. When focusing on pediatric asthma, we focus on the T-helper-2-associated asthma. Allergic asthma, virus induced asthma and exercise induced asthma [12]. Asthma is often not limited to just a single phenotype and multiple causes contribute to dyspnea in children.

1.2.1 Allergic asthma

This group of patients often develops their symptoms as children and carry them over into adulthood. Children display asthmatic symptoms in response to inhaling allergens and almost always have a family history of allergies and asthma [13]. Allergies can be determined using a skin prick test, or serum sample test for specific antibodies [13, 14]. Children often experience extended periods of mild symptoms in between exacerbations [12].

1.2.2 Virus induced asthma

Children suffering from virus induced asthma display symptoms in response to virus inflammations. It is the most common cause of asthmatic exacerbations in young children [10]. Viruses may cause acute airway inflammation, resulting in bronchial hyper responsiveness.

Virus induced asthma is often paired with symptoms caused in other virus induced inflammations, such as fever, sneezing and head-aches [10]. Children do not experience any asthmatic symptoms in between exacerbations [12].

1.2.3 Exercise induced asthma

Exercise induced asthma (EIA) is a symptom of asthma that over 80% of asthma patients, children and adults alike, experience [15]. It is diagnosed by means of an exercise challenge test(ECT), combined with lung function testing to determine bronchoconstriction [15, 16]. Exercise induced bronchoconstriction (EIB) is more prominently present in children with a sedentary lifestyle [17]. Children are prone to decrease in amounts of physical activity when suffering from EIA, further spiraling into a sedentary lifestyle. One of the main goals to treat pediatric asthma is to ensure children can participate in everyday physical activity and playing [18]. Whereas EIB in adults is often acquired, EIB is highly specific for asthma in children and occurs in 80-90% of pediatric asthma patients [18–21].

1.3 Bronchoprovocation testing

The current gold standard for assessing pediatric asthma is a bronchoprovocation test by means of an exercise challenge test (ECT), as described by the American Thoracic Society [22]. For children under the age of eight a jumping castle is used as a replacement for the treadmill as an exercise challenge, first described by van Leeuwen in 2012 [18]. A decrease of over 13% in forced expiratory volume in one second (FEV_1) after sub-maximal exercise is defined as an asthmatic reaction [22]. A standard ECT takes up to one hour to complete, requires specialised facilities and knowledge and is therefore only applicable in clinical practise in the outpatient clinic.

1.4 Electromyography of respiration

Electromyography (EMG) of the diaphragm and accessory breathing muscles has first been applied near the end of the 1970's. EMG measures electrical activity of skeletal muscles [23]. The largest source of electrical activity in the thorax is the heart and the distortion presented by the heart is between 10 to 20 times the size of the EMG signal broadcasted by the diaphragm and accessory breathing muscles. The gating technique designed by O'Brien et al. back in 1983 is capable of detecting QRS complexes in the measured electrical activity and filling the QRS gate with a running average [24]. The remaining signal is a good representation of electrical activity from the diaphragm and accessory breathing muscles. The gating technique was tested and reproducible EMG signals were successfully obtained by Maarsingh and Hutten [25,26]. Changes in diaphragm activity were detectable in preterm and aterm infants, as well as children and adults using EMG amplifiers [25–28].

1.5 Rationale

The technique of using electromyography to measure the activity of the diaphragm and accessory breathing muscles has been known for years. With the current technology, EMG can be measured using a portable device, removing the limits of only measuring in controlled environments. Recent studies have proven the viability of EMG to accurately measure reproducible diaphragm and accessory breathing muscle signals [25–28].

The aim of this study therefore is:
To determine the accuracy at which electromyography can detect and assess the severity of exercise induced bronchoconstriction in children when compared to the outcomes of a gold standard exercise challenge test

Secondary research questions include:

- What are the most important parameters when assessing pediatric asthma using EMG?
- What are the most important parameters when assessing a dysfunctional breathing pattern using EMG?
- Which muscle group is the most important when assessing pediatric asthma or dysfunctional breathing?
  - What are the changes in the relation between the amount of activity in independent muscle groups?
  - What are the changes in total EMG activity for the independent muscle groups and as a whole?
- What is the relationship between increasing dyspnea and the respiratory rate recovery time?

2 Background information

2.1 Normal breathing physiology

The initial necessity of breathing is to supply the body with oxygen (O_2) and to release the body of carbon dioxide (CO_2). During quiet inspiration the intrathoracic size increases by inferior movement of the diaphragm and by elevation of the ribs by the external intercostal muscles (Overview shown in Figure 1). During breathing two main physiological processes are involved to achieve adequate gas exchange between the environmental air and the blood. Firstly ventilation, during which air is transported from the outside air into the alveoli. Secondly the actual gas exchange, to transport oxygen from the alveolar air into the blood.

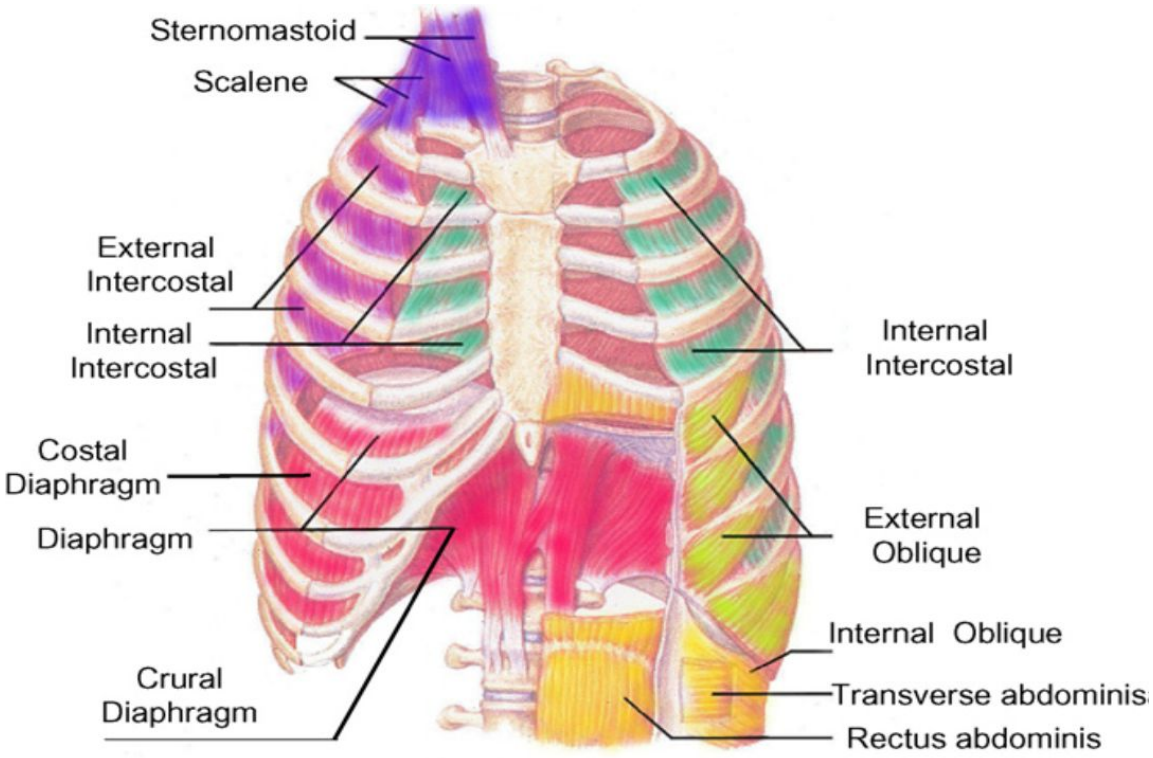

Figure 1: *During quiet inspiration the diaphragm moves inferiorly to expand the intrathoracic space and increase the anterior-posterior diameter. When ventilation intensifies, the diaphragm's efforts are increased. Additionally the accessory breathing muscles (Intercostal, sternocleidomastoid-, scaleneus- and trapezoid muscles) may be recruited to further enhance the expansion of the intrathoracic space.*

2.1.1 Gas exchange

Air is inhaled through either nose and/or mouth, and by means of the trachea and bronchi eventually reaches the alveoli. Some air remains in the anatomical dead space. The alveoli are the smallest structures within the lung, and is the place where the actual gas exchange occurs. Through diffusion O_2 is transported over the alveolar wall into the bloodstream, where it binds to haemoglobin. CO_2 is diffused over the alveolar wall in the opposite direction, to be exhaled. The diffusion of gasses over a barrier is described by Fick's law [29, 30]. A simplified version of Fick's law is given:

$$\dot{V}_{net} = D_L(P_1 - P_2) \tag{1}$$

Fick's law states that the net flow ($\dot{V}_{net}$) is dependent on the diffusion capacity (D_L) and the partial pressure gradient ($P_1 - P_2$). The diffusion capacity of a surface is dependent upon the area of the barrier (A) and the concentration gradient of the gas in water (s). The capacity is inversely dependent upon the barrier thickness (a) and the square root of the molecular weight (MW) (following from Graham's law). Finally the proportionality constant (k) affects both area and thickness and describes the interactivity of the gas with the barrier [29].

$$D_L = k\frac{A \cdot s}{a\sqrt{MW}} \tag{2}$$

Combining these equation for the lung, we find that the flow of oxygen in the lung over the alveolar wall is described by the following:

$$\dot{V}_{O_2} = D_{L_{O_2}}(P_{A_{O_2}} - P_{C_{O_2}}) \tag{3}$$

In this equation the partial pressure gradient is determined by the partial pressure of O_2 in the alveolar air ($P_{A_{O_2}}$) and the partial pressure of O_2 in the pulmonary capillary blood vessel ($P_{C_{O_2}}$). Inspiration causes the alveoli to stretch, thus maximising the surface area and the minimising thickness of the alveolar-capillary membrane. Furthermore the influx of oxygen into the lung increases the partial alveolar pressure, together establishing a condition in which oxygen flow over the alveolar wall is maximal [29].

2.1.2 Ventilation

The interaction between the lungs and the thoracic wall determines the lung volume at any given time. The lungs have a tendency to collapse due to their elastic recoil, whereas the chest wall has an elastic recoil in the opposite direction. Instead of being directly attached, the pushing and pulling of chest wall and lung occurs through the intrapleural space which is filled with pleural fluid. The intrapleural pressure (P_{IP}) is a relative vacuum, maintained by the pulling on either side of the pleurae (Figure 2) [29]). The maintained relative vacuum prevents the lungs from collapsing.

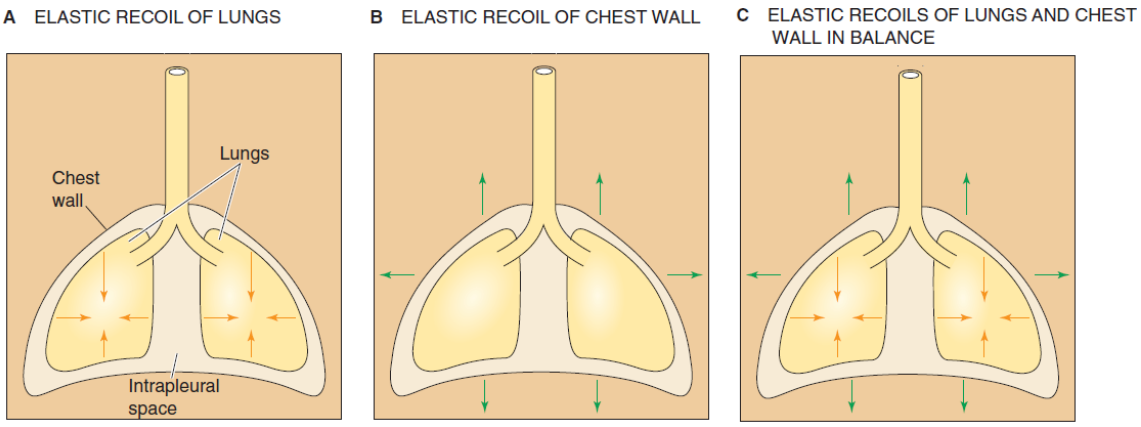

Figure 2: *The pulling on either side of the pleurae helps to maintain a relative vacuum in the interpleural space ensuring the lungs do not collapse. (Adapted from Medical Physiology [29])*

Boyle's law states that the pressure (P) is inversely proportional to its volume (V) (equation 4). Important to note is that the volume described by Boyle is the available volume in a container to a fixed amount of gas.

$$P \propto \frac{1}{V} \tag{4}$$

Hagen-Posseuille's law states that a decrease in pressure results in a laminar airflow through a pipe (equation 5). The flow (Q) is dependent on the radius of the pipe (r), the viscosity of the fluid (η), the pressure difference between either end of the pipe (ΔP) and the pipe length (L) and is only applicable in laminar airflow.

$$Q = \frac{\pi r^4}{8\eta} \frac{|\Delta P|}{L} \tag{5}$$

Hagen-Posseuille's law for small pipes is bounded by Bernoulli's principle, which states that an increase of gas flow occurs simultaneously with a decrease in pressure (equation 6). The gas density (ρ), gas velocity (v), gravitational acceleration (g), elevation opposite to g (z) and pressure (P) have to remain constant.

$$\frac{1}{2}\rho v^2 + \rho g z + P = constant \tag{6}$$

Hagen-Posseuille's law for small pipes provides unrealistically high flow rates, necessitating a description of the limitation of flow, which is given by Bernoulli's principle under less restrictive conditions. The amount of flow (Q) may also be described as the derivative of volume (V) over time (t), which may also be described as the velocity (v) of the gas through the pipe:

$$Q = \frac{dV}{dt} = v\pi r^2 \tag{7}$$

Velocity is also described in Bernoulli's principle (equation 6) in the first term, which may be regarded as dynamic pressure (ΔP). The bounded maximal flow is given by:

$$Q_{max} = \pi r^2 \sqrt{\frac{2\Delta P}{\rho}} \tag{8}$$

Equation 8 is found by rewriting ΔP as the kinematic energy in Bernoulli's equation.

$$Q_{max} = \pi r^2 \sqrt{\frac{2\frac{1}{2}\rho v^2}{\rho}} \tag{9}$$

Which can be simplified to:

$$Q_{max} = \pi r^2 \sqrt{v^2} = \pi r^2 v \tag{10}$$

The description above applies to static tubes. A complicating factor is the fact that the airways may narrow in response to high air flows and ultimately close when the airway walls touch, causing a choked flow. When translated to parameters specific for the lung, we find that the airflow is dependent upon the pressure difference between the outside air and the air inside the alveolus and inversely dependent upon the total airway resistance R_{AW}.

$$Q = \frac{\Delta P}{R_{AW}} \tag{11}$$

The airway resistance within a tube is described by Posseuille's law (equation 12). The total airway resistance is built up out of the individual resistances of the branches of the bronchial tree in addition to the mouth, nose and throat (MNT) area. Equation 13 describes the first two generations of branches of the bronchial tree in terms of resistances (R_{Br_n}). The bronchial contains 23 generations of branches before reaching the alveoli, each contributing to the total airway resistance.

$$R_{Tube} = \frac{8\eta L}{\pi r^4} \tag{12}$$

$$R_{AW} = R_{MNT} + R_{Trachea} + \frac{R_{Br_1} R_{Br_2}}{R_{Br_1} + R_{Br_2}} + \frac{R_{Br_3} R_{Br_4} R_{Br_5} R_{Br_6}}{R_{Br_3} + R_{Br_4} + R_{Br_5} + R_{Br_6}} ... \tag{13}$$

The pressure differences described in both laws are caused by actively inspiring air. A decrease in pressure in the pleural space passively causes the lungs to increase in size. Taking Boyle's law into account (equation 4), an increase in volume will cause the pressure to decrease. A decrease in pressure will increase (ΔP) between the outside air and air in the lung, which via Hagen-Posseuille's law will cause air to flow until ΔP stabilises (equation 8). During expiration the respiratory muscles relax and the stored energy in the elastic recoil causes the lung to return to its original size before inspiration (Figure 3) [29].

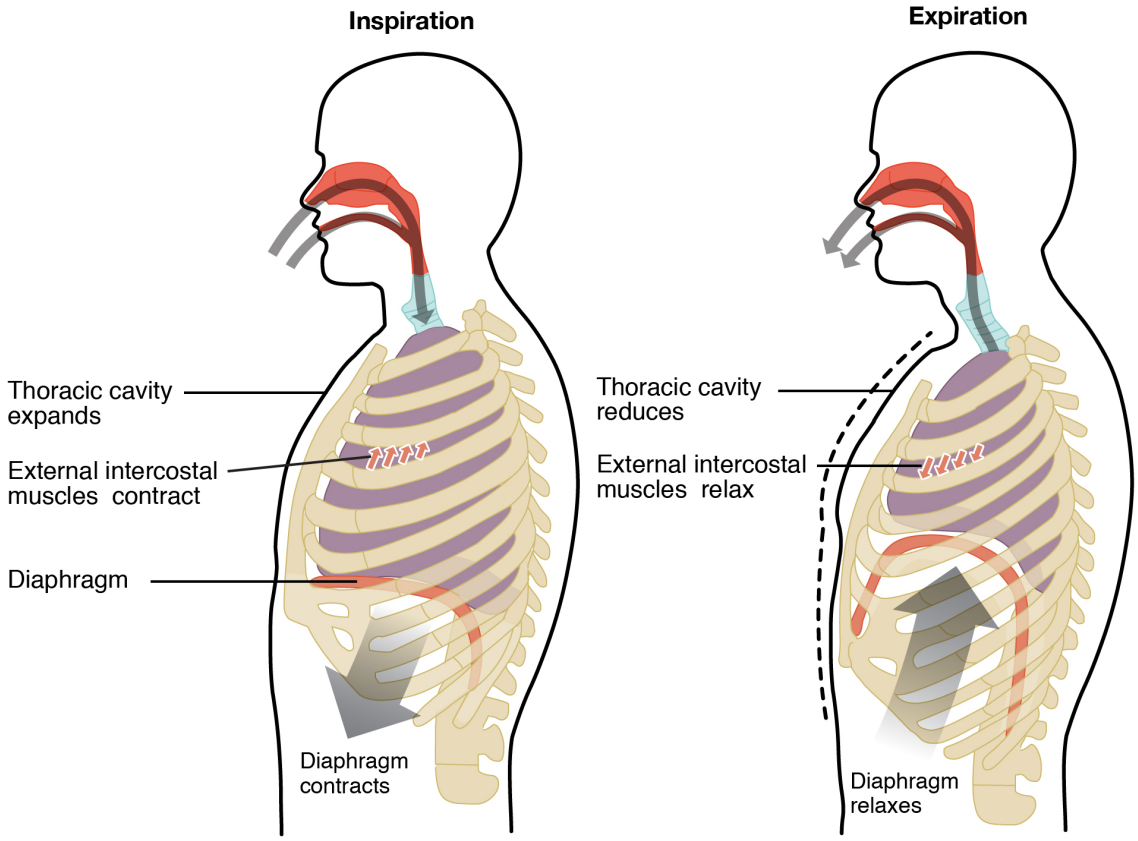

Figure 3: *The contraction of the diaphragm and other respiratory muscles causes the thoracic cavity to expand, increasing the volume of the lung and causes interthoracic pressure to decrease. The decrease in pressure causes an airflow into the lung. During expiration the diaphragm and other respiratory muscles relax, reducing the size of the thoracic cavity, the elastic recoil causes the lung to decrease in size and forces air to flow out.*

2.2 Physiology of asthma

Asthma is a chronic inflammatory disease, of which various groups of symptoms are known [1]. An overview of the most common symptoms is given in the below sections, concluding with a possible life style change.

2.2.1 Airway inflammation

The inflammatory response in asthma is triggered by various allergens. The allergic response causes an increase in mucus production and thereby narrows the airways (Figure 4) [31, 32].

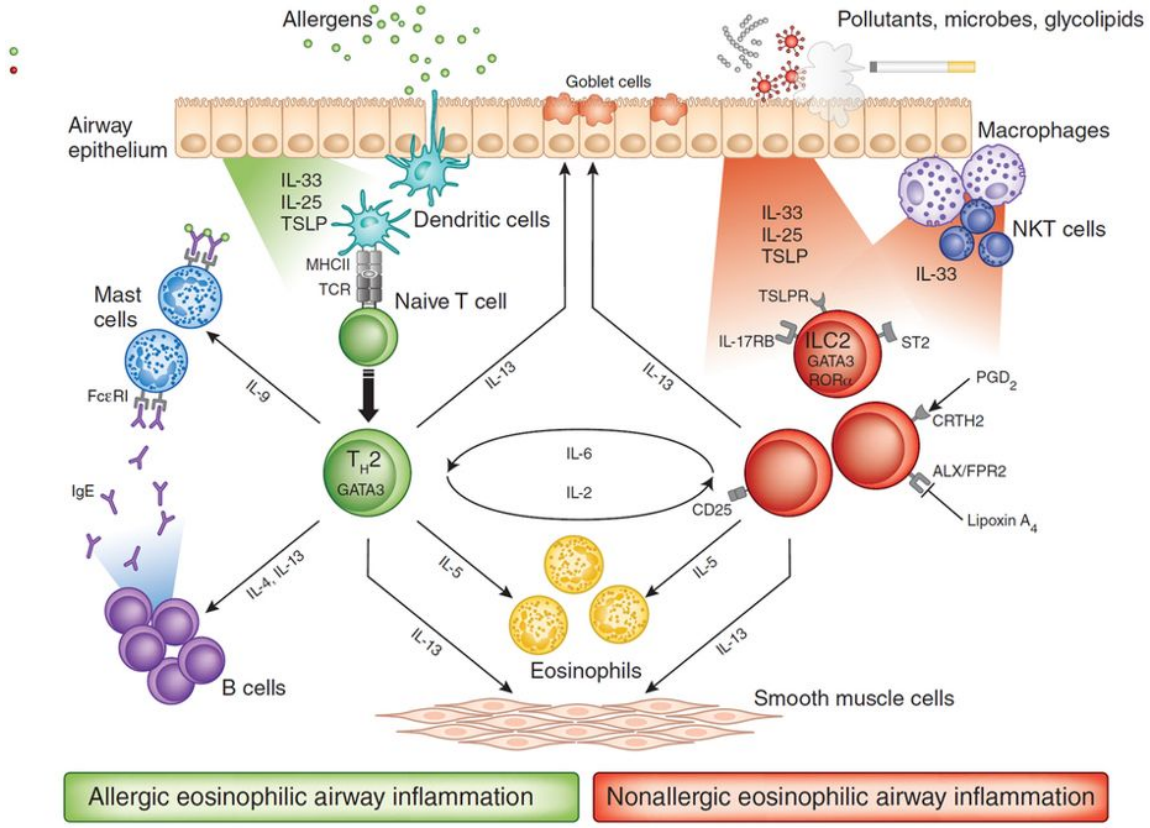

Figure 4: *The inflammatory response to allergens. Dendritic cells present the inhaled allergens to T-cells, causing T-helper-2-cells to produce an array of interleukins. These cause B cells to release IgE, cause an increase in mucus secretion by goblet cells and eosinophilia, contributing to an increase in smooth muscle cell contraction. Pollutants may cause the release of the same interleukins, causing a cascade from the type 2 innate lymphoid cells. (Image adapted from [32])*

The increase in mucus production, together with bronchoconstriction, decreases the lumen and via Posseuille's law (equations 11 and 12) increases R_{AW} and decreases Q if ΔP remains constant.

2.2.2 Bronchoconstriction

During inflammation the bronchial wall thickens and starts producing larger amounts of mucus, resulting in a decrease in bronchial lumen [33]. The bronchial wall appears thickened in all asthma patients regardless of disease severity, but the degree of thickening is related to disease duration and severity [34–36]. Furthermore the smooth muscle cells lin-

ing the bronchial wall contract, further decreasing lumen size (Figure 4) [32]. Going back to Posseuille's law (equation 12), it becomes clear that a narrowing of the airway ($r \downarrow$) causes a large increase in R_{AW}. Subsequently leading to a decrease in airflow (equation 11).

The decreased airflow can be measured using spirometry, which is the most common method of assessing childhood asthma [37]. For a spirometric measurement the patient is required to fully inhale, and then exhale with maximal force. These measurements provide sufficient information to accurately monitor asthma, but require maximal cooperation and training to be performed properly. Furthermore it is difficult to achieve maximal cooperation and performance in each measurement in young children (ages six and under). The younger the child is, the more difficult it gets to achieve full cooperation and performance and non-maximal effort and cooperation may lead to an underestimation of the lung function parameters [38, 39].

Using the forced oscillation technique (FOT) it is possible to directly measure airway resistance. These measurements do not require maximal effort and can be used in a younger population reliably [40–43]. Application and clinical experience of FOT in conjunction with airway disease is not applied as widespread as spirometry is.

2.2.3 Hyperinflation

Being an obstructive disease, asthma patients display increased functional residual capacities (FRC) due to air trapping, subsequently leading to a lower R_{AW} [29,44,45]. Breathing on a higher FRC makes patients more dependent of the recruitment of their accessory breathing muscles [46, 47]. Not only does hyperinflation lead to a lower R_{AW}, the inflated lung also improves the diffusion capacity by providing a larger area over which diffusion may take place (equation 2). The effects offer short-term relief, but a sustained increased FRC will lead to muscle fatigue of the accessory breathing muscles. Furthermore the tidal volume decreases, causing the amount of gasses actually exchanged between the body and the outside air to decrease due to a lower dead-space ventilation. Subsequently the partial pressure differences described by Fick's law decrease (equation 3), limiting the diffusion capacity.

2.2.4 Respiratory sounds

The constricted airways cause an oscillation in the airflow, which can be heard as the wheezing sound. During expiration air passes through the narrowed airways. Bernoulli's principle (equation 6) explains that for a flow to remain the same, the pressure drop has to increase and/or flow speed has to increase. The airway pressure on the alveolar side will increase, and the transition between the alveoli and narrowed airways produces the sound waves heard as wheezing [48].

Wheezing patterns are known predictors of narrowed airways [49]. Although children

who wheeze are known to be suffering from obstructed airways, not all children who experience airway obstruction wheeze [50, 51].

2.2.5 Dyspnea

One of the charactarising symptoms of an asthma exacerbation are episodes of dyspnea. Bronchoconstriction causes the airways to narrow and restricts airflow, especially during expiration. With a limited outward airflow, air is trapped within the lungs, the CO_2 levels in the blood will rise and O_2 levels will decrease (respiratory acidosis). Both CO_2 and O_2 flows over the alveolar wall will decrease due to a change in partial pressures (equation 1) [44].

In response the body induces an increase in heart- and breathing rate. Additionally the body increases the use of the accessory breathing muscles. These responses cause short term relief attempt to restore arterial blood gasses to normal values. Persistent bronchoconstriction however cause muscle fatigue and blood gas levels will gradually deteriorate [44].

2.2.6 Physical activity

Children suffering from asthma are not as active as their healthy peers and may be afraid that physical activity will provoke bronchoconstriction [2, 3]. The interaction between asthma and obesity works both ways, children with obesity are more likely to experience asthma exacerbations, while on the other hand a lack of physical activity is a risk factor for developing obesity [5, 6](Figure 5). Physical activity however is especially beneficial in children suffering from asthma, as it alternates airway inflammation and mediates the synergy between asthma and obesity [52, 53]. Increasing physical activity in asthma patients has proven to improve their asthma [17]. Without appropriate care, asthma and obesity support each other in a vicious cycle (Figure 5). A decrease in physical activity is intelligible, but may provide long-term problems. Physical consequences include obesity, a decreased cardiovascular condition and psychomotor underdevelopment. Being unable to play with their peers may also cause a decrease in social development. Furthermore, childhood acquired activity patterns are likely to be carried over into adulthood [54].

2.3 Exercise challenge testing

EIB in children is known to be an indicator for childhood asthma, making an exercise challenge test the ideal method of determining the control of asthma [21, 55, 56]. The current gold standard in assessing asthma severity in children is by means of spirometry [57, 58]. A decreased FEV_1 combined with reversibility in response to a bronchodilator are indicators of asthma. Repeated spirometry in a single patient provides insight into the normal values for each individual and aides in detecting deterioration. Furthermore repeated spirometry after initiation of corticosteroid treatment provides detailed insight into treatment effectiveness [59]. Spirometry alone provides insight into the current lung

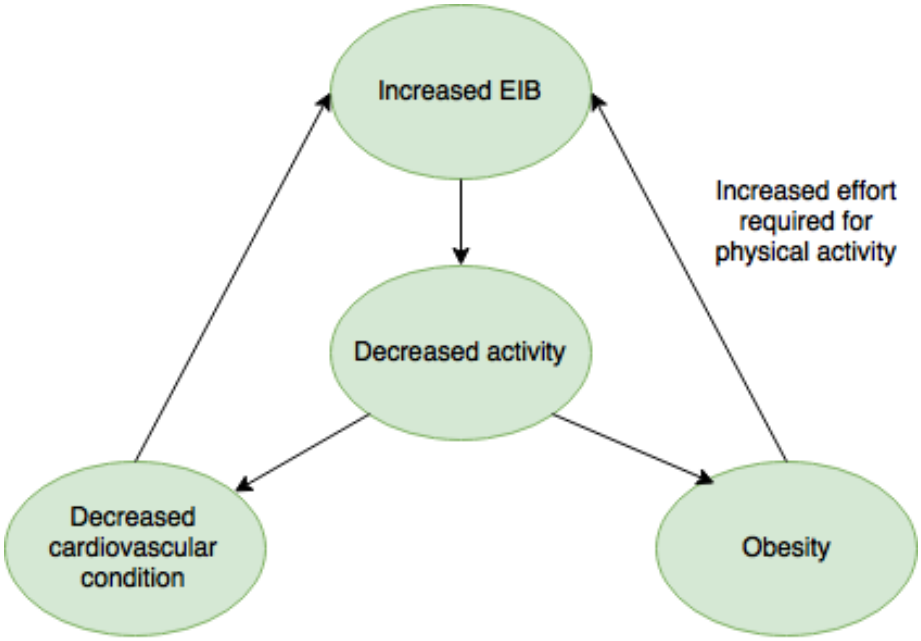

Figure 5: *Increased EIB may lead to a decrease in physical activity, which leads to a decreased cardiovascular condition (CVC). When CVC decreases, the ventilation per workload increases and patients experience increased EIB episodes. Long term physical inactivity may lead to obesity, meaning a higher effort and ventilation frequency is required to complete the same physical tasks and increase the burden of EIB.*

functioning state, but a single measurement does not fully describe the possible severity of symptoms. By means of an ECT, an asthmatic reaction within the lungs is provoked. Spirometry is performed before and repeatedly after exercise, providing insight in the deterioration of the asthmatic reaction and grants an understanding of the measure of discomfort the patient experiences.

2.3.1 Pathogenesis of exercise induced asthma

There are two hypotheses describing the pathogenesis of exercise induced asthma, summarised in figure 6.

Both hypotheses describe the effects of dehydration of the mucosa. Dehydration induces an increased osmolarity of the airway fluid lining layer, causing mast cell degranulation and release of inflammatory mediators. These mediators cause smooth muscle contraction, oedema and increased mucus production, which combined lead to airway narrowing (Figure 7) [60–63].

The second hypothesis states that evaporation as an endothermic process causes the

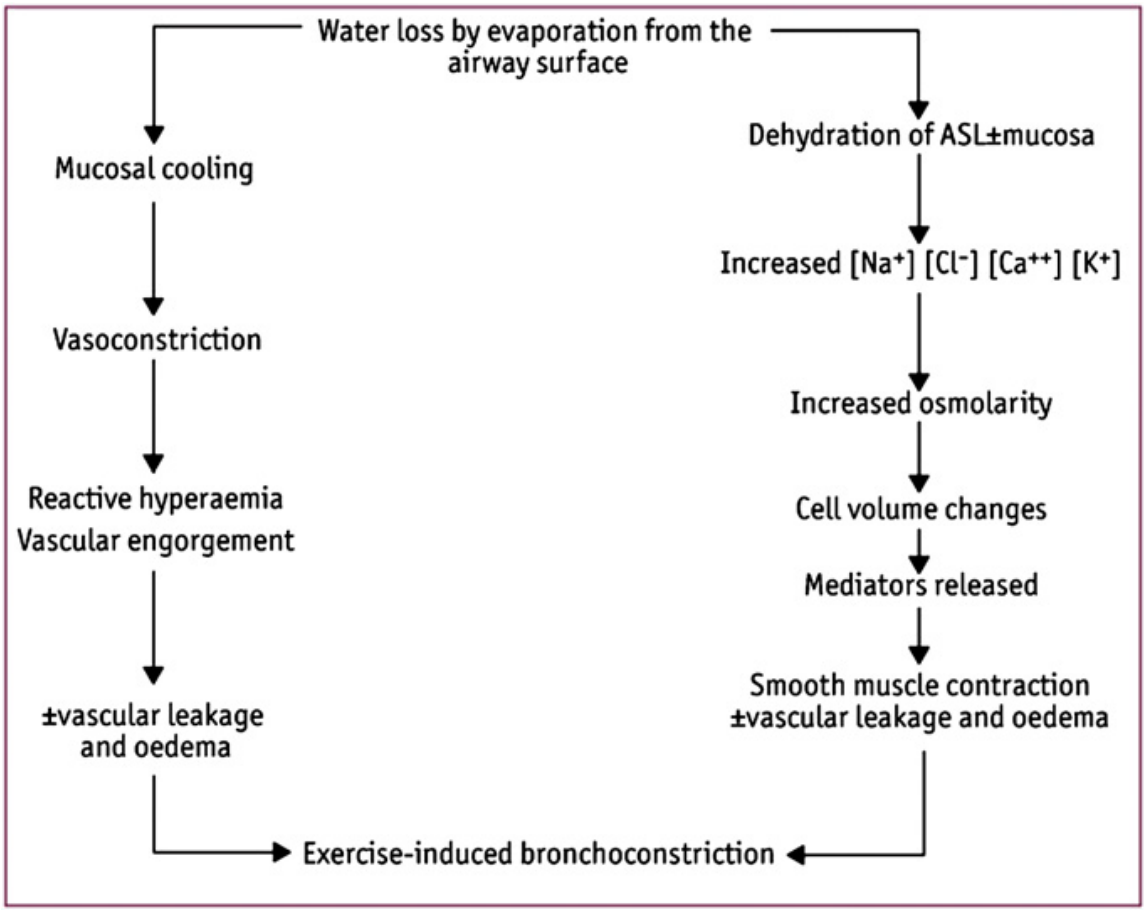

Figure 6: *The two pathways describing the pathogenesis of exercise induced bronchoconstriction. The cooling of the airways and dehydration of the mucosa of the airways both cause oedema, eventually leading to bronchoconstriction. (Figure adapted from [60])*

mucosa to cool. When exercise is ceased and the temperature in the airways is restored, the blood flow to the airways increases. The excess of blood causes the airway mucosa to swell [60, 64].

2.3.2 Exercise challenge test protocol

Both processes described in the above section are enhanced during exercise, when large volumes of air are delivered to the lungs in a short time [65–67]. The most important factor is the rate of evaporation of water in the airways, achieved in an ECT by introducing various stimuli. Exercise is required to be sufficiently intense and long enough [68–70]. Furthermore it is important that the air is dry [19, 71, 72]. Exercise challenge tests are

Figure 7: *Healthy airways have a clean airway lining and smooth muscle tissue lies along the airways non-contracted (left). People suffering from asthma experience a chronic inflammation of the airways, causing the mucosa to swell and some mucus to be secreted into the airways (middle). During an asthma exacerbation the inflammation intensifies. Additionally the smooth muscle tissue contracts causing further narrowing of the airways (right).*

performed according to the guidelines of the American Thoracic Society [22].

Baseline measurements The primary unit of measurement during the ECT is the forced expiratory volume in one second (FEV_1). FEV_1 is determined by spirometry measurements, during which children are encouraged to fully inhale and then exhale as forcefully as possible. At least two, preferably three measurements with comparable outcome are required at maximal effort. Effort is determined by a physician both visually and by examining the flow-volume curves. The largest FEV_1 is used as the baseline parameter. In some cases FEV_1 decreases during baseline measurements, this phenomenon is known as spirometer induced bronchospasm and is a sign of poorly controlled asthma [73, 74]. In case of spirometer induced bronchospasm the exercise challenge test is to be forfeited, as poor control of asthma has been identified.

Exercise Children exercise on a treadmill for six minutes, of which at least four minutes at sub maximal level as described by equation 14 [68–70].

$$HR_{submax} = 0.8 * (220 - Age_{years}) \tag{14}$$

The treadmill speed and slope are determined by monitoring the heart rate. During exercise children wear a nose clip, as nasal breathing reduces water loss in the airways [75].

Air modification Children exercise in an airconditioned room at 10°C, ensuring the air is both cool and dry to enhance the effects described in the above section [19, 71, 72].

Airway response Children perform additional spirometry measurements at at least one, three and six minutes post exercise. The time to reach maximal bronchoconstriction is age-dependent and occurs quicker in younger children [76]. If FEV_1 is still in decline spirometry is to be repeated until the point of natural recovery is reached, at either nine, twelve or fifteen minutes post exercise [77, 78]. Adults are measured at five, ten and fifteen minutes post exercise. A decrease of FEV_1 of 10% is considered an abnormal response in research [79]. A decrease of 15% is considered to be more accurate for EIB, especially when conducting measurements in the field [80]. For children the cut-off is chosen at 13% [81]. For young children it may be impossible to reliably produce FEV_1, as they due to their lung size are often capable of exhaling their total lung capacity within one second. Young children who cannot yet produce reliable FEV_1 are assessed based upon their forced expiratory volume in 0.5 seconds ($FEV_{0.5}$). Young children are often capable of exhaling their FVC in one second. For the $FEV_{0.5}$ a 13% decrease is also chosen as a cut-off value [81].

Response to bronchodilation After the maximal decrease in FEV_1 has been identified, patients are administered $200\mu g$ of salbutamol. An increase of 10% in FEV_1 above baseline is considered a significant reversibility in patients who did not reach the 13% cut-off for FEV_1 decrease [22]. A return to baseline levels after a decrease in lung volume is considered to be an indicator for asthma, whereas not returning to baseline levels indicates a more severe asthma [82].

2.4 Principles of electromyography

Muscle contraction is caused by a small current locally within the body. The current itself cannot be measured, the potential difference however between two points does give an indication of local neuromuscular activity. EMG is the technique with which multiple sources can be measured in reference to a stable reference point.

2.4.1 Source of bio-electricity

The source of measurable current within the body lies within the cell surface membrane. The transport of Na^+, K^+, Cl^- and Ca^{2+} ions through ion specific channels changes the charge of the cell. In rest the potential difference between the in- and outside of the cell is about 70 mV, in which the cell is negatively charged on the inside and positively charged on the outside. This value is dependent upon the ion concentrations on the in- and outside of the cell. At this resting moment the cell is polarised. Cells in the heart have the tendency to spontaneously depolarise, during which the potential flips, causing the inside

of the cell to be positively charged and the outside negative. Afterwards the cells rapidly return to their original state, known as repolarisation. Other cells, like muscle cells, may also de- and repolarise, but they do so only when neighbouring cells depolarise. Depolarising neighbour cells cause the local potential difference over the cell surface membrane to decrease. Only when the local potential difference reaches the so called critical value, the cell will depolarise. This process in neural cells contributes to information transport within the body via so called action potentials. Depolarisation in muscle cells primarily focuses on regulation of the Ca^{2+} concentration within the muscle cell, causing the muscle to contract and relax (Figure 8) [29, 83].

The electric activity of a single cell is incredibly small and in order to detect voltage

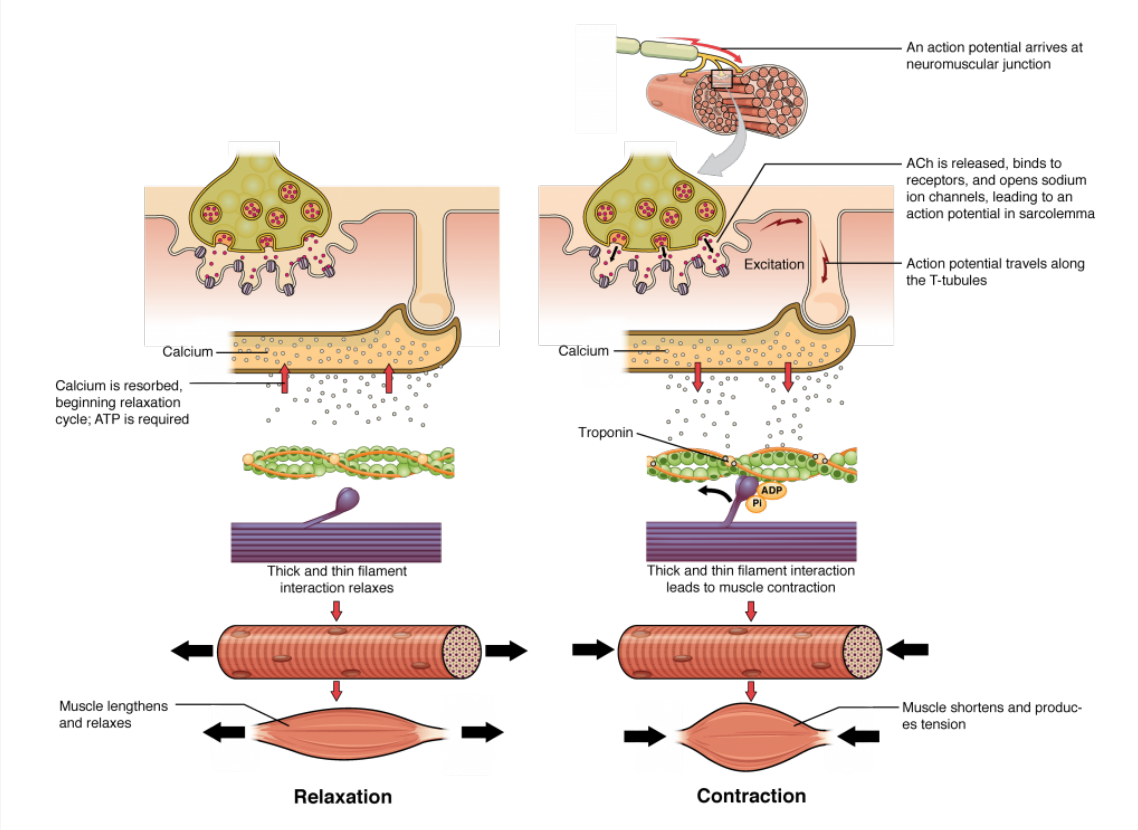

Figure 8: *The arrival of an action potential at the muscle fiber causes acetylcholine release at the neuromuscular junction. The opening of Na^+ channels causes an action potential within the fiber, in turn causing Ca^{2+} to release. Ca^{2+} binds to troponin, causing muscle contraction. Afterwards, ATP binds to the active Ca^{2+} channels on the cells, causing Ca^{2+} to actively be resorbed and the muscle fibers to relax.*

away from the source the potential gradients of each contributor from source to detector are added together. This is related to the linearity of the conductive medium, together describing the superposition principle. The superposition principle states that the net response to a signal produced by multiple sources is equal to the sum of each individual source (equations 15,16).

$$F(x+y) = F(x) + F(y) \tag{15}$$

$$yF(x) = F(xy) \tag{16}$$

In reality the measured signals from the body are the sum of many cells contributing to that signal, and the signal measured from a muscle is the sum of each individual contributing fibre.

2.4.2 Potential differences

Sources of bio-electricity are not measurable on their own, but their effects are. Instead potentials, more specifically potential differences are measured. The electric potential is the amount of work required per unit of charge to move a charge from point A to point B [83].

2.4.3 Electromyography

Surface EMG is the method used to non-invasively measure potential differences of muscles in the body compared to a ground electrode [84]. The ground is placed at an inert location, not contributing to the measured muscle contraction being investigated, in case of respiratory measurements the sternum is chosen [25–27, 85]. Electrodes are placed on the skin, used to measure the underlying potential differences. The obtained signal provides a representation of the motor unit action potentials [86, 87]. In order to display a representation of the average electrical activity produced by the muscle fibers the root-mean-square (RMS, equation 17) is calculated [83, 86].

$$RMS(f) = \sqrt{\overline{f^2(t)}} \tag{17}$$

An increase in RMS has two possible explanations, either more muscle fibers are recruited into contraction, or more effort is delivered by the same muscle fibers [86].

2.5 Summary

In the context of this study we induce the asthmatic reaction, in which we cause the airways to narrow by means of an exercise challenge test. The narrowing of the airways causes a vast increase in airway resistance (equation 12), limiting the inspiratory and expiratory flow of air (equation 11). Air traps within the lungs, and while enhancing the diffusion

capacity of the lung (equation 2), the exchange of gasses is limited and the flow will eventually diminish in response to the change in partial pressures of O_2 and CO_2 (equation 1). The body responds by increase heart- and breathing rates, increase breathing muscle work intensity and by recruiting the accessory breathing muscles to increase their contribution to thorax expansion.

The increased muscle activity contributes to a larger amount of generated electrical energy, increasing the potential difference measurable using EMG (equation 15). Making an increase in EMG activity a potential indicator for an increased work of breathing as seen in asthmatic children.

3 Methods

This study was submitted to the Medical Ethics Committee Twente as AACE (Assessment of Asthma in Children using Electromyography in a standard exercise challenge test), and was approved 06-03-2018 with trial number K18-12.

3.1 Population

3.1.1 Power calculation

The sample size for this study was calculated based upon Maarsingh's study [25]. Cohen's d was calculated with the sample size and largest outcome p-value of Maarsingh's study using Wilson's method [88]. Maarsingh's outcome parameters however were different from the parameters used in this study, as he administered histamine until the point of clinical symptoms of dyspnea. The calculated Cohen's d was 1.43. The sample size was then calculated using:

$$n = \frac{(Z_\alpha + Z_\beta)^2 + \sigma^2}{d^2} \tag{18}$$

A type I error of $\alpha = 0.01$ and type II error of $\beta = 0.9$ were chosen, providing a required sample size of n = 34 patients. A population of 50 was chosen for this study to compensate for the alternate measurement protocol and possible dysfunctional breathing patients present in the population.

3.1.2 In- and exclusion

A single center study was performed at the outpatient clinic of the MST hospital in Hengelo. Children referred to the outpatient clinic with signs of dyspnea, regardless of origin, between the ages of six and seventeen were eligible to participate in this study. Children under the age of six were deemed ineligible because it is very difficult to instruct them. Measurements are prone to actifacts and roper measurements according to protocol are necessary to obtain optimal data. A full overview of in- and exclusion criteria is shown in table 1.

Written informed consent was obtained from either parents (patients under the age of twelve), parents and patients (patients between the ages of twelve and sixteen) or patients (patients ages sixteen and over).

3.2 Devices and software

Measurements were performed using the Dipha-16 (DEMCON Macawi Respiratory systems BV, Enschede the Netherlands). A multifunctional head was used, containing eight EMG-leads and a ground lead attached to nine Red Dot Ag/AgCl latex-free electrodes (3M). Data was wirelessly transferred from the Dipha device to a laptop for pre-processing and storage. Measurement software was custom designed in Polybench by the manufacturer

Table 1: *Full overview of inclusion and exclusion criteria*

Inclusion criteria	**Exclusion criteria**
Ages: 6-17	Children and/or parents that do not speak Dutch
Children submitted for an ECT with signs of dyspnea	Children with a pacemaker and/or ICD
	Children born prematurely ($<$ 37 weeks)
	Children with chronic diseases other than asthma
	Children with psychomotor retardation

with consultation of the researchers.

Pre-processing during measurements entailed the detection of QRS complexes in the measured data, deleting them and replacing them with a running average. O'Brien et al. describes this technique as their so called gating technique [24]. The signal is delayed by a variable delay line, while the QRS complex is detected on a second channel. The output of the detection channel is sent to a one-shot or pulse stretcher, creating a standard pulse with the width of the QRS complex. The output of the one-shot controls an electronic switch, gating the delayed signal with a running average with the length of the standard pulse. Afterwards the RMS of the pre-processed data is determined, plotted and stored. An overview of the stages of signal processing is displayed in Figure 9. The heart rate is determined in the same process, each deleted QRS complex is defined as a single heart beat. Important to note is that the P- and T-waves are not detected and/or eliminated using the gating technique, and still contribute to the output signal.

Further data processing was performed in a custom made interface created using Matlab R2018a (Mathworks).

IBM SPSS Statistics 25 was used for statistical analysis.

3.3 Study procedure

Clinical parameters were obtained prior to starting the measurements. The final parameter, the result of the ECT, was obtained after all measurements were completed. An overview of clinical parameters is displayed in table 2.

The study's measurements entail the entire gold standard exercise challenge test as performed at the OCON in Hengelo. EMG leads were applied before the first FOT measurements and are removed after the final spirometry measurement. Leads were placed bilaterally at the diaphragm and second intercostal space mid-clavicular. Patients were instructed to twist their neck both left and right to reveal the sternocleidomastoid mus-

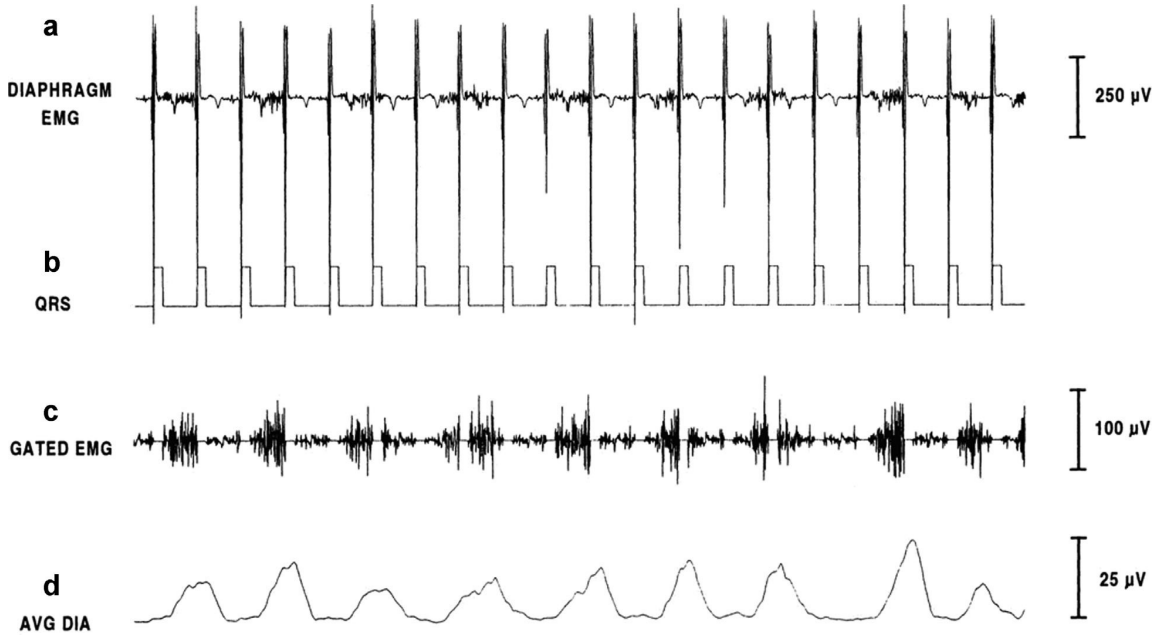

Figure 9: *Overview of the different stages of signal processing using the gating technique. a) The raw measured data, containing clear large QRS complexes. b) Detection of QRS complex as a standard pulse with the width of the QRS complex. c) Gated EMG signal, the QRS complex is replaced with a running average at the length of the QRS complex. d) Averaged EMG signal by computing the RMS of the gated EMG signal, the signal used for analysis. (Adapted from O'Brien et al. [24])*

cle, where the fifth and sixth lead were placed bilaterally. Finally the seventh and eight lead were placed in the neck at the trapezoid muscle, the reference lead was placed on the sternum (Figure 10). The device was worn in a pocket during the measurement period.

3.3.1 Exercise challenge test

All measurements were performed during a scheduled ECT at the outpatient clinic in Hengelo. The ECT was performed conform the standards of the American Thoracic Society [22]. Treadmill slope was set at 10% to account for poor running technique and reduce running speed while maintaining exercise intensity. Children below the age of eight were alternatively challenged using a jumping castle conform the protocol of van Leeuwen [63]. Each ECT took up to one hour to complete. At first the patients' medical history was acquired, focusing primarily on any discomforts regarding breathing abnormalities. Further information acquired includes medication adherence (if applicable), family history of asthma, eczema and/or allergies in the first or second degree. During physical examination

Table 2: *Overview of baseline parameters*

Parameter	**Measurement unit**
Sex	Male/female
Age	Years
Height	cm
Weight	kg
Corticosteroid use	Yes/no
Salbutamol use	Yes/no
Allergies (inhalation)	Yes/no
Forced Expiratory Volume in one second FEV_1	Liters, % of predicted value at each interval
FEV_1 drop	% in reference to own baseline
FEV_1 reversibility	% in reference to own baseline
Diagnosis	Asthma (controlled/uncontrolled), upper airway inflammation, dysfunctional breathing

the physician paid close attention to signs of allergies (Dannie-Morgan lines, Meyers' nasal crease).

Baseline measurements were performed using the Forced Oscillation Technique (FOT) and spirometry. Patients were then equipped with a heart rate monitor (Polar) and taken to the climate controlled room at the outpatient clinic. Patients exercised on a treadmill set at a 10% angle in cold air (10°C) for six minutes with a clip on the nose at a submaximal level (80% of maximal predicted heart rate). These conditions provide the maximal stress for the airways to provoke an asthmatic reaction. Children under the age of eight were not equipped with a heart rate monitor and exercised on the jumping castle for six minutes instead. To ensure an appropriate exercise challenge children were encouraged actively to keep jumping for the full six minutes.

Patients performed spirometry in duplo at one, three and six minutes after exercise. If FEV_1 was still declining after six minutes an additional measurement was performed at nine minutes after exercise. A FOT measurement was performed at five minutes after exercise.

After the final spirometry measurements patients inhaled $200\mu g$ of salbutamol and five minutes thereafter a final FOT and spirometry measurement was performed to evaluate the effect of medication. A full overview of all actions during an ECT is shown in figure 11.

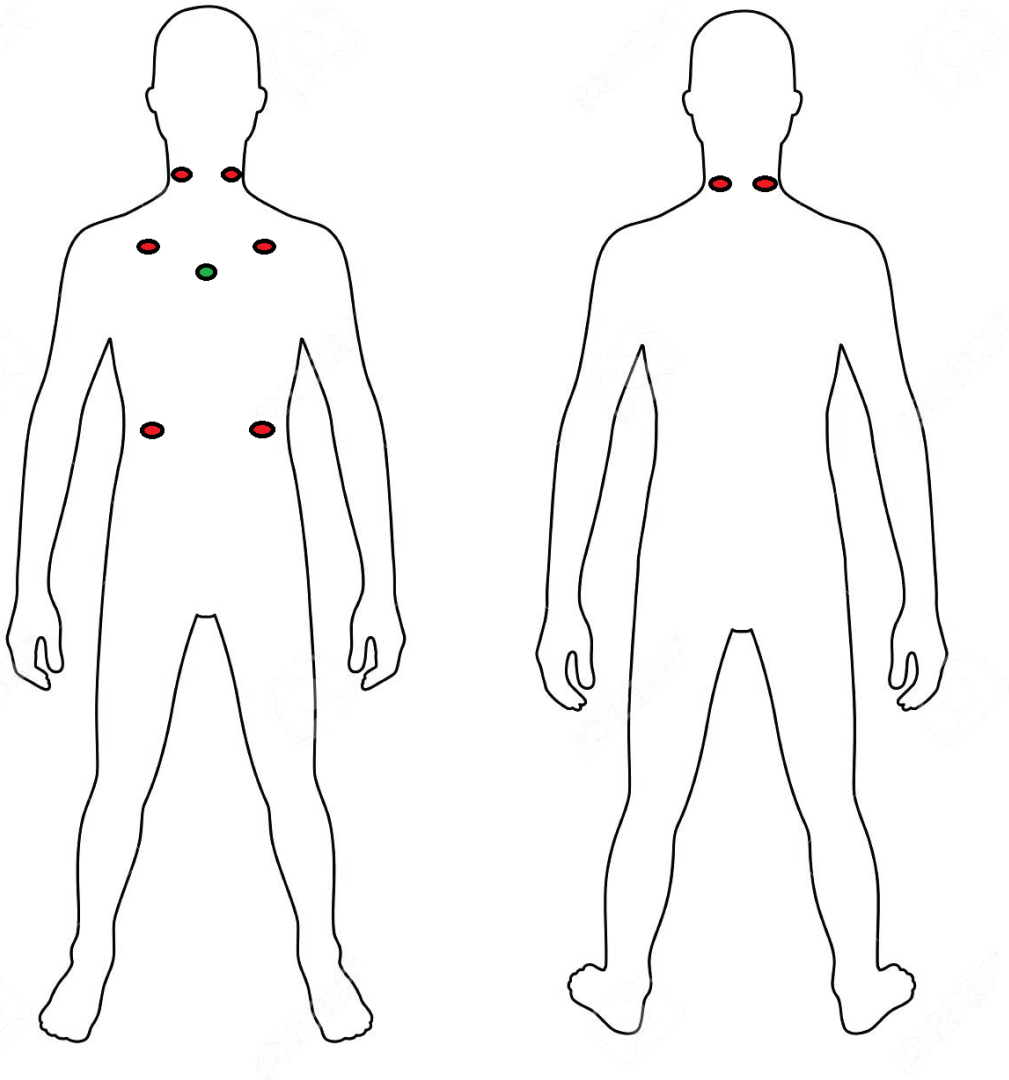

Figure 10: *Overview of placed electrodes on the body. All measurement electrodes are displayed in red, the reference electrode in green. The electrodes were connected to the Dipha device which was carried in a side pocket.*

3.3.2 EMG measurements

Patients performed the ECT according to protocol, with intervals of 30 seconds in between spirometry measurements during which they were asked to sit still and place their hands

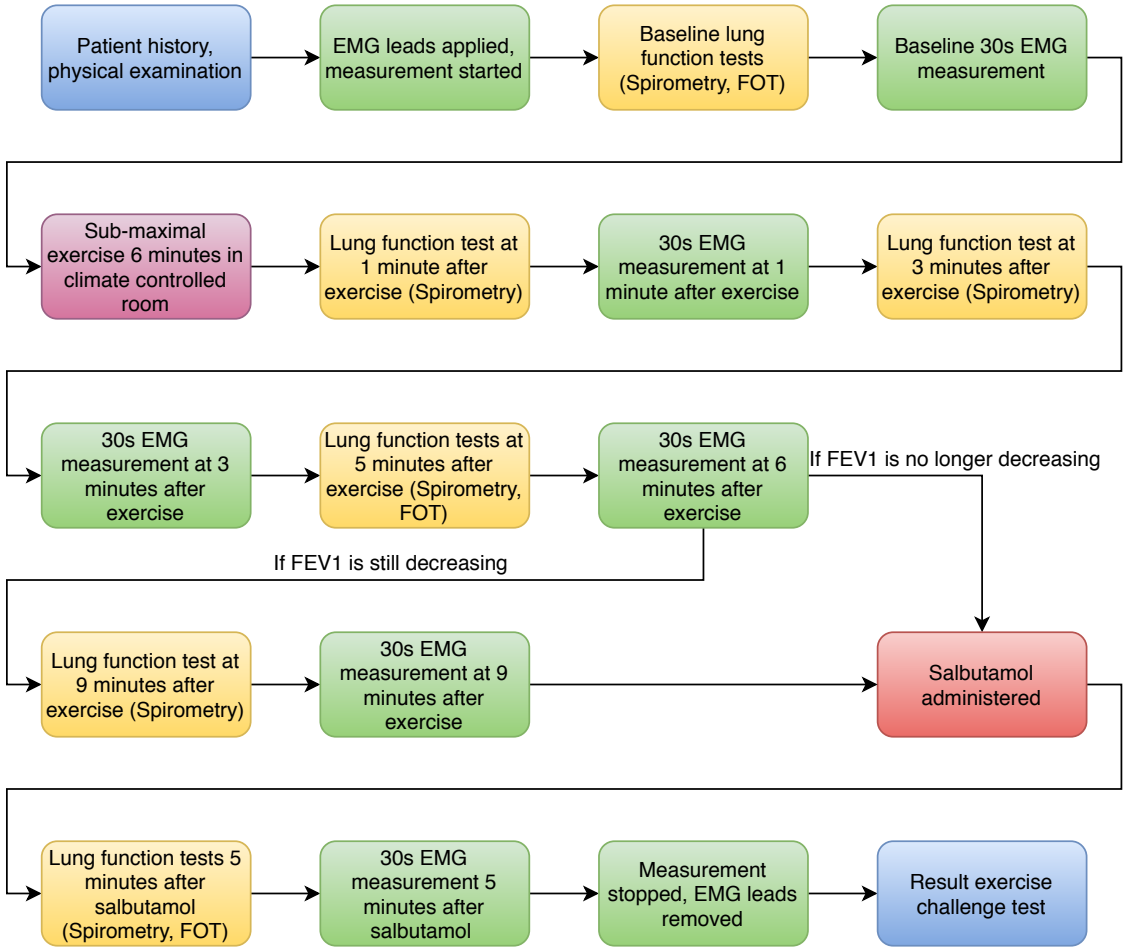

Figure 11: *An overview of all actions during an exercise challenge test. All baseline and outcome actions are displayed in blue, the regular care lung function testing is displayed in yellow, medication usage is displayed in red, exercise is displayed in purple. All additional actions regarding EMG measurements are displayed in green.*

on their legs. Patients were purposely not instructed to normalise their breathing to obtain natural breathing patterns. The 30 second intervals were used for analysis. Patients wore the Dipha during exercise, these periods however were not used for analysis purposes. A full overview of measured parameters is displayed in table 3. The diagnosis is provided by either a pediatrician or sports physician. Controlled asthma is defined as a decrease in FEV_1 of under 13% in patients currently using corticosteroid inhalers. Uncontrolled asthma is defined as a decrease in FEV_1 of over 13% in patients using corticosteroid inhalers, or a decrease of over 20% in FEV_1 in patients not using corticosteroid inhalers.

Patients not using corticosteroid inhalers with a decrease in FEV_1 between 13 and 20% are classified as mild asthma. Furthermore it is possible that a decrease in FEV_1 is associated with an upper airway inflammation, these patients were classified as such by a pediatrician or sports physician. Patients who experienced respiratory symptoms without a decrease in FEV_1 were classified as dysfunctional breathers.

Table 3: *Overview of parameters measured using the Dipha.*

Parameter	**Unit**
RMS of diaphragm activity	μV
RMS of intercostal muscle activity	μV
RMS of sternocleidomastoid muscle activity	μV
RMS of trapezoid muscle activity	μV
Heart rate	Beats per minute

3.4 Data analysis

Data analysis was performed in a custom, self made Matlab interface, designed specifically for the purpose of this study. Pre-processing was performed in four steps, afterwards breath analysis was performed for each section individually and comparisons were drawn.

3.4.1 Pre-processing

First the area of exercise was determined based upon a baseline elevation combined with high amplitude signals in that section. Secondly the areas of interest were identified based upon the area of exercise. The user was prompted with possible areas of interest in various time frames. Each interval used for spirometry measurements was also used as an indicator for EMG measurements. Periods of three minutes around each spirometry measurement were prompted and the user selected the correct 30 second interval to be stored for analysis. Thirdly each segment was submitted for spectral analysis. The user manually reviewed each segment and compared the data to the frequency components of the signal. The QRS complex was removed from the signal using O'Brien's algorithm, however P and T waves remained in the signal and were filtered afterwards. Heart rate filtering was performed using a 4th order butterworth low-pass filter over the average heart frequency in the 30 second interval. Abdominal muscle activity was also filtered using a 4th order butterworth filter, at a manually selected frequency. The butterworth filter output follows from the transfer function:

$$H(s) = \frac{1}{1 + S + S^2 + S^3 + S^4} \tag{19}$$

The paired gain is then given by:

$$G^2(\omega) = |H(i\omega)|^2 = \frac{G_0^2}{1 + (\frac{i\omega}{i\omega_c})^{2n}} \tag{20}$$

In which G_0 is the DC gain, ω is the equal to $2\pi f$, ω_c is the cut-off frequency and the order n = 4. Finally resulting into the frequency response of the filter.

$$G(\omega) = |H(i\omega)| = \frac{G_0}{\sqrt{1 + \frac{i\omega}{i\omega_c}^{2n}}} \tag{21}$$

The cut-off frequency for the heart rate was determined by calculating the average heart rate over the 30 second period, and subtracting 10% of that value to account for possible short-term heart rate variability:

$$f_{HR} = \frac{HR}{60} \tag{22}$$

$$f_{cut} = f_{HR} - (f_{HR} * 0.1) \tag{23}$$

The cut-off frequency and frequency response are then applied in a zero-phase filter to actually remove any frequency above the cut-off frequency without any phase alterations to the signal using the Matlab function filtfilt.

$$h(n) = h(-n), n \in \mathbb{Z} \tag{24}$$

Lastly each segment was assessed for individual breath detection. Local maxima and minima were identified, and a breath was identified when a local maximum was both pre- and succeeded by a local minimum.

3.4.2 Breath analysis

Breath analysis entailed the assessment of individual breaths within each time frame. The height difference between the preceding minimum and maximum were used to determine peak height. The distance between minima was used to identify peak width, and an area under the curve was calculated by trapezoidal integration of the EMG signal between the minima (equation 25). The area under the curve between the line drawn from min_1 and min_2 was subtracted from the initial area under curve to obtain the area enclosed between this line and the EMG signal(equation 26).

$$AUC_{all} = \int_{min_1}^{min_2} f(x)dx \approx \frac{min_2 - min_1}{2n} \sum_{k=1}^{n} f(x_{n+1}) + f(x_n)) \tag{25}$$

$$AUC = AUC_{all} - \int_{min_1}^{min_2} g(x)dx \approx \frac{min_2 - min_1}{2n} \sum_{k=1}^{n} (f(x_{n+1}) - g(x_{n+1}) + f(x_n) - g(x_n)) \tag{26}$$

3.4.3 Stored parameters

The peak height, width and area under the curve were determined for the diaphragm, intercostal, sternocleidomastoid and trapezoid muscles as described in the above section. The breathing rate was determined by counting the amount of local maxima over time in each section. The heart rate was determined by R-peak detection in the manufacturers software and extracted from these measurements. A complete overview of stored parameters is displayed in table 4. After parameters are determined for each measurement period,

Table 4: *Overview of stored parameters. Each parameter is stored for the diaphragm, intercostal-, sternocleidomastoid- and trapezoid muscles respectively. The parameters are stored for each measurement period.*

Parameters	**Unit**
Peak height	$\Delta\mu V$ minimum and maximum
Peak width	Δt minimum 1 and 2
Area under curve	$\int_{min1}^{min2} f(x) - g(x)dx$
Breathing rate	Breaths per minute
Heart rate	Beats per minute
Tonic activity	$\bar{\mu}\bar{V}$ minima

ratios and comparisons are calculated using the stored parameters. The difference in heart and breathing rate, peak height, width, area under curve and tonic activity was calculated for each measurement period with respect to the baseline measurement for each muscle group individually. These parameters are then used to determine the contribution of each muscle group to the total amount of activity for each measurement period respectively, changes were calculated with respect to the baseline measurement.

3.4.4 Secondary outcome parameters

Secondary outcome parameters, the heart- and respiratory rate recovery time were determined using the predetermined heart rate from each section, and the calculated respiratory rate in each segment. The respiratory rate recovery time is defined as the time required to return to the respiratory rate measured at baseline [89].

3.5 Statistics

All data was extracted from the custom Matlab interface into Microsoft Excel. Data was sorted into two groups, one with all measurement data at the point of lowest FEV_1 (current gold standard). The second at point of maximal EMG activity.

3.5.1 Baseline characteristics

All baseline characteristics were tested for normality using the Shapiro-Wilk test. Normally distributed data was tested using an independent samples t-test. Not normally distributed data was tested using the Mann-Whitney-U test.

3.5.2 Measured parameters at baseline

All measured parameters were tested for normality using the Shapiro-Wilk test. An overview of the distributions was created using a Mann-Whitney-U test.

3.5.3 Changes in parameters

The changes in parameters were calculated at both the point of lowest FEV_1 on spirometry and the highest amplitude of the diaphragm. The baseline parameter was subtracted from either timeframe to determine the absolute difference. The relative change was determined by:

$$P_{relative} = ((\frac{P_{Frame}}{P_{Base}}) * 100) - 100 \tag{27}$$

A Mann-Whitney-U test was performed for each individual muscle group to determine statistically significant differences between controlled an uncontrolled asthma patients on both absolute and relative parameters. Muscle groups with low amounts of reliable measurements at baseline were only assessed at the values after exercise.

3.5.4 Regression analysis

Stepwise integration of parameters was performed to determine linear regression models for both timeframes using all statistically significantly changing parameters.

3.5.5 Receiver operator characteristic curves

Receiver operator characteristic (ROC) curves were computed varying the cut-off values of the statistically significantly changing parameters. The ideal cuf-off was determined based upon the calculated sensitivity and specificity. These were used in order to determine the accuracy at which a single changing EMG parameter can detect uncontrolled asthma.

3.5.6 Dysfunctional breathing patients

Dysfunctional breathing patients were compared to both the controlled and uncontrolled asthma groups at multiple points in time using a Mann-Whitney-U test.

3.6 Single patient overview

In the follow section the full data extraction process is displayed for a single patient (Patient 50). Each patient was assessed individually following the same protocol.

3.6.1 Measurement data

Measurement data was obtained from the Dipha device and loaded into a custom Matlab interface (Figure 12). A full overview of the interface functionality is given in Appendix A.

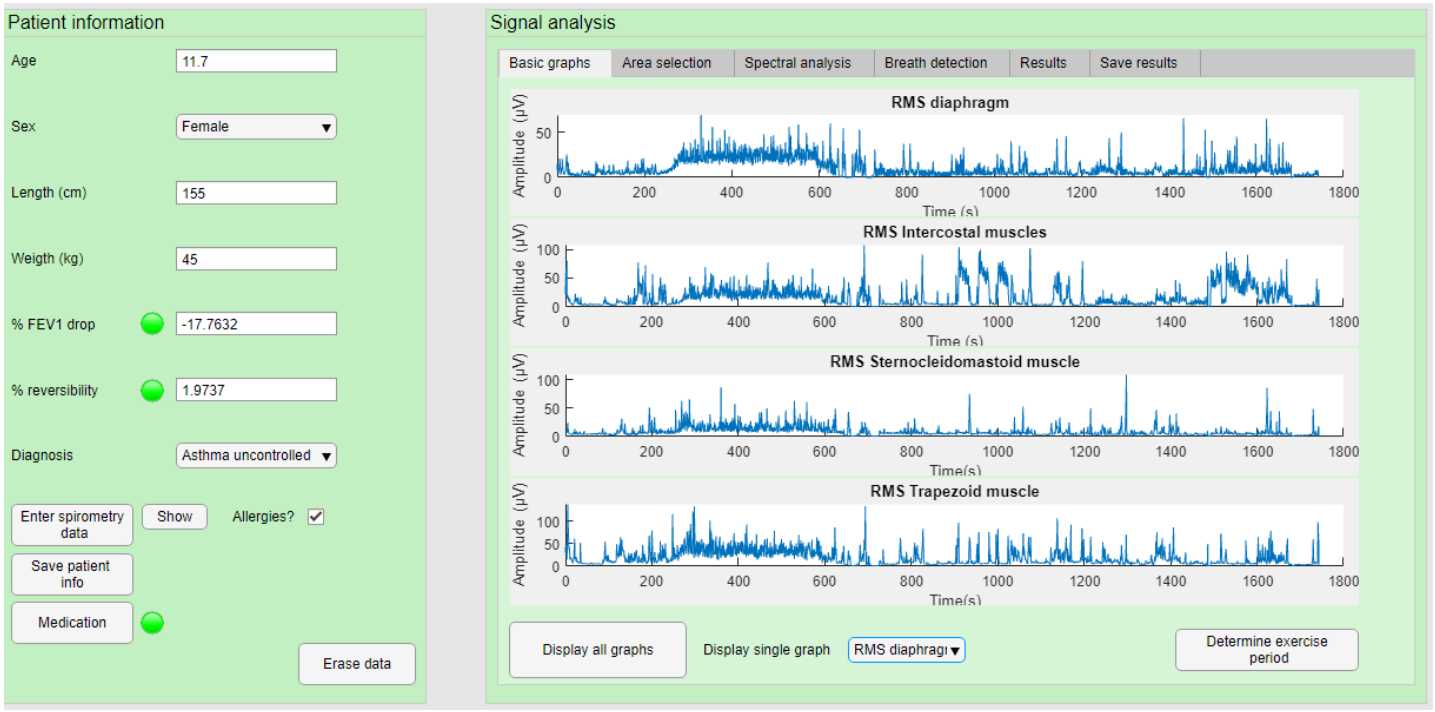

Figure 12: *Overview of the interface used for analysis. All predetermined baseline parameters are found on the left. Measured signals and analysis functions are found on the right.*

3.6.2 Determining areas of interest

Periods of data were selected from the activity found in the RMS of the diaphragm (Figure 13). The first area to be selected was the area of exercise, clearly visible as an area of high amplitude and elevated baseline.

From the determined exercise period the areas of interest before and after exercise were extracted (Figure 14).

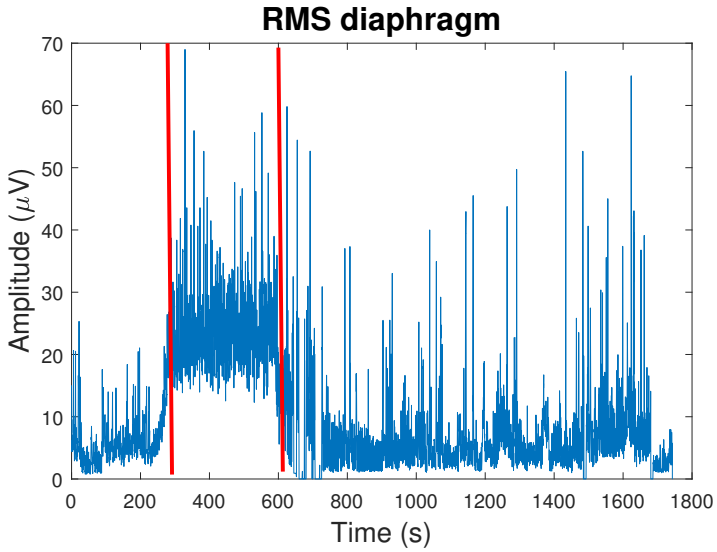

Figure 13: *The full recording of the RMS of the diaphragm for a single patient. The area in between the red lines signifies the area of exercise*

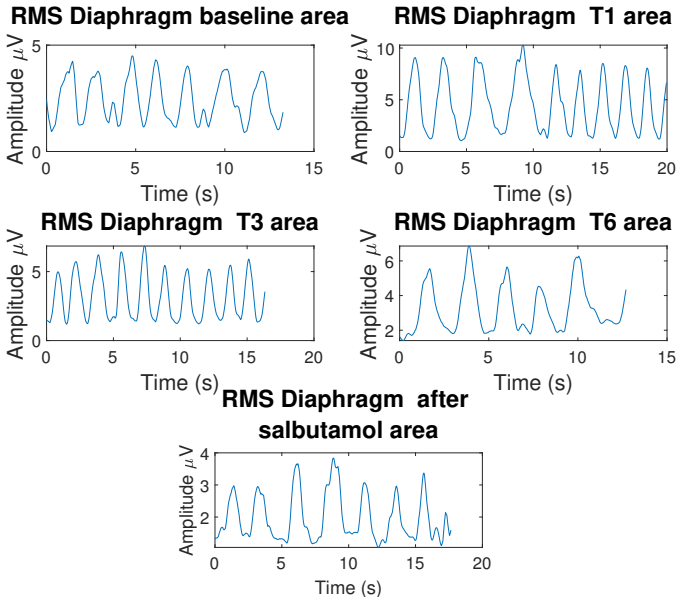

Figure 14: *The areas of interest were selected from time frames based upon the exercise period, corresponding with the times at which spirometry was performed during the standard ECT protocol.*

3.6.3 Determining relevant frequencies

Data was filtered based upon the frequencies present in the signal. O'Brien's algorithm removed QRS complexes from the measured data, the remaining P and T waves were successfully removed from the data using the custom interface (Figure 15). The abdominal muscle activity was subsequently removed upon visual inspection of the frequency spectrum.

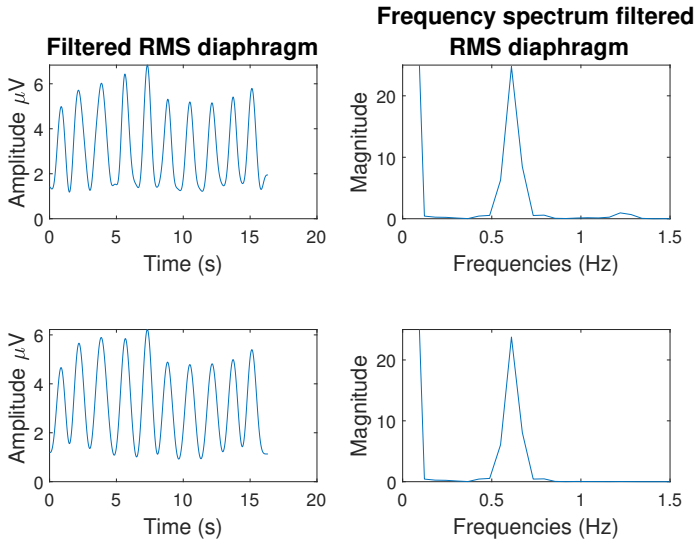

Figure 15: *The filtered RMS signal of the diaphragm at $T = 3$ minutes after exercise. On the top left the heart frequency is removed from the signal, providing a smoother signal. On the top right the frequency spectrum is given of the signal on the top left side. Clearly visible is the dominant breathing frequency of $0.61Hz$ as well as abdominal muscle activity of $1.22Hz$. On the bottom left this frequency is removed using a cut-off frequency of $1Hz$, the bottom right frequency spectrum shows that the peak around $1.22Hz$ has successfully been removed. The remaining low frequent peak $< 0.01Hz$ contains the offset data.*

3.6.4 Detecting individual breaths

All filtered graphs were successfully loaded into the breath detection algorithm in which they were inspected. The diaphragm was used to determine the breathing pattern, with which the accessory breathing muscles were compared. Mean peak height, peak width, area under curve and tonic activity were calculated automatically (Figure 16).

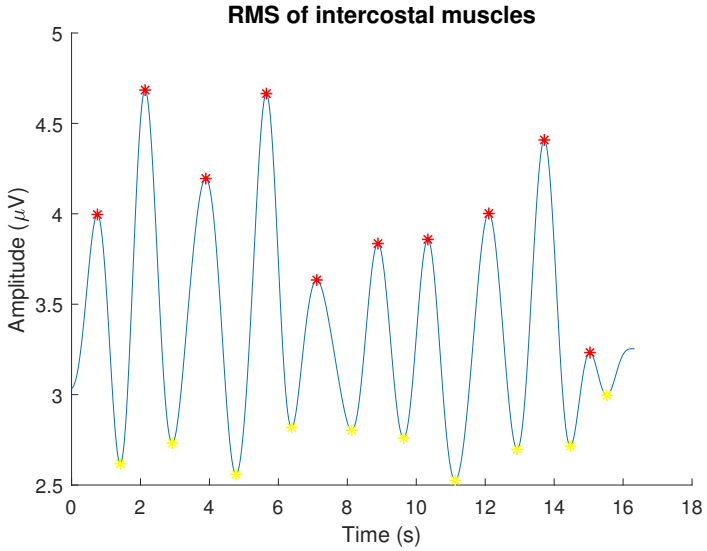

Figure 16: *RMS data of the intercostal muscles at T=3 minutes after exercise. Breaths were detected and are labeled with a red asterisk. The yellow asterisks signify the beginning and end of a breath and are also used to determine the tonic activity.*

3.6.5 Overview of results

After inspection of all segments for each muscle group an overview over time of all calculated parameters was presented (Example in table 5). These parameters were stored in Excel for further sorting and processing. A quick glance at figure 17 provides insight into the intensity of the use of the (accessory) breathing muscles in response to exercise and to the use of a bronchodilator.

Table 5: *Overview of peak heights (In μV) for all intervals. Empty cells indicate peaks were not present and/or reliably measurable for a certain muscle group at that particular interval.*

Muscle group	**Baseline**	**T1**	**T3**	**T6**	**T8**	**Salbutamol**
Diaphragm	2.63	7.06	4.13	3.76		1.80
Intercostal	0.68	1.65	1.47	1.45		0.55
Sternocleido-mastoid		1.40	1.39	2.31		0.30
Trapezoid						

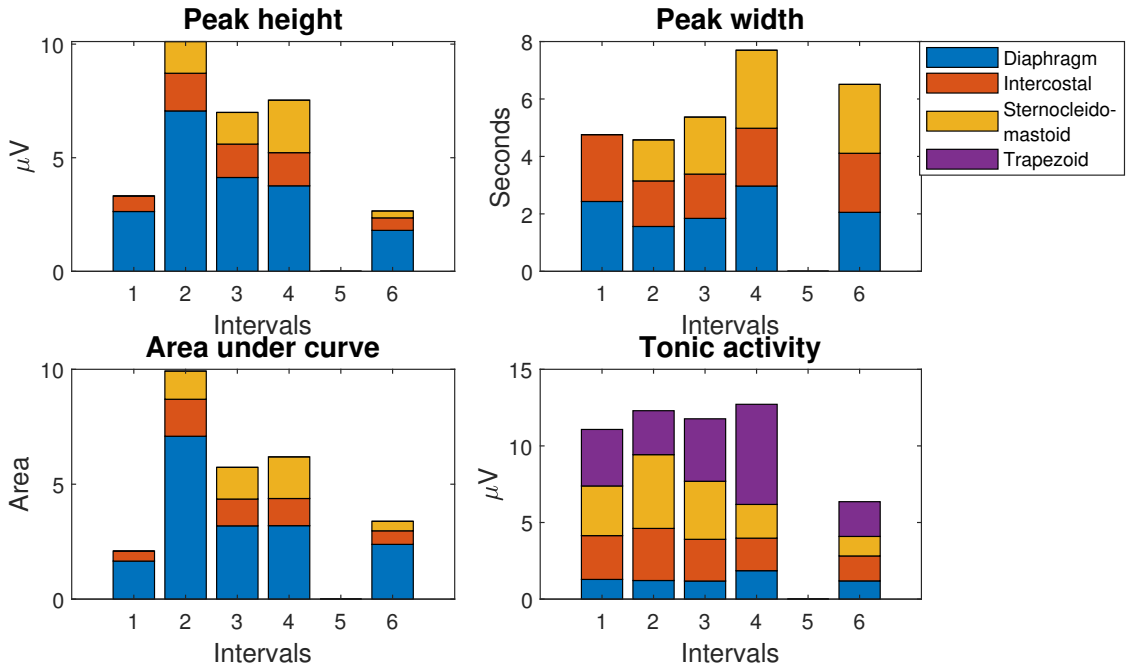

Figure 17: *Overview of all measured parameters for each muscle group. The baseline measurement is visible at interval 1, T=1 minute after exercise at 2, T=3 minutes after exercise at 3, T=6 minutes after exercise at 4, T=8 minutes after exercise at 5 and post SABA at 6. This patient was in natural recovery based upon spirometry at T=6 and therefore did not perform spirometry at T=8. An increase in peak height at the diaphragm and intercostal muscles after exercise is visible, after exercise the sternocleidomastoid muscles were also recruited into breathing. Post-SABA diaphragm and intercostal muscles returned to below baseline levels.*

4 Results

4.1 Population

Informed consent was obtained successfully from 50 patients and/or parents. An overview of baseline characteristics is displayed in appendix C. All baseline characteristics were tested for normality and were found to be normally distributed. One patient was excluded from the uncontrolled asthma group due to an acute asthma exacerbation. An overview of population characteristics is displayed in table 6.

Table 6: *Overview of patient characteristics per diagnosis. Age, length and weight are shows as a mean (sd). Sex, inhalation allergies, ICs and SABA usage as percentages. One patient was excluded due to an acute asthma exacerbation, leaving a total of 49 patients.*

Parameters	**Controlled**	**Uncontrolled**	**Upper airway inflammation**	**Dysfunctional breathing**
Amount	13	20	10	6
Age (years)	12.5 (3.0)	13.3 (3.4)	12.0 (3.0)	12.3 (3.30)
Length (cm)	153.0 (20.3)	153.9 (19.3)	155.3 (19.3)	162.0 (13.2)
Weight (kg)	47.5 (19.8)	47.0 (16.2)	51.1 (24.9)	49.3 (14.9)
Sex (% Male)	92	80	80	17
Allergies (%)	69	70	100	0
ICs usage (%)	84	75	10	33
SABA usage (%)	69	65	60	50

Table 7 displays the characteristics of the baseline parameters for the controlled group versus the non-controlled group. Patients without EIB are sorted into the controlled group (controlled asthma and upper airway inflammation), whereas the patients diagnosed with a dysfunctional breathing pattern will be analysed separately Patients diagnosed with EIB were sorted into the uncontrolled group (Baseline characteristics in table 8). The groups are found to not be statistically significantly different from one another on all baseline parameters. The groups are found to be statistically significantly different on two parameters, there were no patients suffering from allergies in the group of dysfunctional breathers. Furthermore the majority of dysfunctional breathers were girls.

4.2 Group comparison

Data was successfully obtained from 49 patients and was assessed at the timeframe of lowest FEV_1 spirometry measurement, as well as at the timeframe of maximal activity of the diaphragm.

Table 7: *Overview of baseline parameters for the controlled and uncontrolled asthma groups. Sex (1 for male, 0 for female), allergies, use of ICs and use of SABA were tested binary.*

Parameters	**Controlled (n=23)**		**Uncontrolled (n=20)**		**Sign.**
	Mean	**SD**	**Mean**	**SD**	**P-value**
Age (years)	12.3	3.0	12.3	3.4	0.96
Length (cm)	153.2	19.38	153.9	19.3	0.91
Weight (kg)	48.8	21.65	47.0	16.2	0.77
Sex (% Male)	87		80		0.55
Allergies (%)	83		70		0.34
ICs usage (%)	52		75		0.13
SABA usage (%)	65		65		0.99

Table 8: *Overview of baseline parameters for the controlled and dysfunctional breathing groups. Sex (1 for male, 0 for female), allergies, use of ICs and use of SABA were tested binary.*

Parameters	**Controlled (n=23)**		**Dysfunctional (n=6)**		**Sign.**
	Mean	**SD**	**Mean**	**SD**	**P-value**
Age (years)	12.3	3.0	12.3	3.3	0.98
Length (cm)	153.2	19.4	162.0	13.2	0.40
Weight (kg)	48.7	21.7	49.3	14.9	0.97
Sex (% Male)	87		17		< 0.001
Allergies (%)	83		0		< 0.001
ICs usage (%)	52		33		0.43
SABA usage (%)	65		50		0.67

4.2.1 Distribution at baseline

The distribution of measured parameters at baseline were assessed for normality, an overview is presented in appendix C. As not all data was found to be normally distributed, the choice was made to test all data non-parametrically.

The diaphragm provides data for all patients, and all but the area under the curve for controlled asthma patients data was found to not be normally distributed. By means of uniformity all data within groups was tested non-parametrically using the Mann-Whitney-U test. The results of the Mann-Whitney test are displayed in figure 18, specific values are shown in Appendix C. None of the measured baseline parameters display any statistical significant differences, therefore all measurements at baseline are considered equal among the controlled and uncontrolled asthma patients.

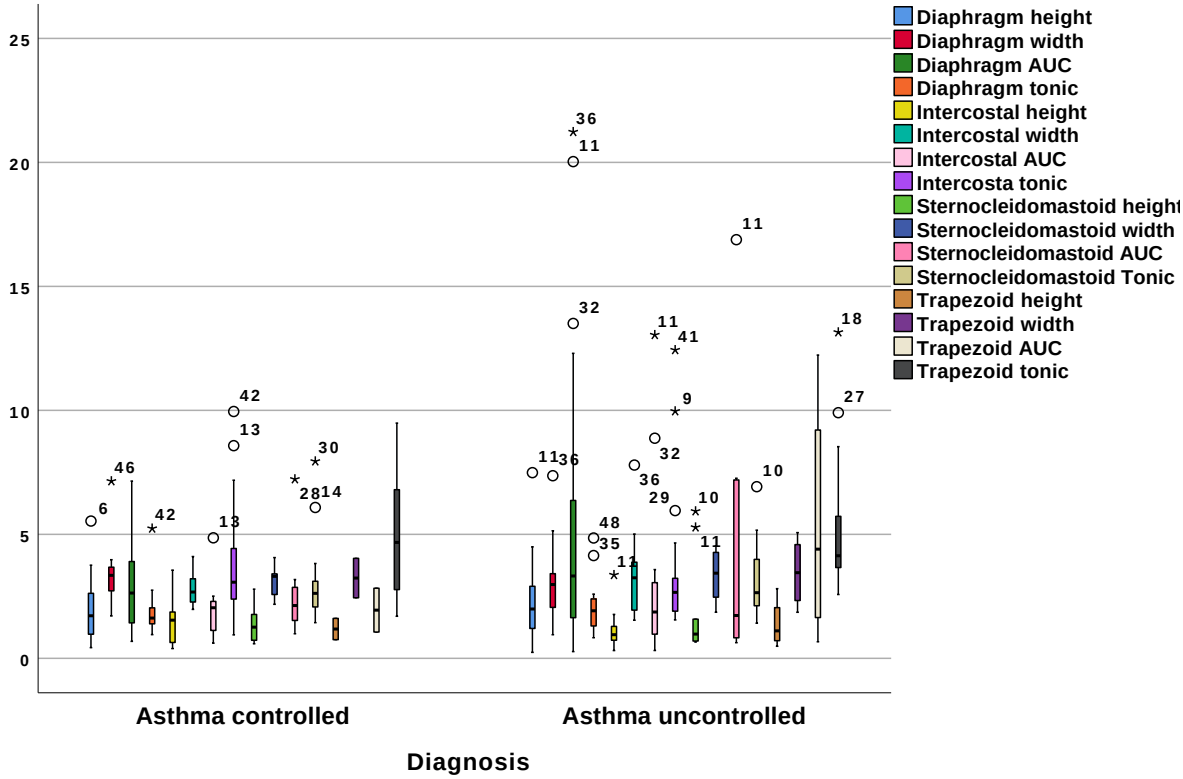

Figure 18: *Overview of distributions for controlled and uncontrolled asthma patients. Outliers are displayed as circles, extreme values (Defined as outside 1.5 times the interquartile range) are displayed as asterisks. Peak height and tonic activity are in μV, width in seconds and the AUC is the area enclosed between the baseline of the peaks and the peak curve.*

4.2.2 Data comparison at minimal pulmonary function

Diaphragm To assess the difference in parameters of the diaphragm at the timeframe of lowest FEV_1 a Mann-Whitney-U test was performed. An overview of distributions is displayed in figure 19, an overview of all numbers can be found in Appendix D. There are statistically significant increases in peak heights for uncontrolled asthma patients both absolute($0.20\mu V\,(-0.10-0.54)$ and $4.85\mu V\,(1.82-7.84)$, $P<0.001$) and relative ($12\%\,(-6-57)$ and $204\%\,(111-533)$, $P<0.001$). A statistically significant decrease in relative peak width was found with a slightly smaller decrease in width in the uncontrolled asthma patients($-21\%\,(-29-(-1))$, $P=0.02$). The area under curve was found to increase significantly in uncontrolled asthma patients both absolute ($-0.25\,(-0.87-0.47)$ and $4.53\,(1.98-13.46)$, $(P<0.001)$) and relative ($-12\%\,(-25-34)$ and $138\%\,(25-577)$, $P<0.001$). There were no statistically significant changes in tonic activity of the diaphragm.

Intercostal muscles The data of the intercostal muscles provides data for 7 out of 23 controlled and 9 out of 20 uncontrolled patients. The difference in parameters of the intercostal muscles at the timeframe of lowest FEV_1 was assessed using a Mann-Whitney-U test. The peak height is found to statistically significantly increase both absolute and relative ($0.12\mu V\,(-0.39-1.04)$ and $2.44\mu V\,(1.73-4.55)$, $P=0.02$ and $21\%\,(-28-19$ and $217\%\,(152-433)$, $P=0.03$ respectively). The area under the curve is found to be statistically significantly increased as well ($0.32\,(-0.26-0.63)$ and $4.03\,(2.25-13.35)$, $P=0.02$ and $44\%\,(-18-54)$and $213\%\,(79-1192)$, $P=0.02$ respectively). An overview of distributions and all calculated parameters is displayed in appendix D.

Sternocleidomastoid muscles The data derived from the sternocleidomastoid muscles provides too little data at baseline to make a significant comparison of the differences before and after exercise between parameters (4 out of 23 and 9 out of 20 respectively). 15 out of 23 patients in the controlled asthma population and 15 out of 20 in the uncontrolled population however displayed peaks at the point of minimal pulmonary function, allowing a comparison of parameters at that point. The peak height was found to be statistically significantly higher in uncontrolled asthma patients ($0.95\mu V\,(0.69-1.22)$ and $4.90\mu V\,(3.08-7.08)$, $P<0.001$). The area under the curve was also found to be statistically significantly higher in uncontrolled asthma patients ($1.40\,(0.96-1.59)$and $7.10\,(4.25-17.10)$, $P<0.001$). Furthermore tonic activity was significantly larger in uncontrolled asthma patients ($2.24\mu V\,(1.70-3.03)$ and $3.35\mu V\,(2.63-4.89)$, $P=0.02$). An overview of distributions and all calculated parameters are found in appendix D.

Trapezoid muscles The data derived from the trapezoid muscles provides too little data at baseline to make a significant comparison of the differences before and after exercise between parameters (0 out of 23 and 3 out of 23 respectively). 5 out of 23 patients in the controlled asthma population and 9 out of 20 in the uncontrolled population however

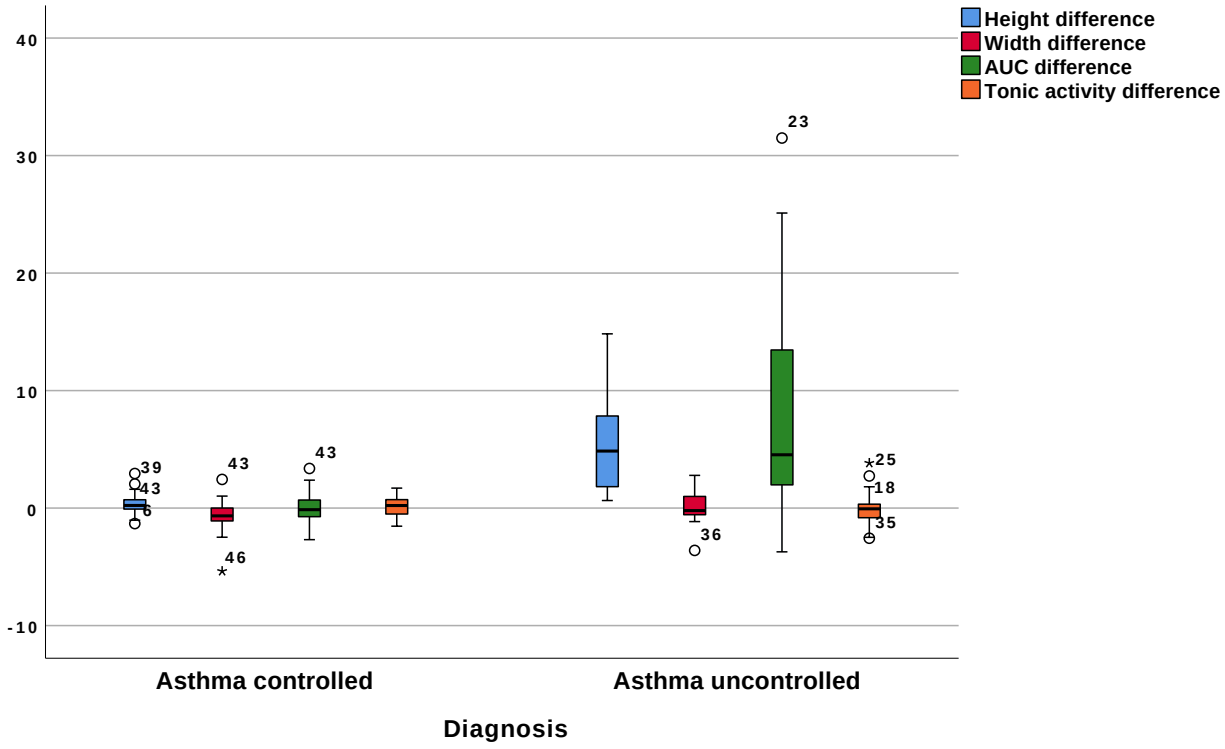

Figure 19: *Overview of changes in parameters of the diaphragm activity at timeframe of lowest FEV_1 on spirometry when compared to baseline measurements. Outliers are displayed as circles, extreme values (Defined as outside 1.5 times the interquartile range) are displayed as asterisks.*

displayed peaks at the point of lowest FEV_1, allowing a comparison of parameters at that point. Peak height ($0.56\mu V\,(0.38-0.86)$and $1.89\mu V\,(1.26-4.28)$, $P<0.01$), area under curve($0.68\,(0.39-1.03)$and $3.40\,(3.11-7.58)$, $P<0.01$) and tonic activity ($2.80\mu V\,(1.88-3.12)$and $4.21\mu V\,(3.12-6.00)$, $P=0.03$) were found to be statistically significantly higher in uncontrolled asthma patients. An overview of distributions and calculated parameters

is displayed in appendix D.

Predictive value Linear regression was performed for the changes diaphragm and intercostal muscle parameters found to be statistically significant in the above paragraphs. Scatter plots of the data are displayed in figures 20 and 21. An overview of coefficients is displayed in tables 9 and 10. The difference in peak height of the diaphragm explains 57.9% of the variance of the drop in FEV_1 ($R^2 = 0.579$, $F(1, 42) = 58.579$, $P < 0.001$). The difference in area under curve of the intercostal muscles explains 20.0% of the variance of the drop in FEV_1 ($R^2 = 0.200$,$F(1, 15) = 4.747$, $P = 0.047$).

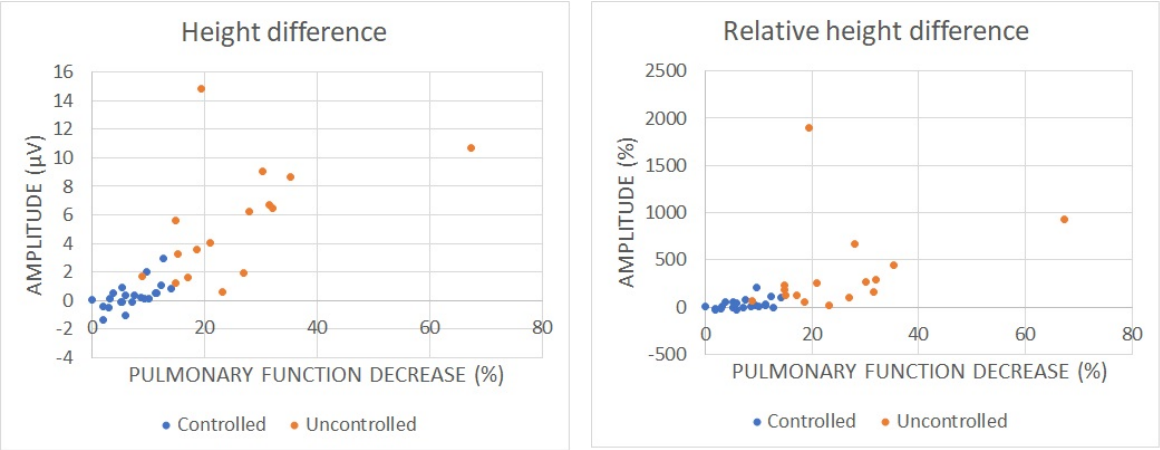

Figure 20: *Scatter plots of the absolute and relative increase in peak height of the diaphragm in comparison to the drop in FEV_1. Patients in the control group are labeled blue, uncontrolled patients are labeled orange.*

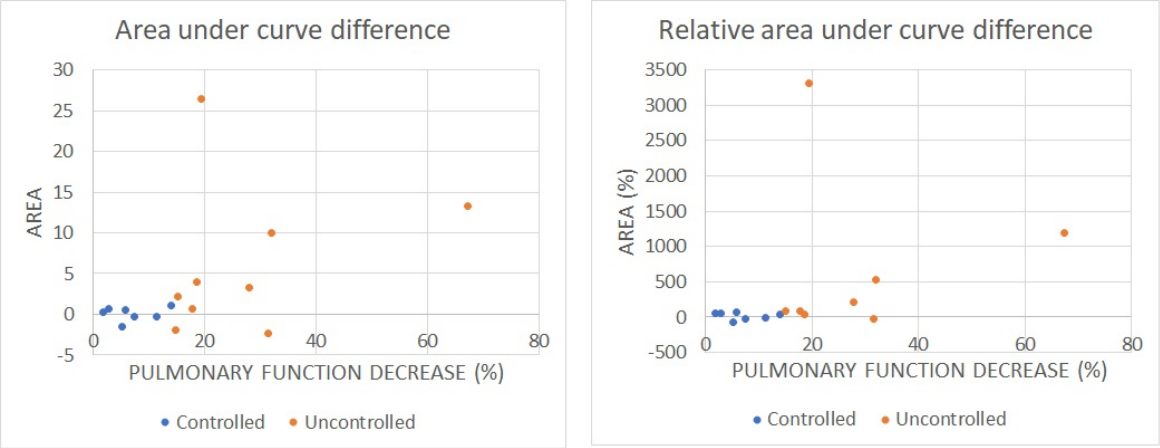

Figure 21: *Scatter plots of the absolute and relative increase in area under curve of the intercostal muscles in comparison to the drop in FEV_1. Patients in the control group are labeled blue, uncontrolled patients are labeled orange.*

Table 9: *Linear regression results of the statistically significant parameters of the diaphragm using stepwise linear regression. The most accurate model was found by only integrating the peak height difference into the model.*

Parameter	**Pearson's R**	**Significance**
Peak height difference	0.77	< 0.001
Area under curve difference	0.62	0.76
Relative peak height difference	0.51	0.92
Relative area under curve difference	0.32	0.38

The peak height difference and area under curve difference of the diaphragm and intercostal muscles were used to compute receiver operator curves (Figure 22). An overview of the results is displayed in table 24. The largest area under curve of the ROC was found for the peak height difference of the diaphragm (AUC = 0.97), providing an excellent separator for finding patients diagnosed with uncontrolled asthma. Using a cut-off peak height difference of $1.15\mu V$ a sensitivity of 95.0% is found with a specificity of 90.9%. The highest area under curve of the ROC of the intercostal muscles was found for the area under curve

Table 10: *Linear regression results of the statistically significant parameters of the intercostal muscles using stepwise linear regression. The most accurate model was found by only integrating the area under curve difference into the model.*

Parameter	**Pearson's R**	**Significance**
Peak height difference	0.30	0.80
Area under curve difference	0.43	0.05
Relative peak height difference	0.50	0.66
Relative area under curve difference	0.37	0.66

difference (AUC = 0.86), providing a good separator for finding patients diagnosed with uncontrolled asthma. Using a cut-off peak height difference of 0.67 a sensitivity of 88.9% and a specificity of 77.4% (Curves and table displayed in Appendix D).

Table 11: *Overview of the ideal cut-off values of the ROC curves of the changes in significant diaphragm parameters.*

Parameter	**Cut-off**	**Sens/spec**	**AUC**
Height	$1.15\mu V$	95.0%/90.9%	0.973
Relative height	67.29%	90.0%/78.3%	0.909
AUC	1.47	85%/90.9%	0.873
Relative AUC	60.55%	70%/86.4%	0.820

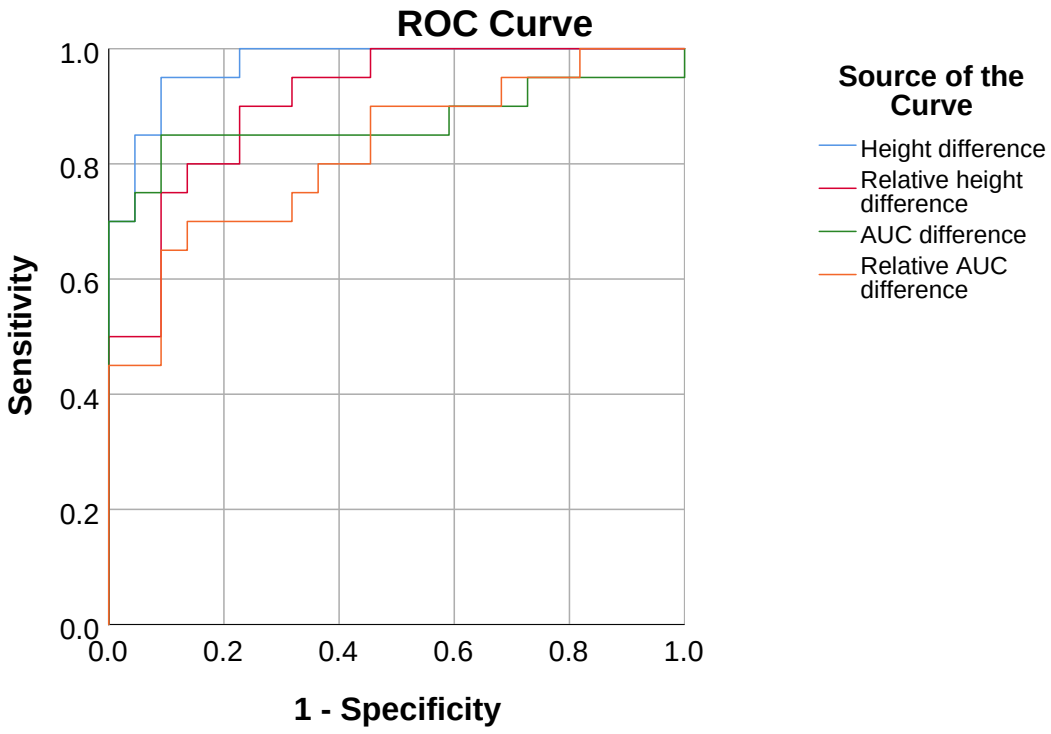

Figure 22: *Receiver operator characteristic curves of the statistically significant parameters found in the diaphragm measurements. The largest area under curve was found for the peak height difference at 0.973.*

4.2.3 Comparison of data at maximal EMG activity

Diaphragm To assess the difference in parameters of the diaphragm at the timeframe of maximal amplitude at the diaphragm a Mann-Whitney-U test was performed. An overview of distributions of both the timeframe of maximal EMG activity and the timeframe of minimal pulmonary function is displayed in figure 23. All results are displayed in appendix D. There are statistically significant increases in peak heights for uncontrolled asthma

patients both absolute ($1.20\mu V\,(0.86-2.33)$ and $8.29\,uV\,(3.96-10.60)$, $P<0.001$) and relative ($63\%\,(-54-200)$ and $371\%\,(177-556)$, ($P<0.001$)). The area under curve was found to increase significantly in uncontrolled asthma patients both absolute ($1.03\,(0.20-3.23)$ and $8.06\,(2.34-16.23)$, $P<0.001$) and relative as well ($32\%\,(18-150)$ and $151\%\,(37-681)$, $P=0.01$). The distribution of the relative changes and the full table of calculated parameters can be found in appendix D. The peak heights and area's under the curve are found to be larger at maximal EMG activity in both the controlled and uncontrolled group. There were no statistically significant changes in peak width and tonic activity of the diaphragm in these timeframes.

Intercostal muscles The data of the intercostal muscles provides data for 9 out of 23 controlled asthma patients and for 10 out of 20 uncontrolled patients. The difference in parameters of the intercostal muscles at the timeframe of maximal diaphragm amplitude was assessed using a Mann-Whitney-U test. An overview of distributions and calculated parameters is found in appendix D. Statistically significant increases in peak height was found both absolute ($-0.06\mu V\,(-0.31-0.15)$ and $3.25\mu V\,(1.08-4.55)$, $P<0.01$) and relative ($P<0.01$). The area under curve was found to be significantly increased in the intercostal muscles as well, both absolute and relative ($P=0.02$).

Sternocleidomastoid muscles The data derived from the sternocleidomastoid muscles provides too little data at baseline to make a significant comparison of the differences before and after exercise between parameters. 14 out of 23 controlled and 18 out of 20 uncontrolled asthma patients however displayed peaks at the point of maximal diaphragm amplitude, allowing a comparison of parameters at that point. Peak height, width and area under curve were found to be statistically significantly higher in uncontrolled asthma patients (Height $1.90\mu V\,(0.74-2.08)$ and $4.70\mu V\,(3.36-8.40)$, $P<0.001$). An overview of distributions is displayed and all calculated differences are found in appendix D.

Trapezoid muscles The data derived from the trapezoid muscles provides too little data at baseline to make a significant comparison of the differences before and after exercise between parameters. 8 out of 23 controlled and 15 out of 20 uncontrolled asthma patients however displayed peaks at the point of maximal diaphragm amplitude, allowing a comparison of parameters at that point. No statistically significant differences were found for the trapezoid muscles. An overview of distributions is and calculated parameters is found in appendix D.

Predictive value Linear regression was performed for the changes of the diaphragm and intercostal muscle parameters found to be statistically significant in the above paragraphs. Scatter plots of the data are displayed in figures 24 and 25. An overview of coefficients is displayed in table 12. The difference in peak height of the diaphragm explains 51.6%

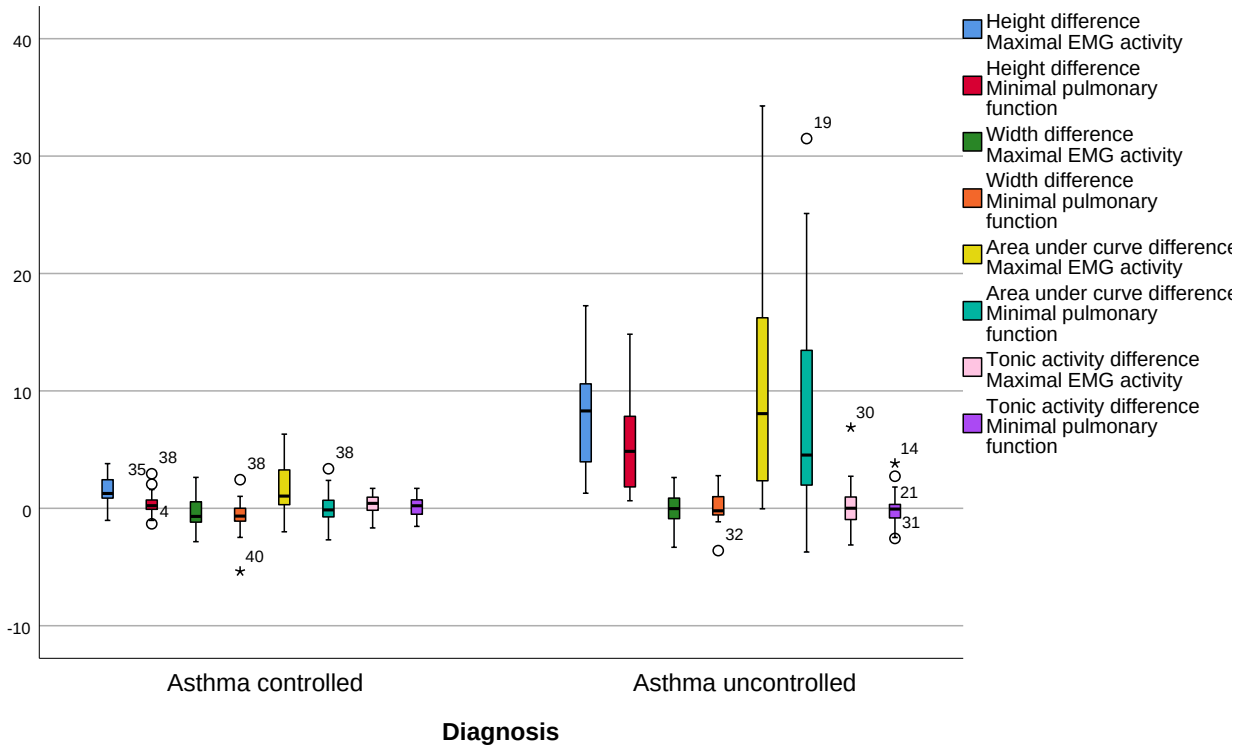

Figure 23: *Overview of changes in parameters of the diaphragm activity at both the timeframe of maximal amplitude of the diaphragm on EMG and the timeframe of minimal pulmonary function when compared to baseline measurements. Outliers are displayed as circles, extreme values (Defined as outside 1.5 times the interquartile range) are displayed as asterisks.*

of the variance of the drop in FEV_1 ($R^2 = 0.516$, $F(1, 40) = 44.761$, $P < 0.001$). The relative difference in peak height of the intercostal muscles explains 27.7% of the variance of the drop in FEV_1, but does not provide a statistically significant model ($R^2 = 0.277$, $F(1, 17) = 7.900$, $P = 0.12$). The table for the calculated parameters of the intercostal

muscles is found in appendix D.

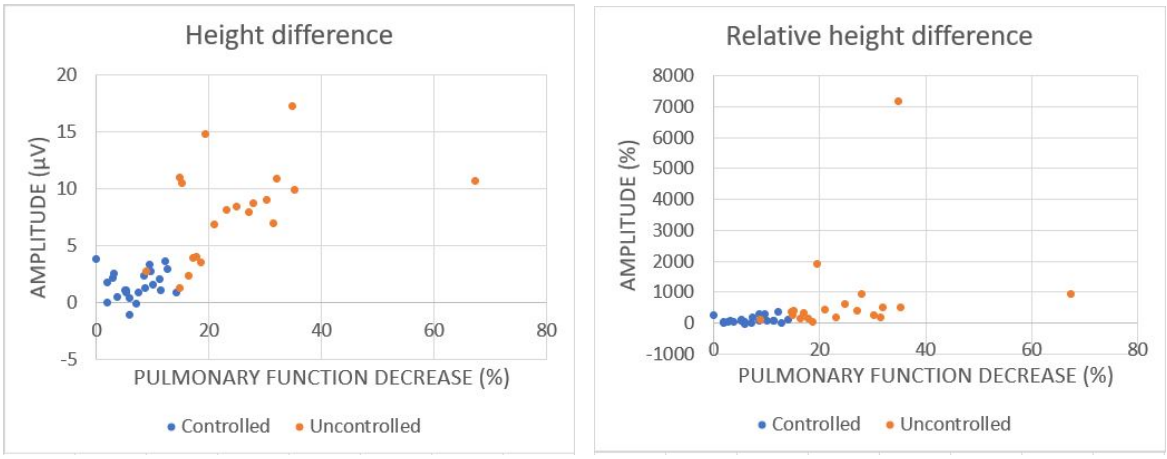

Figure 24: *Scatter plots of the absolute and relative increase in peak height of the diaphragm in comparison to the drop in FEV_1 at the timeframe of maximal diaphragm amplitude. Patients in the control group are labeled blue, uncontrolled patients are labeled orange.*

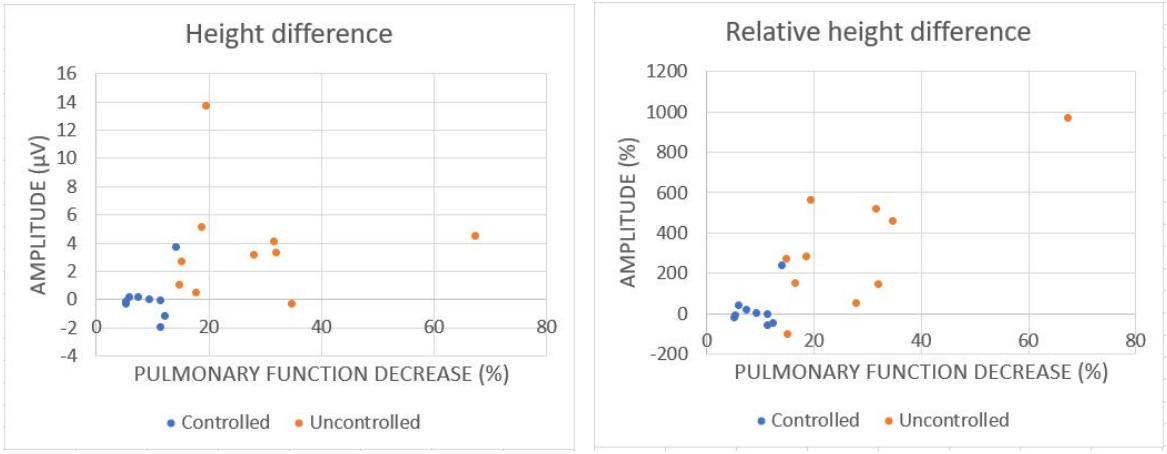

Figure 25: *Scatter plots of the absolute and relative increase in peak height of the intercostal muscles in comparison to the drop in FEV_1 at the timeframe of maximal diaphragm amplitude. Patients in the control group are labeled blue, uncontrolled patients are labeled orange.*

Table 12: *Linear regression results of the statistically significant parameters of the diaphragm using stepwise linear regression. The most accurate model was found by only integrating the peak height difference into the model.*

Parameter	**Pearson**	**Significance**
Peak height difference	0.73	< 0.001
Area under curve difference	0.39	0.334
Relative peak height difference	0.59	0.128
Relative area under curve difference	0.31	0.057

The peak height difference and area under curve difference of the diaphragm and intercostal muscles were used to compute receiver operator curves (Figure 26). An overview of the results is displayed in table 13, figure and table for the intercostal muscles is found in appendix D. The largest area under curve of the ROC was found for the peak height difference of the diaphragm (AUC = 0.95), providing an excellent separator for finding patients diagnosed with uncontrolled asthma. Using a cut-off peak height difference of $3.48\mu V$ a sensitivity of 85% is found with a specificity of 90.9%. The highest area under curve of the ROC of the intercostal muscles was found for the relative peak height difference (AUC = 0.91), providing a good separator for finding patients diagnosed with uncontrolled asthma. Using a cut-off relative peak height difference of 48% a sensitivity of 90.0% and a specificity of 88.9%.

Table 13: *Overview of the ideal cut-off values of the ROC curves of the changes in significant diaphragm and intercostal muscle parameters.*

Muscle group	**Parameter**	**Cut-off**	**Sens/spec**	**AUC**
Diaphragm	Height	$3.48\mu V$	85.0%/90.9%	0.95
	Relative height	125.44%	90.0%/72.7%	0.87
	Area under curve	3.32	70.0%/81.8%	0.83
	Relative area under curve	51.00%	70.0%/68.2%	0.73

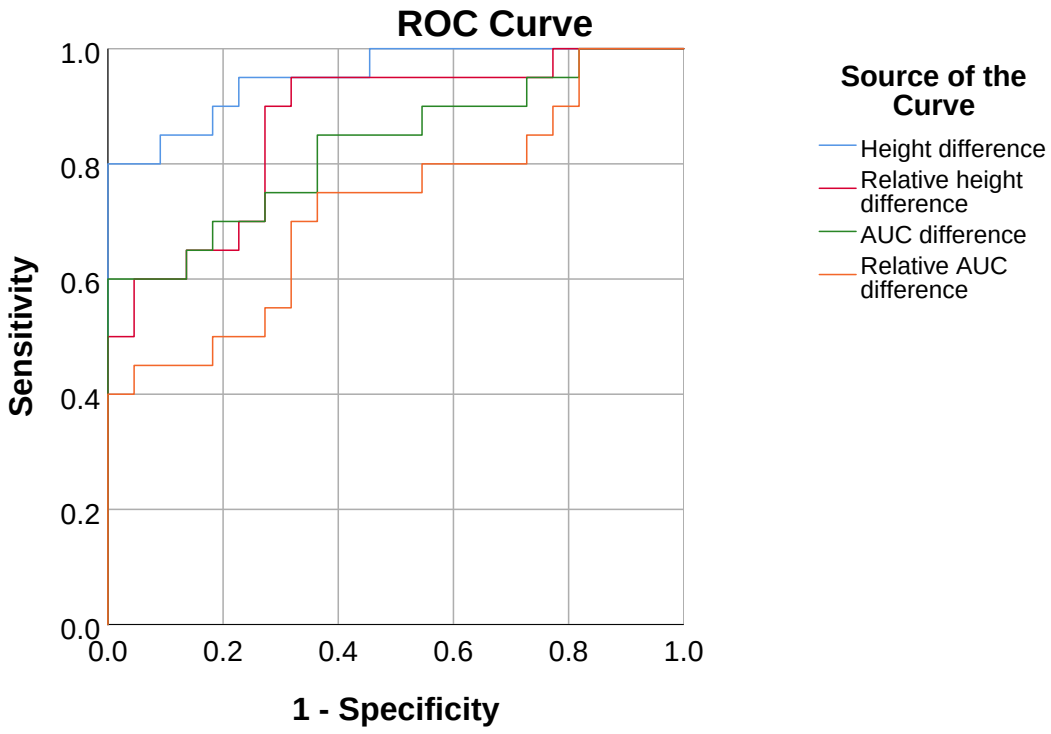

Figure 26: *Receiver operator characteristic curves of the statistically significant parameters found in the diaphragm measurements. The largest area under curve was found for the peak height difference at 0.95.*

4.2.4 Dysfunctional breathing patients

Baseline The peak height and area under curve were assessed at baseline for the dysfunctional breathing patients, compared to both the controlled and uncontrolled asthma patients. An overview of distributions is given in figure 27, an overview of parameters is displayed in table 14. Patients in the dysfunctional breathing group do not statistically significantly differ in any of the measured parameters from either the controlled or

uncontrolled asthma group.

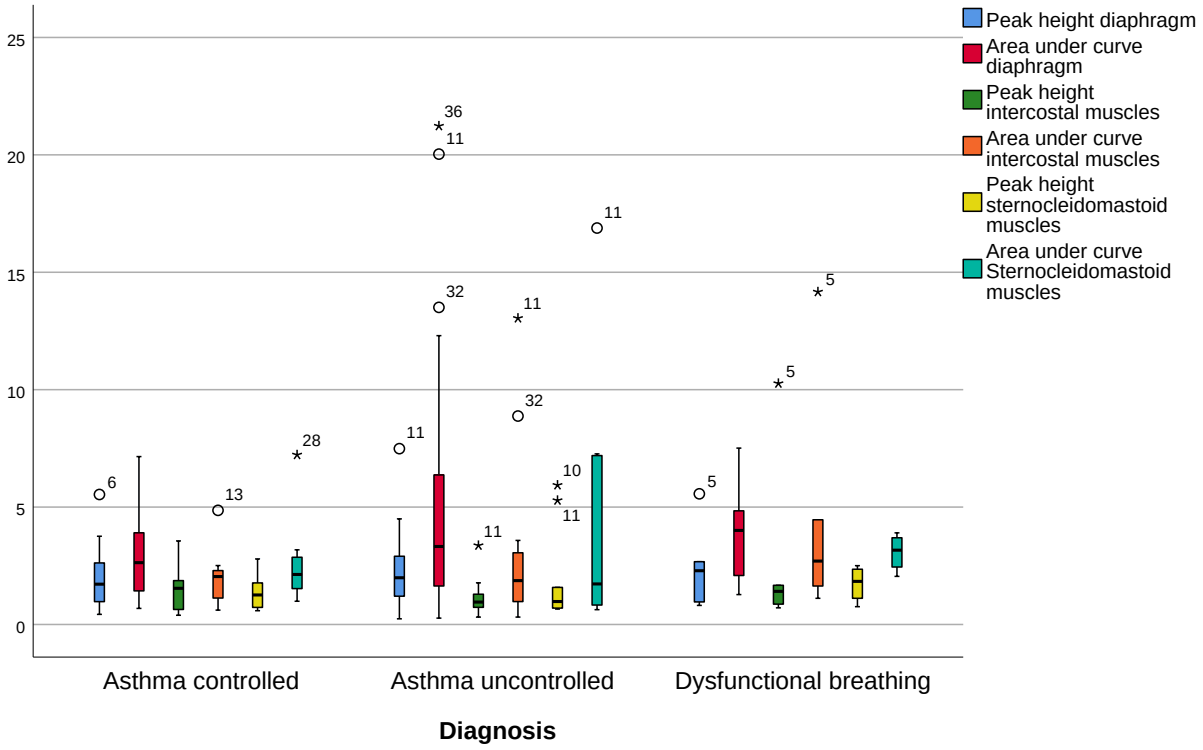

Figure 27: *Overview of the measured parameters at baseline in all three groups. Outliers are displayed as circles, extreme values (Defined as over 1.5 times the interquartile range) are displayed as asterisks.*

Table 14: *Overview of the results of the Mann-Whitney-U test at baseline. The dysfunctional breathing patients do not differ statistically significantly from either the controlled or uncontrolled asthma patients on any of the measured parameters. The significance column overlaps in the controlled and dysfunctional group as well as in the dysfunctional and uncontrolled group, indicating two separate comparisons.*

Muscle group	**Parameter**	**Diagnosis**	**Median**	**IQR**	**P-value**
Diaphragm	Height	Controlled	1.71	2.62-0.97	0.54
		Dysfunctional	2.29	2.67-0.96	
		Uncontrolled	1.99	2.91-1.20	0.81
	AUC	Controlled	2.63	3.91-1.43	0.29
		Dysfunctional	4.01	4.84-2.09	
		Uncontrolled	3.32	6.37-1.64	0.86
Intercostal	Height	Controlled	1.54	1.87-0.64	0.54
		Dysfunctional	1.41	1.67-0.87	
		Uncontrolled	0.95	1.29-0.73	0.81
	AUC	Controlled	2.04	2.30-1.13	0.62
		Dysfunctional	2.70	4.46-1.64	
		Uncontrolled	1.87	3.05-0.97	0.32
Sternocleido	Height	Controlled	1.26	1.77-0.73	0.35
		Dysfunctional	1.84	2.35-1.11	
		Uncontrolled	0.98	1.58-0.70	0.32
	AUC	Controlled	2.13	2.86-1.53	0.26
		Dysfunctional	3.16	3.69-2.45	
		Uncontrolled	1.73	7.19-0.83	0.40

One minute after exercise The peak height and area under curve were assessed one minute after exercise for the dysfunctional breathing patients, compared to both the controlled and uncontrolled asthma patients. An overview of distributions and calculated parameters are displayed appendix D. Patients in the dysfunctional breathing group displayed statistically significant increases in peak height for the diaphragm ($2.86\mu V$ ($1.99 - 3.67$) and $6.12\mu V$ ($4.57 - 6.66$), $P < 0.01$), intercostal muscles ($1.47\mu V$ ($1.11 - 1.93$) and $2.32\mu V$ ($1.98 - 3.10$), $P = 0.03$) and sternocleidomastoid muscles ($1.37\mu V$ ($0.74 - 2.13$) and $2.91\mu V$ ($1.97 - 3.76$), $P = 0.05$) when compared to the controlled asthma group. The dysfunctional breathing group however does not statistically significantly differ from the uncontrolled asthma group on any of the measured parameters.

Three minutes after exercise The peak height and area under curve were assessed three minutes after exercise for the dysfunctional breathing patients, compared to both the controlled and uncontrolled asthma patients. An overview of distributions and calculated parameters is displayed in appendix D. Of the dysfunctional breathing patients, 5 out of 6 displayed peaks at the sternocleidomastoid muscles. Patients in the dysfunctional breathing group display statistically significantly larger peaks heights at the diaphragm when compared to the controlled asthma patients($2.59\mu V$ ($1.75 - 3.24$) and $4.26\mu V$ ($3.18 - 4.90$), $P = 0.03$). Peak heights have decreased when compared to one minute after exercise in dysfunctional breathing patients as well as in controlled asthma patients. Peak heights in uncontrolled asthma patients further increased. We find significantly lower peak heights at the diaphragm for dysfunctional breathing patients when compared to uncontrolled asthma patients ($4.26\mu V$ ($3.18 - 4.90$) and $9.28\mu V$ ($5.76 - 10.89$), $P = 0.03$).

Six minutes after exercise The peak height and area under curve were assessed six minutes after exercise for the dysfunctional breathing patients, compared to both the controlled and uncontrolled asthma patients. An overview of distributions is given and an overview of parameters is displayed appendix D. Of the dysfunctional breathing patients, 3 out of 6 displayed peaks at the intercostal and sternocleidomastoid muscles. Patients in the dysfunctional breathing group display statistically significantly larger peaks heights at the diaphragm when compared to the controlled asthma patients ($2.10\mu V$ ($1.29 - 2.36$) and $3.31\mu V$ ($2.73 - 3.75$), $P = 0.03$). Also, patients in the dysfunctional breathing group display statistically significantly lower peak heights and when compared to the uncontrolled asthma group ($3.31\mu V$ $2.73 - 3.75$ and $5.44\mu V$ ($3.69 - 10.31$), $P = 0.02$).

Activity pattern When comparing the median peak height values of the controlled asthma, uncontrolled asthma and dysfunctional breathing patients we find larger increases in peak height in the uncontrolled asthma and dysfunctional breathing groups when compared to the controlled asthma group. The median peak height further increases in uncontrolled asthma patients, but decreases in the dysfunctional breathing patients. After

the use of a bronchodilator median peak heights again are at comparable levels in all three groups (Figure 28).

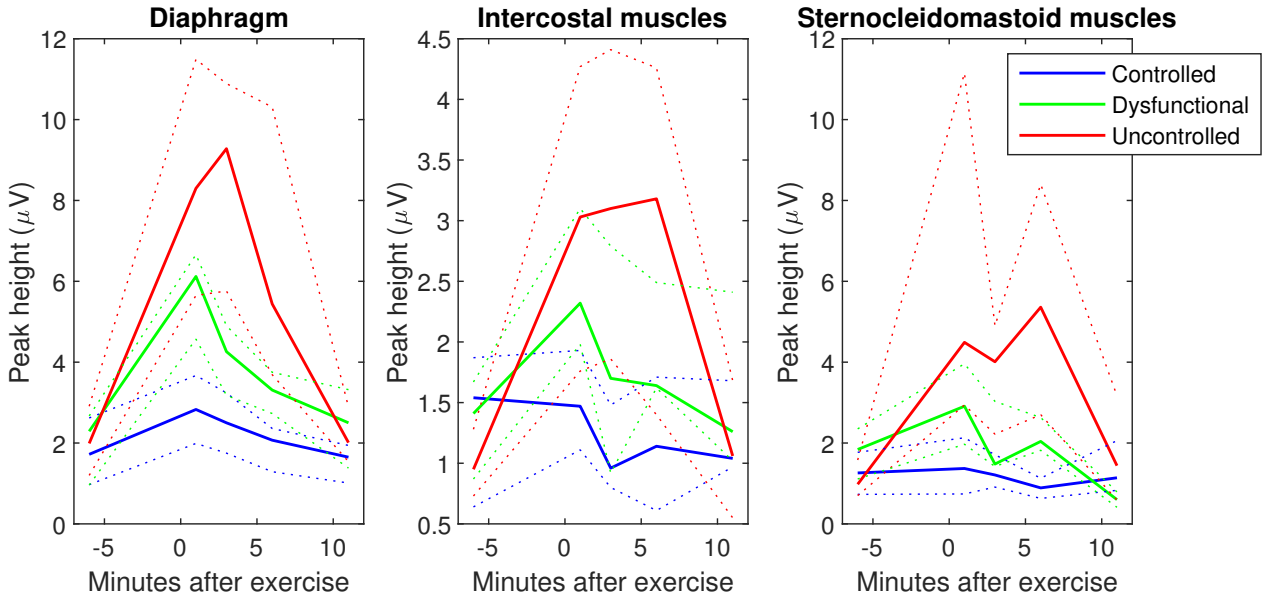

Figure 28: *Overview of the median peak heights of the three reliably measurable muscle groups in dysfunctional breathing patients. The dotted lines display the 95% confidence interval of the interquartile ranges. A similar pattern is visible in all muscle groups, only the diaphragm provided statistically significant differences.*

5 Discussion

In this study the use of EMG to assess the severity of childhood asthma was investigated. This section will discuss the results and limitations of this study and some future perspectives.

5.1 Interpretation of results

Results were computed for the three different outcomes; comparisons of the EMG parameters at the timeframe of largest bronchoconstriction, comparisons of the EMG parameters at the timeframe of largest measured amplitude of the diaphragm and the comparison EMG parameters of dysfunctional breathing patients to both controlled and uncontrolled asthma. Each will be discussed separately.

5.1.1 Comparisons at baseline

EMG parameters At baseline none of the measured parameters on any of the muscle groups were found to be statistically significantly different between either controlled and uncontrolled as well as dysfunctional breathing patients. These findings imply that the increased persistent chronic inflammation of the airways in uncontrolled asthma patients does not significantly impact the amount of work the diaphragm and accessory breathing muscles deliver before being exposed to provocative stimuli when compared to controlled asthma patients. It is uncertain whether the effects of asthma suppressed by medication impact measurements, as no healthy control group was measured. Symptoms of dysfunctional breathing in EMG parameters were also not reliably measurable before exercise. Before exercise dysfunctional breathing patients are similar to both controlled and uncontrolled asthma patients. At baseline the groups also displayed similar measured as equal on EMG, ensuring changes in parameters can be attributed to the effects of asthma or dysfunctional breathing.

Patient characteristics At baseline none of the patient characteristics were found to be statistically significantly different between the controlled and uncontrolled asthma patients. In both groups we find more boys than girls, the distributions among groups is the same. The dysfunctional breathing group contains statistically significant more girls than boys. Asthma is known to be more prevalent in prepubertal boys than girls [9,90,91]. Dysfunctional breathing is known to be more prevalent in girls than boys [92,93]. Furthermore we find a slightly higher use of inhaled corticosteroids in the uncontrolled asthma group. Most patients tested in the uncontrolled group were being treated for their asthma, making a larger percentage of patients on medication understandable.

5.1.2 Comparison of EMG parameters at largest bronchoconstriction

Diaphragm The uncontrolled asthma group shows larger differences in measured peak height and area under curve on EMG of the diaphragm. This means that more action potentials are measured around the diaphragm, indicating an increase of diaphragm contraction power. These findings are conform the expected reaction in uncontrolled asthma patients. Bronchoconstriction causes an increase in airway resistance, limiting flow (equation 11). In order to meet the enhanced demand of ventilation after exercise the difference in transthoracic pressure needs to increase, mainly accomplished by increasing diaphragm contractility.

Intercostal muscles The uncontrolled asthma group shows larger differences in peak height and area under curve of the EMG signal when compared to the controlled asthma group. The increase in measured peak height and area indicate a similar response as we find in the diaphragm. The intercostal muscles are one of the accessory breathing muscles, typically recruited when the diaphragm alone does not suffice in supplying adequate airflow to the lungs. Therefore an increase in accessory breathing muscle activity was expected in uncontrolled asthma patients [25]. A larger amount of uncontrolled asthma patients displayed reliably measurable intercostal muscle EMG after exercise, which implies that the recruitment of the accessory breathing muscles is more prominently visible in the uncontrolled asthma group.

Sternocleidomastoid muscles The sternocleidomastoid muscles were used less at baseline than the intercostal muscles were. After exercise 15 patients had reliable sternocleidomastoid muscle measurements in both groups, indicating exercise causes the sternocleidomastoid muscle to be recruited. After exercise both groups displayed more reliable measurements of the sternocleidomastoid muscles with a larger increase in the uncontrolled asthma group. Similar to the intercostal muscles, this indicates that uncontrolled asthma causes the accessory breathing muscles to be recruited. Sternocleidomastoid activity during exhaustive exercise has been assessed by Segizbaeva in 2013 in healthy adult men [94]. Activity of the sternocleidomastoid muscles increased in all subjects of Segizbaeva's study, possibly explaining the increase in reliably measurable patients in both groups. Due to the large discrepancy between the total patient group and the amount of reliably measurable patients before exercise the choice was made not to compare the differences in EMG parameters between before and after exercise. Instead all parameters were compared at the values measured in the timeframe of minimal pulmonary function, which does display larger peak heights and areas under curve for the uncontrolled asthma patients. The larger EMG activity measured in uncontrolled asthma patients indicates a larger reliance on the use of the accessory breathing muscles when compared to the controlled asthma patients, as expected.

Trapezoid muscles Similar to the intercostal- and sternocleidomastoid muscles, the trapezoid muscles provided a small amount of patients with reliable measurements. After exercise reliable measurements were obtained from a larger amount of patients, with larger measured peaks heights and areas under the curve in the uncontrolled group. Increases implying a larger reliance on thorax expansion by the accessory breathing muscles in the uncontrolled asthma group. The small amount of reliable measurements however allows assessment of under one third of the total population and does therefore not allow solid judgment of contribution of the trapezoid muscle to (impaired) breathing.

Extreme values Patients 23 and 29 in the uncontrolled group are found as extreme outliers for peak height and area under curve differences in both the diaphragm and intercostal muscle measurements. Patient 23's measurements at baseline were among the lowest of all patients ($0.24\mu V$) and had an FEV_1 decrease of 34.5% after exercise. The absolute difference in peak height was within the interquartile range at $7.48\mu V$, but relatively speaking this is an increase of over 3000%. The same can be said for the area under curve of this patient, which was only 0.27 at baseline. After exercise however this increased to 31.76 (close to 11800% increase) which was the highest of all patients. Patient 29 was also on the low end of baseline measurements at the diaphragm with an average peak height of $0.78\mu V$, which increased to $15.61\mu V$ (over 2000%) and an area under curve of 0.35, which increases to 25.47 (close to 7300% increase). This patient had an FEV_1 decrease of 19.5%, which is average in the uncontrolled group. This patient did however have a baseline pulmonary function of 119% of the predicted pulmonary function, making the absolute decrease in volume larger than in most patients. At this time it is unclear whether high baseline pulmonary function influences EMG measurements.

Predictive value Linear regression analysis was performed in order to compare the changes in statistically significant parameters measured in diaphragm and intercostal muscle activity to the drop in FEV_1 on spirometry. A strong correlation was found between the peak height difference of the diaphragm and moderate correlations were found found between the drop in FEV_1 and the relative peak height change of the diaphragm, as well as the absolute and relative changes in area under curve of the diaphragm. Poor correlations were found between the statistically significant changes of the intercostal muscles when compared to the drop in FEV_1. No model was computed using both the parameters measured in the diaphragm together with the measured parameters of the intercostal muscles due to the large difference in reliable measurements before and after exercise (43 for the diaphragm, 16 for the intercostal muscles). The peak height difference of the diaphragm before and after exercise explains 57.9% of the variance of the drop in FEV_1, indicating a decent model fit. One patient (29) showed mild bronchoconstriction (19.5%) and displayed the largest increase of all patients in EMG parameters. This is believed to in part be explained by the baseline pulmonary function test performed, indicating an above average

lung function of 119% of predicted for patients of her age, length and weight. The absolute decrease in lung volume is therefore much larger than volumes found in other patients. If this patient is excluded from the table, we find a Pearson correlation coefficient of 0.870 and an R^2 of 0.75. Although clinical decision making would not be influenced by doing so.

The ROC curves computed using the statistically significant parameters measured at the diaphragm in order to separate uncontrolled asthma patients from controlled asthma patients displays that the absolute peak height difference is the best separator. A cut-off value of $1.15\mu V$ provides an excellent separation at 95% sensitivity and 90.9% specificity. Two other important points in the curve also fairly close to the top left corner are found at cut-offs $0.59\mu V$, below which we are certain that the measurement belongs to a controlled asthma patient. At $2.7\mu V$ we are certain that the patient belongs to the uncontrolled asthma group. These two additional points are important to note when looking at clinical decision making.

Patients unjustifiably categorised in the uncontrolled group using the cut-off value of a peak height difference of $1.15\mu V$ were patients 39 and 49. Patient 39 was the heaviest patient measured (102kg) and also the only smoker in the group, which possibly affected the effects of exercise on his body when compared to non-smoking patients on a normal weight. He was a controlled asthma patient with the largest increase in peak height ($2.05\mu V$). Patient 49 had an increase of $1.59\mu V$, but does not display any outstanding measurement parameters that explain possible missclassification. Patient 20 was diagnosed with uncontrolled asthma and only had an increase in peak height at the diaphragm of $0.64\mu V$. This patient however on baseline already had a peak height at the diaphragm of $4.50\mu V$, which was the second highest value measured in all patients at baseline. It is possible that persistent bronchoconstriction due to inflammation caused a high baseline value, which did not increase much further when provoked by exercise. The peak height measured after exercise of $5.14\mu V$ lies within the interquartile range of uncontrolled asthma patients and outside of the interquartile range of controlled asthma patients.

The ATS guidelines provide more than one cut-off value for the decrease in FEV_1 to be significant [22]. A 10% decrease is regarded significant for research, whereas 15% is more specific for EIB. Furthermore a 20% decrease is often considered to be uncontrolled for patients not using inhaled corticosteroids. When selecting these values to divide groups, the corresponding sensitivities and specificities are comparable (Table 15).

Use of accessory breathing muscles Accessory breathing muscles were reliably measurable at baseline in under half of the controlled and uncontrolled asthma patients. The use of accessory breathing muscles during quiet respiration was not expected, but could in theory be explained for asthmatic patients. Patients in both groups displayed an increase of the use of accessory breathing muscles after exercise. 11 patients in both groups displayed use of the intercostal muscles before exercise, versus 13 controlled and 15 uncontrolled after exercise respectively. The same can be said for the use of the sternocleidomastoid muscles, 7 patients in the controlled and 10 patients in the uncontrolled group displayed

Table 15: *Overview of sensitivities and specificities at different cut-off values of the FEV_1. The best cut-off value is found at an FEV_1 decrease of 13%.*

Cut-off FEV_1	**Cut-off peak height**	**Sensitivity/ specificity**	**AUC**
10%	$0.59\mu V$	88/88	0.91
13%	$1.15\mu V$	95/91	0.97
15%	$1.24\mu V$	94/84	0.95
20%	$4.04\mu V$	82/94	0.91

activity, versus 14 and 15 after exercise. These numbers were even smaller for the trapezoid muscles, making it questionable whether these measurements should at all be considered. The small amount of reliable measurements before exercise grant poor ability to determine changes in parameters. The comparisons between groups made at the sternocleidomastoid and trapezoid muscles after exercise however show the same pattern as the changes in diaphragm and intercostal muscle parameters. Larger peak heights and areas under the curve in uncontrolled patients. Considering the small amount of reliable measurements with the same outcome, it is arguable whether they have any additional value to the measurements conducted at the diaphragm.

5.1.3 Comparisons at maximal EMG amplitude of the diaphragm

Maximal EMG activity was found in 26 out of 43 patients at one minute after exercise, controlled and uncontrolled alike. Maximal EMG activity is found at the same timeframe as maximal pulmonary function decrease in 28% of patients. Four patients displayed maximal EMG activity after the point of maximal pulmonary function decrease (3 controlled, 1 uncontrolled). This implies that exercise contributes to an increase in EMG activity regardless of pulmonary function decrease, and does not provide any information about the gold standard timeframe of maximal dyspnea. An overview of maximal EMG activity timeframes compared to lowest pulmonary function timeframes is displayed in figure 29, an overview of the relative amounts of patients in displayed in table 16.

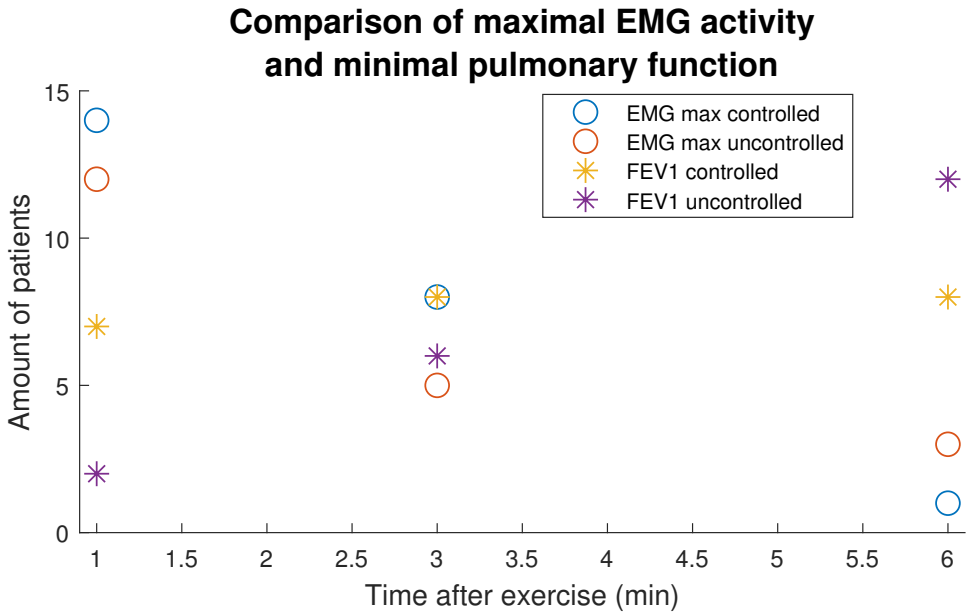

Figure 29: *Overview of the timeframes of maximal EMG activity and minimal pulmonary function. The timeframe of largest EMG activity is found at one minute after exercise 60% of the patients in both groups. The maximal decrease in pulmonary function is equally distributed in the controlled asthma group over time, but increases with time in the uncontrolled asthma group.*

Table 16: *60% of the patients displayed their maximal EMG activity one minute after exercise. Maximal EMG activity was found at the same timeframe as maximal pulmonary function decrease in 28% of the patients. 8% of the patients displayed maximal EMG activity after the timeframe of maximal pulmonary function decrease.*

Diagnosis	**Maximal EMG activity timeframe**	**Amount of measurements**	**Maximal pulmonary function decrease timeframe**	**Amount of measurements**
Controlled	1 minute	61%	1 minute	29%
			3 minutes	42%
			6 minutes	29%
	3 minutes	35%	1 minute	25%
			3 minutes	25%
			6 minutes	50%
	6 minutes	4%	1 minute	100%
			3 minutes	0%
			6 minutes	0%
Uncontrolled	1 minute	60%	1 minute	8%
			3 minutes	25%
			6 minutes	67%
	3 minutes	25%	1 minute	0%
			3 minutes	60%
			6 minutes	40%
	6 minutes	15%	1 minute	33%
			3 minutes	0%
			6 minutes	67%

Results at the timeframe of maximal EMG activity of the diaphragm were comparable to the results at the timeframe of maximal pulmonary function decrease. We find statistically significant increases of peak height and area under curve in both absolute and relative in the diaphragm and intercostal muscles for uncontrolled asthma patients. Furthermore we find larger peak heights and areas under the curve at the sternocleidomastoid muscles at the point of maximal activity of the diaphragm. No statistically significant differences were found at the trapezoid muscles.

Comparison to timeframe of maximal pulmonary function decrease Median values were higher than at the timeframe of maximal pulmonary function decrease and also appear increased in the controlled asthma group. Peak height and area under curve differences at the point of maximal pulmonary function were close to zero for the controlled

asthma patients. As table 16 also shows, the majority of patients in either group displayed maximal EMG activity a minute after exercise. Diaphragm activity has been found to increase in COPD patients after exercise in response to a decrease in pressure generating capacity [95]. Wu et al. explored the response of EMG measurements of the diaphragm during exercise and found significant increases in activity in COPD patients [96]. A similar process is imaginable when the airway resistance increases in asthma patients during exercise. Waltherspracher et al. found increased activity of the diaphragm and recruitment of the accessory breathing muscles in healthy adults in response to exercise [97]. It is likely that the same effect is seen in the controlled asthma patients, explaining the increased muscle activity directly after exercise.

Choosing a timeframe Both compared timeframes display statistically significant differences between controlled and uncontrolled asthma patients. The measurements closely after exercise are prone to contain the short-term persistent effects of exercise on the intensity at which respiratory muscles function. This suggests that in order to be certain that exercise is no longer influencing the desired measured effect, the most reliable results are found by looking at the timeframe of maximal pulmonary function decrease.

5.1.4 Dysfunctional breathing

Dysfunctional breathing patients show a pattern of increasing activity of the respiratory muscles in response to exercise, which quickly after cessation recovers. This pattern is most prominently visible in the diaphragm, contrary to the findings of Martin et al. in 1980 regarding hyperinflation [46]. Martin found that hyperinflation was sustained mostly by the use of the accessory breathing muscles. A comparison to a healthy control group is required to fully comprehend the alternate pattern found in dysfunctional breathing.

Baseline At baseline dysfunctional breathing patients do not show any significant differences in measured EMG parameters when compared to both controlled and uncontrolled asthma patients in all muscle groups.

One minute after exercise Immediately after exercise we find a significant increase in median peak height and area under curve for dysfunctional breathing patients when compared to controlled asthma. We find a smaller increase in peak height and area under curve at the diaphragm, not significantly separating dysfunctional from uncontrolled asthma. These changes uphold for all measured muscle groups.

Three minutes after exercise Three minutes after exercise we still find the parameters measured at the diaphragm to be elevated compared to the controlled asthma patients. The area under curve is also significantly larger at the intercostal muscle measurements when compared to the controlled asthma patients, and peak height is significantly smaller at

the sternocleidomastoid muscles when compared to the uncontrolled patients. Activity over all measured muscle groups has decreased. The most important parameters in this timeframe are found at the diaphragm. Activity of the dysfunctional breathing patients has decreased over two minutes and now is also significantly lower than the uncontrolled asthma patients, in whom activity of the diaphragm has increased when compared to a minute after exercise. Placing the dysfunctional breathing group in between the controlled and uncontrolled asthma patients at three minutes after exercise.

Six minutes after exercise Six minutes after exercise we find the same significant differences at the diaphragm, placing the dysfunctional breathing patients between the controlled and uncontrolled group. Furthermore we find significantly larger areas under the curve at the intercostal muscles and sternocleidomastoid muscles when compared to the controlled asthma patients.

Activity patterns Dysfunctional breathing patients show a distinct pattern of increase in EMG activity at the diaphragm directly after exercise, quickly decreasing over time. The pattern is found in all reliably measured muscle groups, but statistically significant differences are only found for the pattern at the diaphragm measurements throughout the pattern.

Whilst the pattern appears distinct and is in fact statistically significant, it is important to note that the pattern was only statistically significantly different when comparing medians. Principle component analysis was attempted to distinguish individual patients from one another in groups, but was unsuccessful. The overlap in interquartile ranges renders principle component analysis incapable of completely separating groups. For details, see appendix D. Chapter 2 further explains that hyperinflation is also present in asthmatic patients, possibly contributing to the overlap in patterns. While it is true that all measured dysfunctional breathing patients used their accessory breathing muscles in all timeframes, the changes in EMG parameters at the intercostal- and sternocleidomastoid muscles were found not to significantly vary over time, which is striking. Dysfunctional breathing is mostly regarded as a disorder of the accessory muscles [98–101]. The increased activity of the diaphragm in response to breathing in a hyperinflated state may be explained by regarding equation 11. During hyperinflation the pressure within the lungs is increased, closer to the atmospheric pressure than usual. In order to generate a pressure difference on top of that the diaphragm is required to contract beyond quiet breathing levels.

Conclusions on dysfunctional breathing The distinct patterns of dysfunctional breathing provide insight to the rapid onset and decrease of non-asthma related pulmonary distress and increased work of breathing. EMG may provide insight into the objective diagnosis and monitoring of dysfunctional breathing. The large overlap of not only uncontrolled but also controlled asthma patients when regarding individual peak height patterns indi-

cates a possible misdiagnosis of dysfunctional breathing patients who do not experience physical discomfort in response to exercise. The small amount of patients (six) in the dysfunctional breathing patients group however makes it difficult to give substance to these findings and further research into this phenomenon using EMG is recommended.

5.2 Programming design choices

Windows in measurement application The measurement application uses the algorithm designed by O'Brien et al [24]. The algorithm detects and deletes QRS-complexes from the raw measurement data before computing the RMS of the signals derived from the individual muscle groups. In the process, this means P- and T-waves remain in the signal and contribute to the computed RMS used for analysis. The heart frequency is later low pass filtered anyway, in order to delete P- and T-wave disturbances. O'Brien in his article states that the same algorithm may be applied to P- and T-waves in addition to QRS-complexes. In doing so however, the P- and T-wave areas are filled with the same running average the deleted QRS-complexes do. Being smaller in amplitude and duration, it was decided not to apply O'Brien's algorithm to P- and T-waves to retain as much true signal as possible.

Applied filters Baseline drift was not removed from the RMS signals. The variations in baseline values may cause difficulties in signal processing. However, preliminary testing revealed large increases in baseline activity in response to voluntary hyperinflation. This increase implied that the offset contained information about the tonic activity of the respiratory muscles. This study provided evidence that there are no significant differences between controlled and uncontrolled asthma patients regarding tonic muscle activity, and offset removal may be considered for further studies.

After segment selection the frequency spectrum was analysed for each timeframe. The dominant frequency was identified as the respiratory frequency. P- and T-wave frequencies were removed by removing the heart frequency from the signal, providing visible noise reduction, preserving signal morphology. A sizable amount of patients, primarily in the uncontrolled asthma group displayed a peak in the frequency spectrum of significant magnitude at double the respiratory frequency. The signal was not found to be associated with quiet breathing, but instead appeared in advanced manoeuvres. The occurrence of this frequency was investigated and is presumed to be a response of the abdominal muscles and was therefore removed from the signal (Appendix B for details).

5.3 Limitations

General measurement limitations EMG signals of the respiratory muscles are of a small magnitude, making them prone to disturbances. Movements of the arms, legs or neck cause large disturbances and need to be avoided as much as possible. The current

measurement protocol in which children were required to sit still for 30 seconds eliminated most of the large distortions. Slight leg or arm movements poorly visible to the researcher however were present and could only be detected in the signal in hindsight. These movements could be recognised in the measurement signal and could be avoided in analysis, but in the process often reduced the analysable segment size.

The measurement schedule was bound to and not allowed to disturbed the measurement protocol of the exercise challenge test. Failed measurement segments could not be repeated, causing shorter analysis segments.

Measurement software In consultation with the manufacturer a custom made measurement application was provided. The application allowed the placement of timestamps which could be used to signal important areas of the signal. The disturbances in the above paragraph however required deviation of the predetermined analysis segments and the timestamps were not used for selection.

Furthermore the measurement application did not allow segmentation within a single measurement, requiring inspection of the entire measurement before analysis was possible.

Respiratory muscle use ratio's The ratio's at which the respiratory muscles were used were assessed for each timeframe and compared between groups. The use of accessory breathing muscles when compared to the use of the diaphragm was found not to be statistically significantly different between either muscle group at any given time before or after exercise. Breathing remained mostly reliant upon usage of the diaphragm.

Respiratory rate recovery time The study set-up included inquiry into the respiratory rate recovery time, found to be significantly increased in uncontrolled asthma patients [89]. In the current measurement protocol however it was not possible to accurately determine the respiratory rate recovery time. The technique itself is suited to do so, however a different protocol in which children stand or sit still until the respiratory rate has returned to baseline levels. It is questionable whether children who have just reached a state of increasing dyspnea are capable of being instructed into doing so.

5.4 Future perspectives

Custom made software The combination of a measurement application and retrospective analysis in Matlab is acceptable in a research setting. When used in clinical practise however, user-friendly software is required. Use of the algorithm of O'Brien is highly valued, but currently is hidden behind a patent by the manufacturer and may provide problems in further development if unavailable. Proposed software would include the measurement of separate segments and live calculations of results.

By not only calculating relevant measurement parameters, but also including validity detection the system becomes usable for medical professionals and eventually patients.

Use of a database to which individual patients can be compared is a goal that may be reached in the far future, but through additional research and validation processes can be achieved.

Machine learning During this study various statistical tests were performed. One of the major drawbacks however was a large amount of missing data, mostly found in the accessory breathing muscles. Missing data made it difficult to properly assess the combined efforts of the diaphragm and accessory breathing muscles. By applying machine learning algorithms capable of handling missing data, it may in the future be possible to design a more accurate model to assess the severity of EIB in children.

Healthy subjects During this study a clear differentiation was made between controlled and uncontrolled asthma patients. An increase of EMG activity of the diaphragm was found in both groups directly after exercise. At this time it is unclear whether the increase in EMG activity in the controlled asthma patients is a lesser reaction, comparable to the uncontrolled asthma patients, or whether it is the exercise itself that provokes an EMG activity increase. By measuring healthy subjects and adding them to the comparison models the differences measured between healthy, controlled and uncontrolled asthma will provide more insights into the actual health of the child.

Alternate frequencies The additional frequency at about twice the respiratory rate shows a distinct pattern, which when compared to the respiratory frequency is morphologically different and may contain information regarding the levels of pulmonary function decrease. At this time some evidence was found suggesting the additional activity is traceable to the abdominal muscles. Further research is required to fully comprehend the information found outside the respiratory frequency.

Field testing The use of EMG to assess the severity of asthma in children is possible using handheld equipment, making the step from the lab to the field a small one. Simultaneous field testing is the next step in assessing real-life symptoms, measuring children together while playing instead of in a laboratory setting. By performing field tests it becomes possible to assess the breathing discomforts children encounter in real life.

Improvements to patient self-management Asthma is an often under treated disease, due to familiarisation with asthmatic symptoms. Patients and parents alike grow accustomed to the severity of pulmonary function decrease. By integrating EMG measurement technology into clothing or a wearable measurement tool patients can sample and measure their selves, possibly improving patient self-management and self-awareness.

In-hospital monitoring The current assessment of children admitted to the pediatrics ward entails auscultation of the lungs, monitoring oxygen saturation and nebulising. Furthermore patients are often woken up to assess the state of the lungs during nighttime. Most children admitted to the hospital with an asthma exacerbation are often very young and require extensive rest during the night. By monitoring the activity of respiratory muscles we not only objectify the care for these children, but we may also be capable of improving their quality of life in the hospital by adjusting treatment based upon measured EMG parameters.

6 Conclusion

The results of the AACE study show the potential of EMG measurements in asthma care. Electric muscle activity of the diaphragm and accessory breathing muscles is increased in response to an exercise challenge bronchoprovocation test in patients with an uncontrolled asthma when compared to controlled asthma patients at maximal pulmonary function decrease.

Activity of the diaphragm is reliably measurable in all patients, and significantly increase in uncontrolled asthma patients. The increase in diaphragm activity is correlated with the decrease in pulmonary function. Furthermore changes in activity of the diaphragm can be applied to accurately distinguish between controlled and uncontrolled asthma patients.

The use of accessory breathing muscles after exercise is increased in both controlled and uncontrolled asthma patients. The levels of electric activity in the accessory breathing muscles are larger in uncontrolled asthma patients. Accessory breathing muscle activity however is not reliably measurable in all patients and/or in each timeframe. Furthermore the statistically significant differences found in the parameters measured at the accessory breathing muscles are found in the same parameters as differences at the diaphragm were measured, peak height and area under curve. Measured accessory breathing muscle parameters display lower absolute, relative and statistical values than parameters measured at the diaphragm. It is therefore questionable whether measurements of the accessory breathing muscles provide any additional information to measurements of the diaphragm.

Activity changes of the diaphragm display a distinct pattern in dysfunctional breathing patients. The large increase followed by a rapid decline in measured peak height at the diaphragm distinguishes between dysfunctional breathing patients from both controlled- and uncontrolled asthma patients. The small amount of patients and current inability to separate individual patients from one another does not allow a decisive conclusion on the electric activity patterns of dysfunctional breathing patients. Further research is required to fully comprehend this phenomenon and the potential EMG has in diagnosis of dysfunctional breathing.

This study showed that electromyographical measurements of the diaphragm provide an elegant and feasible of assessing the occurrence and severity of exercise induced bronchoconstriction in children and can be used to distinguish between controlled and uncontrolled asthma. Electromyographical measurements of the diaphragm provide an elegant, non-obtrusive method of identifying respiratory distress in children and may in the future be applied to objectively monitor respiratory symptoms in children.

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A Overview Matlab interface features

The Matlab interface used for this study was self made and custom designed to envelop the full EMG measurement exercise challenge protocol. An overview of the start-up screen is displayed in figure 30. The function bar up top allows the user to select a patient or close the application. All general patient information is displayed on the left, all EMG measurement related data is displayed on the right. Furthermore each pane has a button allowing the user to select and export any desired graph as an image.

Figure 30: *Overview of the start-up screen of the custom made Matlab interface. General patient information is displayed on the left, all EMG signal related data is displayed on the right.*

A.1 General patient information

In the patient information menu all non-EMG related data obtained from the ECT required for this study is collected (Figure 31). Patient age, sex, length, weight, known allergies and diagnosis are entered. The decrease in FEV_1 and reversibility are calculated from the entered spirometry data. Finally medication use can be entered using the medication button. The green bulbs indicate that spirometry data and medication have been entered accordingly. By selecting "save patient info" the contents of the patient information window

are stored for that patient, and re-assessing the same patient automatically reloads general patient information into the app.

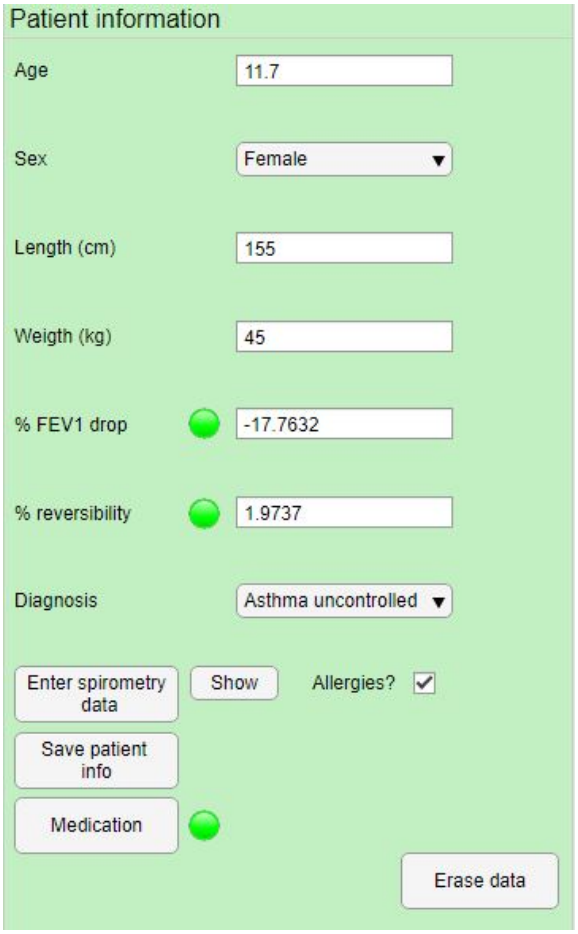

Figure 31: *The patient information panel displays all collected non-EMG related data during the ECT protocol relevant for this study.*

A.2 Basic graphs

The basic graphs area displays the RMS of the measured signal at the diaphragm, intercostal, sternocleidomastoid and trapezoid muscles. Furthermore the determine exercise period button allows the user to select the area of exercise, after which each timeframe of interest in regard to the exercise challenge protocol is automatically calculated.

A.3 Area selection

The area selection panel allows the user to select the areas of interest. These corresponded to the timeframes at which the patient performed spirometry. When hitting the select areas button, the checkboxes are checked for selection. Any selected checkbox prompts the user with an area from which the measurement is to be selected. Each timeframe is calculated based upon the exercise period selected in the previous pane. An area of 2.5 minutes around each timepoint is displayed, from which the user selects the area of interest for analysis. The trim selected areas pane allows the user to cut areas of the beginning and start of the signal to remove artefacts (Figure 32).

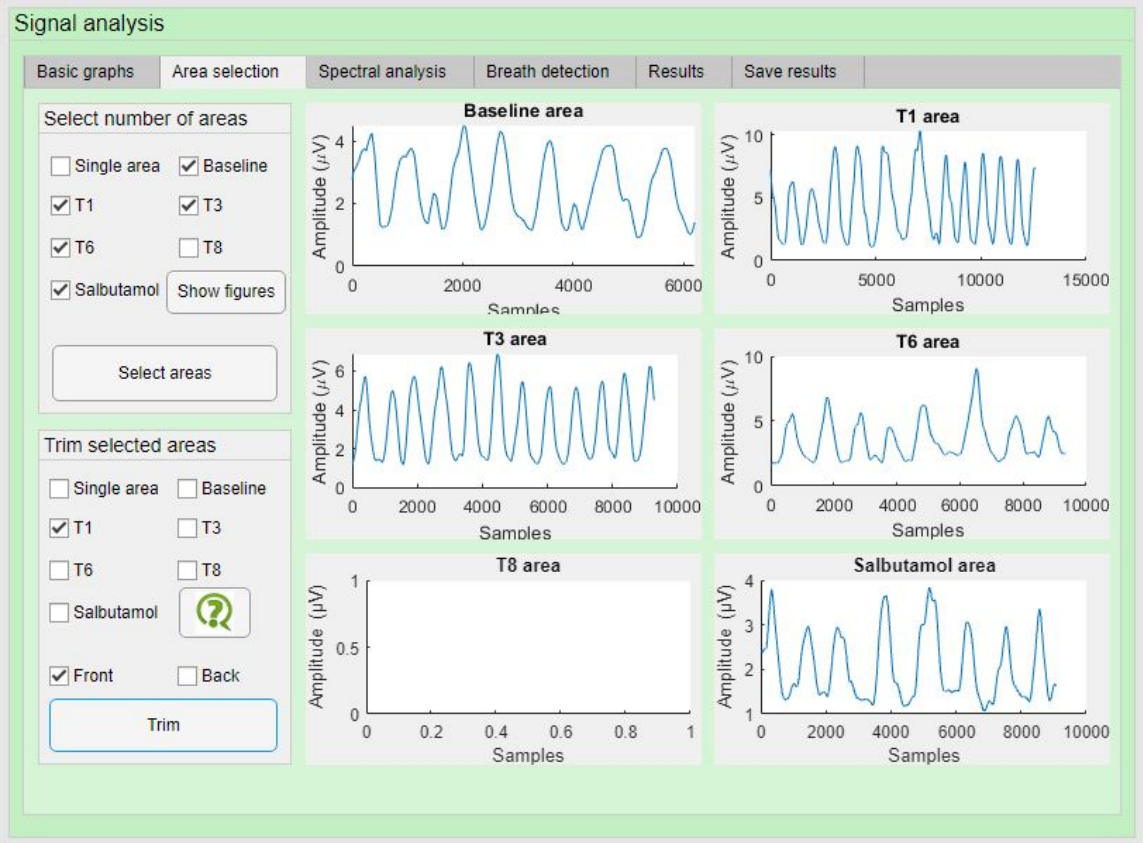

Figure 32: *Area selection panel. The user is required to select the timeframes applicable to the measured patient, corresponding with the amount of spirometry measurements performed.*

A.4 Spectral analysis

The spectral analysis pane allows the user to view the frequencies present in the signal at each individual timeframe. The basic filter options pane allows the user to remove the present heart rate frequency, as well as the drift using a 4th order butterworth filter. The removed heart rate frequency is calculated by taking the mean heart rate within the segment, multiplied by 0.9, ensuring any heart rate variability within the segment is accounted for. The specific band filtering allows the user to select an upper and/or lower bound frequency to which the signal is bounded using 4th order butterworth filters. Furthermore it is possible to filter within the upper and lower bound, allowing the user to remove the band given within the upper and lower bound. By selecting double or triple band analysis the user is allowed to filter the same signal in two or three different bands, after which the ideal filter band can be determined from within one figure. The save icon allows the user to save the filtered signal for each segment, the red and green indicators at the top indicate whether the user has saved the segment for that particular timeframe after filtering (Figure 33).

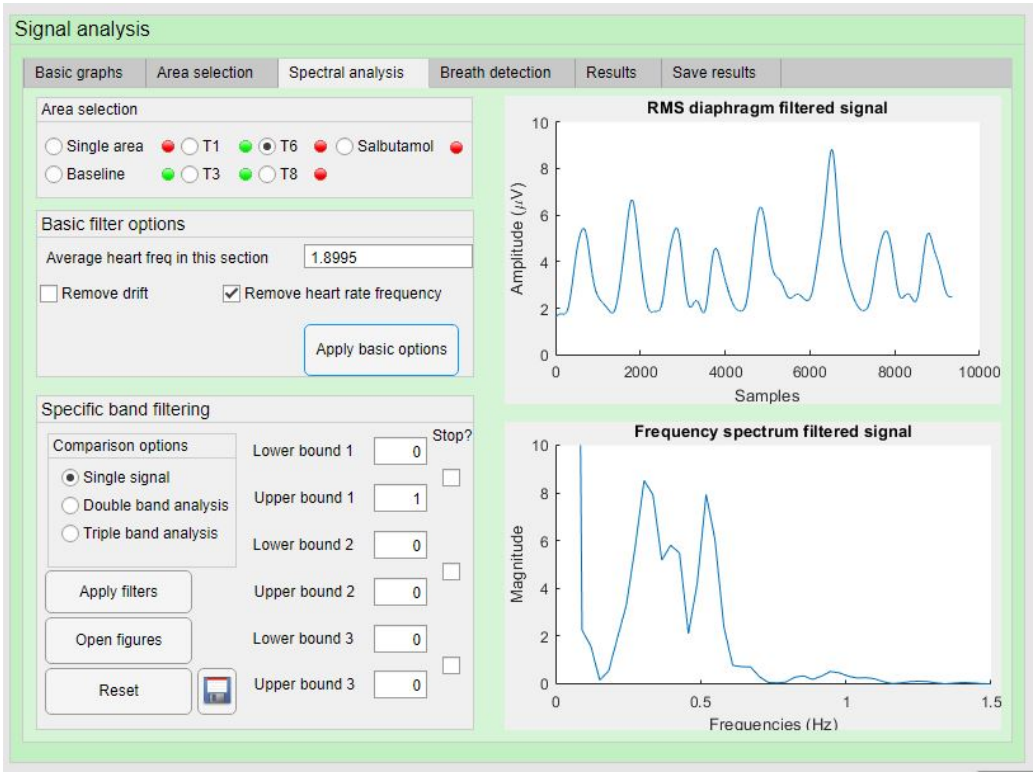

Figure 33: *Overview of the spectral analysis pane. The user is presented with various filtering options to remove any artefact frequencies from the signal.*

A.5 Breath detection

The breath detection pane allows the user to assess the measurements of each muscle group, at each measured timeframe after having filtered the signal in the previous pane. Breaths are detected using Matlab's findpeaks function for both the upper and lower peaks. Each high peak inbetween two low peaks is considered a breath. By default, all peaks underneath the mean of the signal at the selected timeframe is detected as a lower bound, each peak above the mean is considered an upper bound. For varying baseline values the user may manually edit the peak detection criteria using the sliders on screen. The save icon allows the user to save the breaths detected for each segment and muscle group. Furthermore the system detects non-realistic measurements and notices the user that non-realistic values have been found. Furthermore the user is manually allowed to select that realistic breathing patterns cannot be found. (Figure 34).

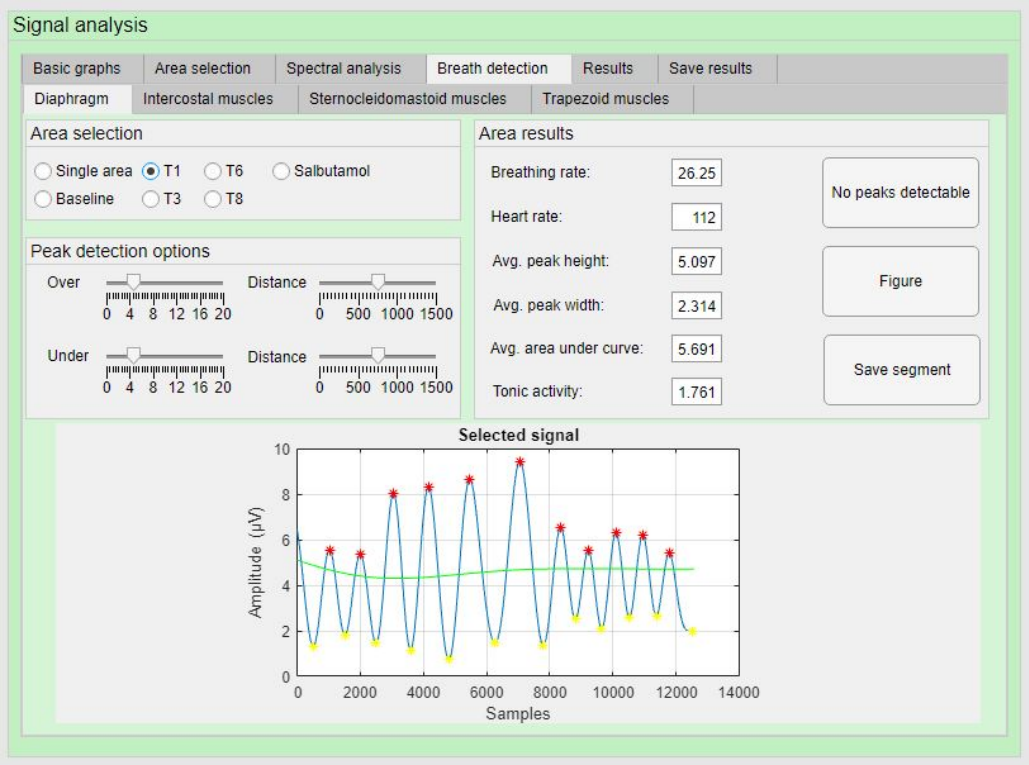

Figure 34: *Overview of the breath detection pane. The user is required to select a muscle group pane and a timeframe. The application then automatically calculates the parameters found on the righthand side. The user may alter the detection thresholds if the standard algorithm does not suffice.*

A.6 Results

The results pane displays tables for each measured parameter and compares the muscle groups to one another. The comparison pane within the results pane displays an overview of bar graphs for all parameters and all muscle groups, providing a quick overview of the patients' response. Finally the save results pane allows the user to store all general and measured parameters to an excel sheet (Figure 35).

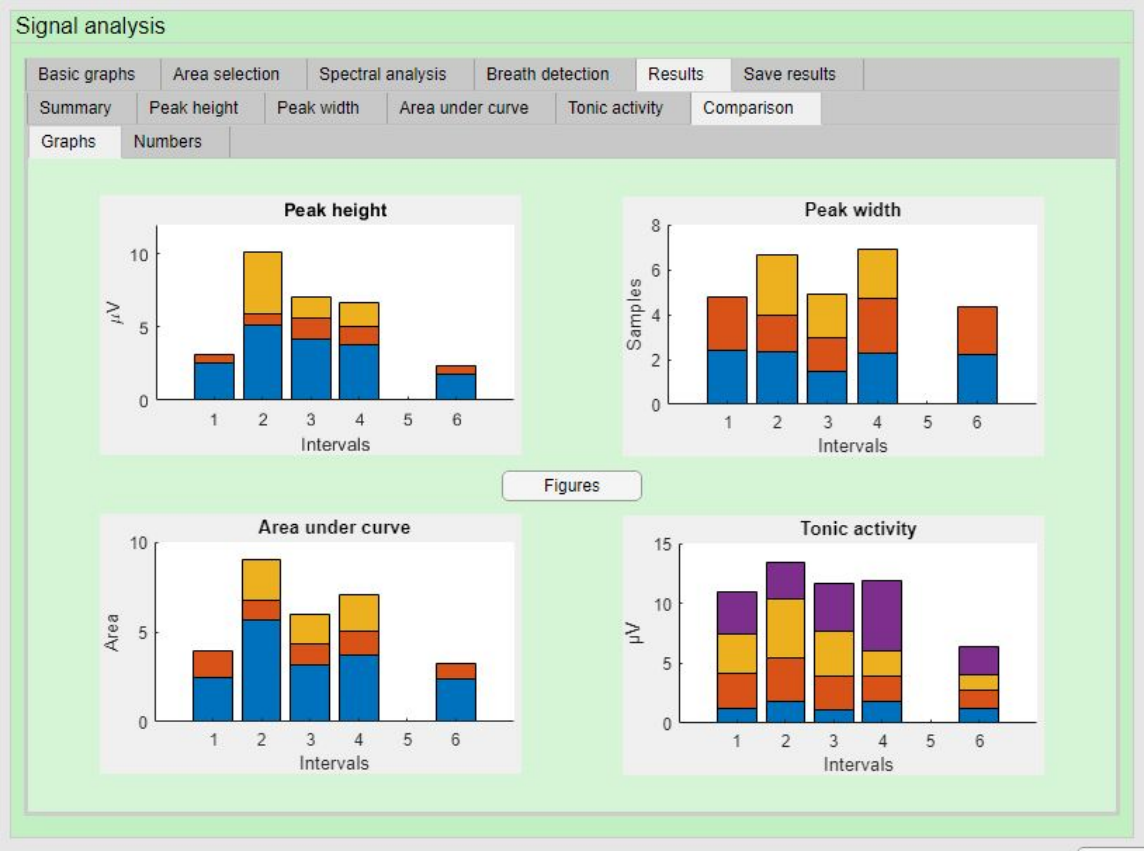

Figure 35: *Overview of the results pane. The comparison pane shown in the figure summarises the other panes, in which the individual timeframes are displayed in tables. Blue represents the diaphragm, orange the intercostal muscles, yellow the sternocleidomastoid muscles and purple the trapezoid muscles.*

B Frequency deletion

Initial analysis of breathing patterns at the diaphragm displayed a peak in the frequency spectrum at about twice the respiratory frequency (Figure 36). For the purpose of this study the second frequency was removed from the signal.

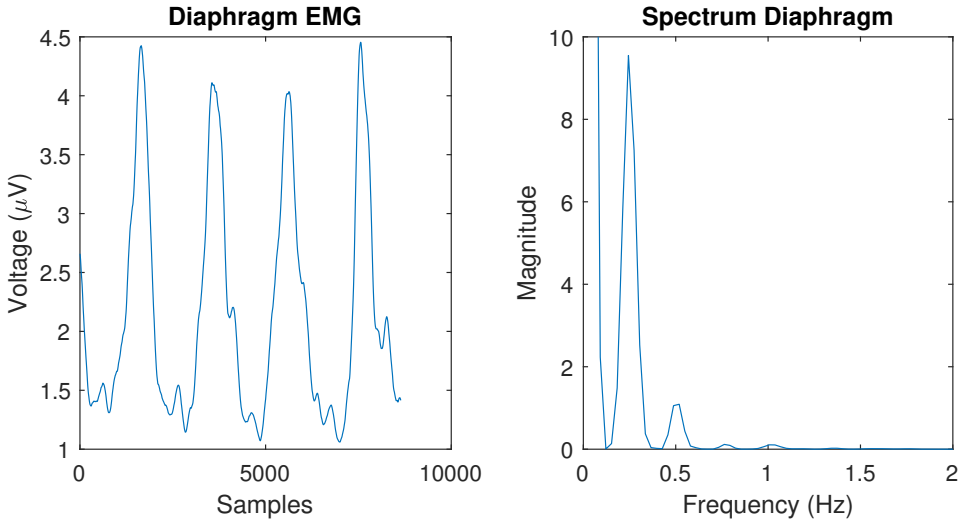

Figure 36: *Fraction of a measurement performed in a healthy adult control of the diaphragm. The frequency spectrum on the right displays a second peak around 0.5Hz.*

B.1 Harmonics

The presence of a frequency in a multitude of the respiratory frequency was at first thought to be the second harmonic of the respiratory frequency. The signal however was not found to be a fraction of the magnitude of the respiratory frequency in all measurements. Medical professionals suggested the frequency may be originating from the abdominal muscles.

B.2 Analysis of external obliques and rectus abdominal muscles

To compare the data measured at the diaphragm, measurements of the rectus abdominal and external oblique muscles were measured in 4 adults. Measurements of the abdominal muscles displayed similar frequency spectra, indicating the second peak may be a sign of abdominal muscle activity (Figure 37). Figures 36 and 37 are recordings of the same subject at the same timeframe. At this time it is unclear whether the found disturbance originates from the abdominal muscles or whether it is a harmonic and that we are looking at a sinc function in the frequency spectrum. The frequency was not visible in every measurement within the patient population, and has for uniformity reasons been filtered in

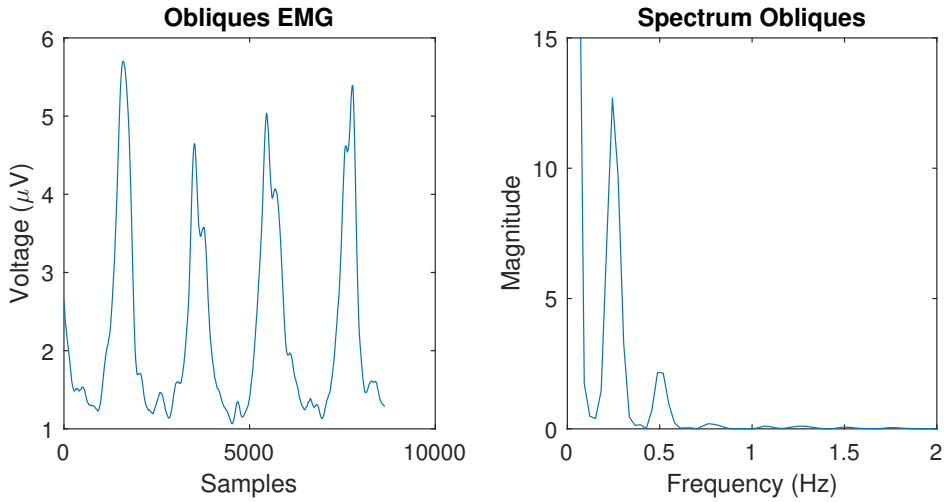

Figure 37: *Fraction of a measurement performed in a healthy adult control of the external oblique muscles. Similar to the measurement at the diaphragm the second peak at about twice the respiratory frequency is visible.*

each occurrence. Further research is advised to comprehend the origins of the sometimes visible frequency at about twice the respiratory frequency.

C Additional population characteristics

Table 17: *Overview of the measured baseline parameters in all patients. The diagnosis was made by the pediatrician supervising the exercise challenge test. Possible diagnosis were controlled asthma (C), uncontrolled asthma (U), upper airway inflammation (A) and dysfunctional breathing (D). Patient 26 was suffering from a severe asthma exacerbation and did not receive an ECT.*

Pat nr.	**Age**	**Sex**	**Length (cm)**	**Weight (kg)**	**Drop in FEV_1 (%)**	**Reversibility (%)**	**Diagnosis**	**Allergy**	**Use of ICs**	**Use of SABA**
1	9.9	Male	139	31	10.06	5.59	C	True	True	True
2	7.7	Male	125	23	3.16	5.06	C	True	True	True
3	8.2	Male	151	51	14.72	36.20	U	True	True	True
4	9.8	Female	152	36	6.98	-0.39	D	False	False	True
5	12.9	Male	175	48	6.91	1.64	D	False	False	False
6	17.4	Male	184	82	1.84	-1.61	C	False	False	False
7	9.2	Female	145	35	8.88	11.24	D	False	False	False
8	9.6	Female	156	44	0	3.18	D	False	True	True
9	7.4	Male	129	25	30.19	32.08	U	False	True	True
10	17.3	Male	180	72	16.37	2.81	U	False	False	False
11	16.9	Female	181	62	18.59	4.46	U	True	True	True
12	17.4	Male	179	62	20.92	-5.61	U	True	True	True
13	16.4	Male	177	75	11.35	-5.21	A	True	False	True
14	10.8	Male	144	33	12.25	-3.92	A	True	False	True
15	12.5	Female	139	38	5.84	2.19	A	True	False	True
16	9.1	Male	135	34	5.15	1.03	A	True	True	True
17	10.5	Male	137	34	8.78	12.20	U	True	False	False
18	9.3	Male	134	23	15.12	11.63	U	False	False	False
19	15.3	Male	175	50	7.41	-3.70	C	True	True	False
20	10.5	Male	140	38	23.13	5.00	U	True	True	True
21	13.0	Male	168	82	3.66	5.28	C	True	True	True
22	12.4	Male	158	54	7.04	4.93	A	True	False	True
23	11.7	Male	147	35	34.74	-2.63	U	True	True	True
24	10.4	Male	139	32	14.08	-4.69	A	True	False	False
25	9.5	Male	140	48	67.25	22.81	U	True	True	True

Pat nr.	**Age**	**Sex**	**Length (cm)**	**Weight (kg)**	**Drop in FEV_1 (%)**	**Reversibility (%)**	**Diagnosis**	**Allergies**	**Use of ICs**	**Use of SABA**
26	11	Female	147	48	No test	32.79	U	True	True	True
27	9.5	Male	141	30	24.82	20.57	U	True	True	False
28	10.8	Male	137	31	2.80	1.87	C	True	True	True
29	13.0	Female	153	53	19.40	6.34	U	False	True	True
30	12.9	Male	127	29	5.80	10.87	C	True	True	True
31	13.3	Male	161	47	8.58	-3/36	C	True	True	True
32	15.0	Male	172	65	31.48	-20.37	U	True	True	True
33	10.9	Male	150	42	5.20	3.60	C	True	True	True
34	6.7	Male	124	23	35.25	5.74	U	False	True	True
35	14.5	Male	175	60	26.98	-7.41	U	False	True	True
36	15.6	Male	181	59	31.96	6.16	U	True	False	True
37	15.8	Female	173	63	9.33	1.60	A	True	False	True
38	9.2	Male	134	31	11.30	1.69	C	True	True	True
39	15.3	Male	188	102	9.64	-5.66	A	True	False	False
40	15.3	Female	166	74	8.92	9.67	D	False	True	True
41	12.0	Male	131	29	17.06	6.47	U	True	True	True
42	17.9	Male	181	58	0	4.01	C	False	True	True
43	9.1	Male	140	38	12.68	6.10	A	True	False	False
44	17.0	Female	178	59	0	1.67	D	False	False	False
45	15.4	Male	167	67	14.81	-6.67	U	True	False	False
46	8.1	Male	140	33	1.87	0.00	A	True	False	False
47	11.1	Female	146	43	5.24	3.66	C	False	False	True
48	14.9	Female	160	59	27.89	3.16	U	True	True	False
49	12.9	Male	162	68	8.51	2.13	C	True	True	False
50	11.7	Female	155	45	17.76	1.97	U	True	True	True

Table 18: *Overview of measured parameters at baseline tested for normality using the Shapiro-Wilk test. Significance values marked with an asterisk are found to be statistically significantly different from a normal distribution. The available data for the trapezoid muscles were found to be too small to compute a test of normality*

Muscle group	**Parameter**	**Diagnosis**	**Significance**
Diaphragm	Height	Controlled (n=23)	0.01*
		Uncontrolled (n=20)	0.02*
	Width	Controlled	< 0.01*
		Uncontrolled	0.03*
	AUC	Controlled	0.05
		Uncontrolled	< 0.001*
	Tonic activity	Controlled	< 0.001*
		Uncontrolled	< 0.01*
Intercostal	Height	Controlled (n=11)	0.21
		Uncontrolled (n=11)	< 0.01*
	Width	Controlled	0.29
		Uncontrolled	0.07
	AUC	Controlled	0.05*
		Uncontrolled	< 0.01*
	Tonic activity	Controlled	0.08
		Uncontrolled	< 0.01*
Sternocleido.	Height	Controlled (n=7)	0.34
		Uncontrolled (n=10)	< 0.001*
	Width	Controlled	0.76
		Uncontrolled	0.20
	AUC	Controlled	0.02*
		Uncontrolled	< 0.01*
	Tonic activity	Controlled	0.17
		Uncontrolled	0.17
Trapezoid	Height	Controlled (n=2)	
		Uncontrolled (n=4)	0.41

Trapezoid	Width	Controlled	
		Uncontrolled	0.89
	AUC	Controlled	
		Uncontrolled	0.67
	Tonic activity	Controlled	
		Uncontrolled	0.03*

Table 19: *Overview of distributions of all baseline parameters. Controlled versus uncontrolled asthma patients do not display any statistically significant differences on all parameters based upon the Mann-Whitney-U test.*

Muscle group	**Parameter**	**Diagnosis**	**Median**	**IQR**	**Significance**
Diaphragm	Height	Controlled	1.72	0.97-2.62	0.45
		Uncontrolled	1.99	1.20-2.91	
	Width	Controlled	3.35	3.68-2.72	0.34
		Uncontrolled	2.98	2.05-3.41	
	AUC	Controlled	2.63	3.90-1.43	0.30
		Uncontrolled	3.32	1.64-6.37	
	Tonic	Controlled	1.62	2.04-1.39	0.48
		Uncontrolled	1.92	1.31-2.40	
Intercostal	Height	Controlled	1.54	0.64-1.87	0.67
		Uncontrolled	0.95	0.73-1.29	
	Width	Controlled	2.67	3.21-2.27	0.67
		Uncontrolled	3.35	1.94-3.88	
	AUC	Controlled	2.04	2.30-1.13	0.92
		Uncontrolled	1.86	0.97-3.05	
	Tonic	Controlled	2.07	4.39-2.12	0.26
		Uncontrolled	2.16	1.90-2.80	
Sternocleido	Height	Controlled	1.26	0.73-1.77	0.85
		Uncontrolled	0.98	0.70-1.58	
	Width	Controlled	3.31	3.41-2.57	0.85
		Uncontrolled	3.43	2.46-4.27	
	AUC	Controlled	2.13	2.86-1.53	0.44
		Uncontrolled	1.72	0.83-7.19	
	Tonic	Controlled	2.61	3.09-2.06	0.64
		Uncontrolled	2.69	2.08-4.25	

Trapezoid	Height	Controlled	1.18	0.75-1.61	1.00
		Uncontrolled	1.11	0.71-2.04	
	Width	Controlled	3.24	4.03-2.44	0.64
		Uncontrolled	3.45	2.33-4.58	
	AUC	Controlled	1.94	1.06-2.83	0.63
		Uncontrolled	4.40	9.21-1.64	
	Tonic	Controlled	2.39	2.62-2.15	0.81
		Uncontrolled	3.66	3.20-3.72	

D Additional figures and tables results

Table 20: *Overview of the Mann-Whitney-U results on changes in diaphragm parameters at the point of lowest spirometry. Statistically significant increases in peak height and area under the curve, both absolute and relative, were found for uncontrolled asthma patients when compared to controlled asthma patients, as well as a statistically significant relative peak width decrease in controlled asthma patients compared to uncontrolled asthma patients.*

Parameter	**Diagnosis**	**Median**	**IQR**	**Significance**
Height	Controlled	0.20	0.54-(-0.10)	<0.001
	Uncontrolled	4.85	1.82-7.84	
Width	Controlled	-0.68	(-0.05)-(-1.10)	0.058
	Uncontrolled	-0.21	(-0.57)-0.99	
AUC	Controlled	-0.25	0.47-(-0.87)	<0.001
	Uncontrolled	4.53	1.98-13.46	
Tonic	Controlled	0.21	0.72-(-0.52)	0.436
	Uncontrolled	-0.06	-0.82-0.33	
Height %	Controlled	12.40	57.42-(-6.02)	<0.001
	Uncontrolled	204.22	111.16-533.63	
Width %	Controlled	-21.42	(-1.41)-(-29.87)	0.018
	Uncontrolled	-8.56	-18.04-39.49	
AUC %	Controlled	-12.20	-24.61-34.01	<0.001
	Uncontrolled	137.79	24.65-577.04	
Tonic %	Controlled	13.31	-27.42-50.42	0.406
	Uncontrolled	-4.90	-53.16-28.57	

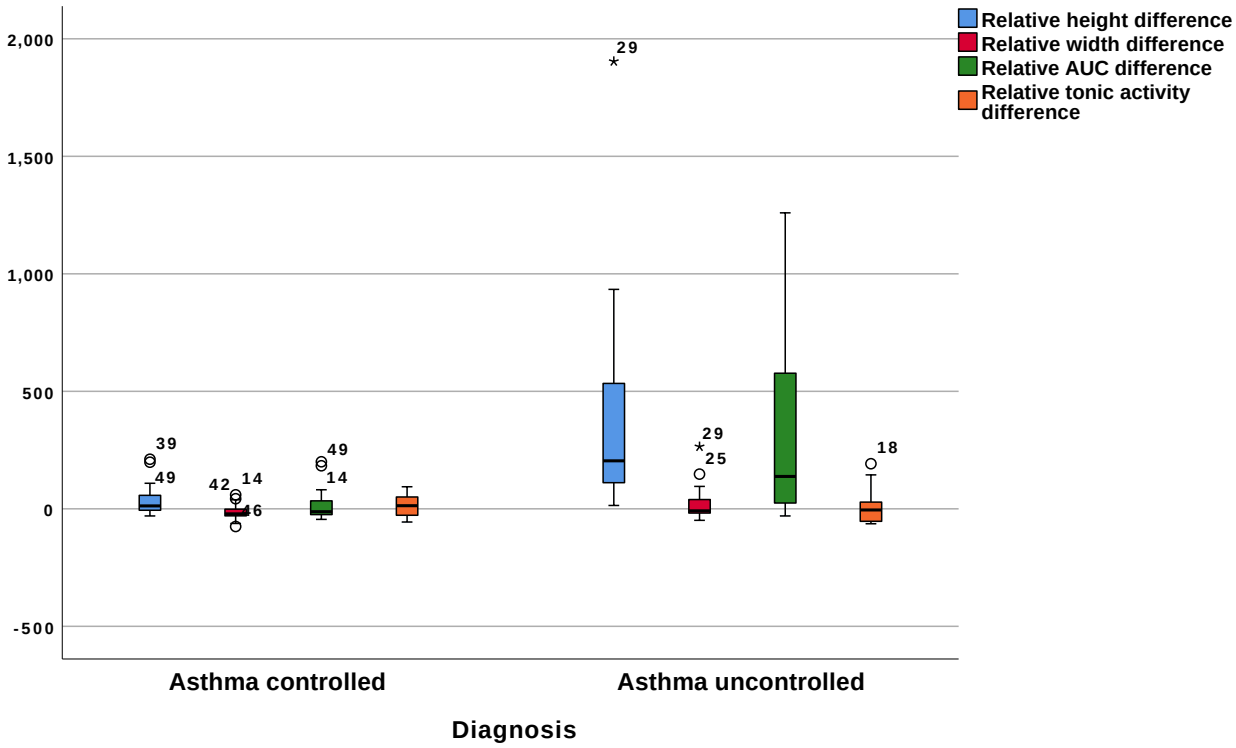

Figure 38: *Overview of relative changes in parameters of the diaphragm activity at timeframe of lowest FEV_1 on spirometry when compared to baseline measurements. Outliers are displayed as circles, extreme values (Defined as outside 1.5 times the interquartile range) are displayed as asterisks.*

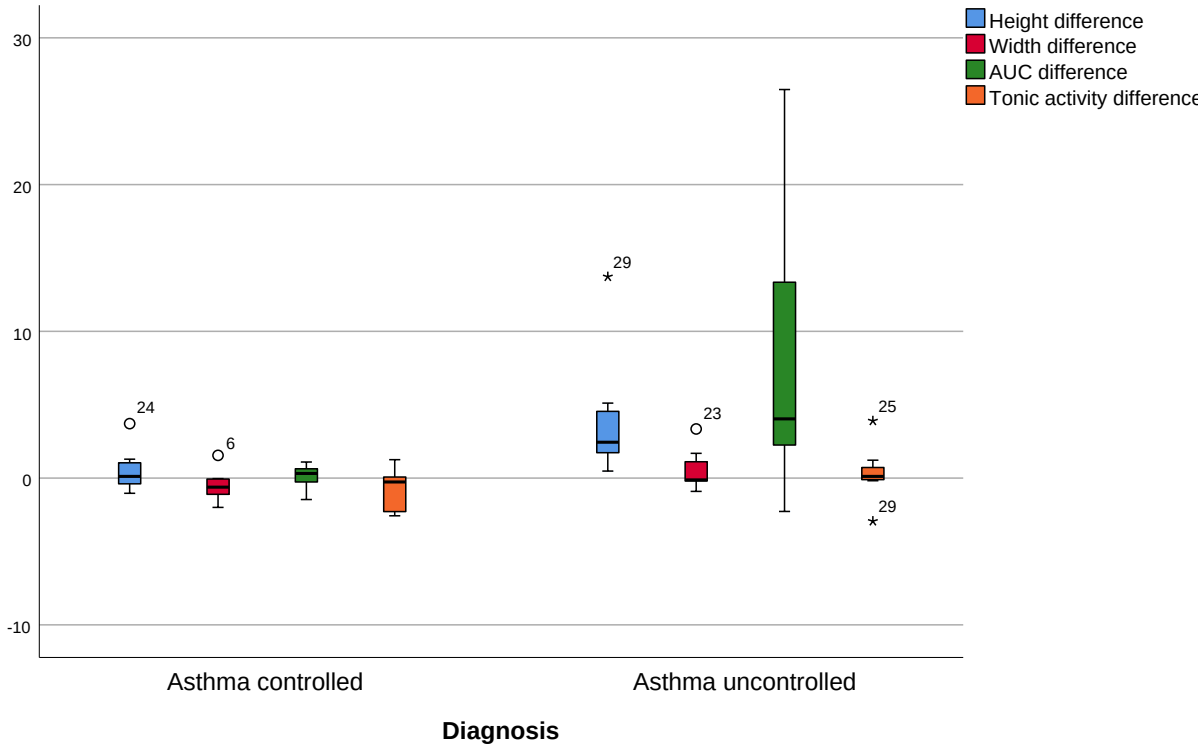

Figure 39: *Overview of changes in parameters of the intercostal muscle activity at timeframe of lowest FEV_1 on spirometry when compared to baseline measurements. Outliers are displayed as circles, extreme values (Defined as outside 1.5 times the interquartile range) are displayed as asterisks.*

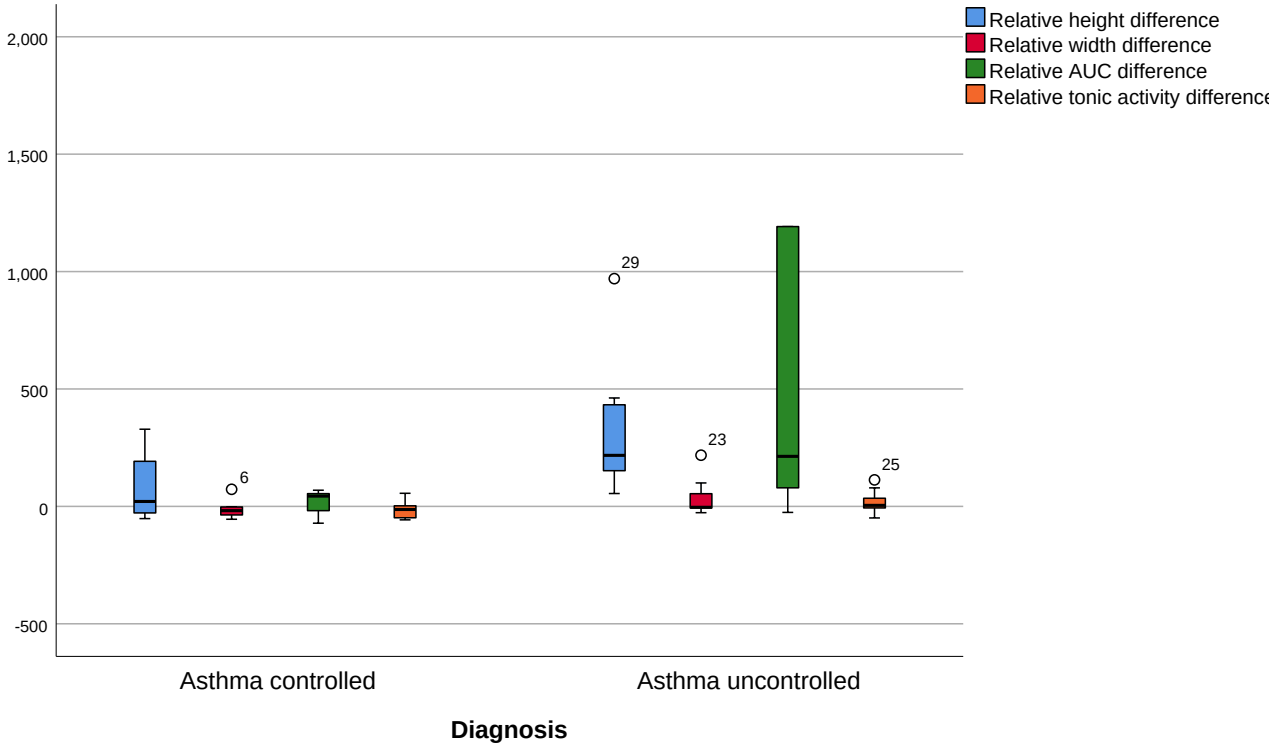

Figure 40: *Overview of the relative changes in parameters of the intercostal muscle activity at timeframe of lowest FEV_1 on spirometry when compared to baseline measurements. Outliers are displayed as circles, extreme values (Defined as outside 1.5 times the interquartile range) are displayed as asterisks. Extreme values of patient 29 outside the 2000% range were not displayed at the area under the curve box for readability.*

Table 21: *Overview of the Mann-Whitney-U results on changes in intercostal muscle parameters at the point of lowest spirometry. Statistically significant increases in peak height and area under the curve, both absolute and relative, were found for uncontrolled asthma patients when compared to controlled asthma patients.*

Parameter	**Diagnosis**	**Median**	**IQR**	**Significance**
Height	Controlled	0.12	-0.39-1.04	0.023
	Uncontrolled	2.44	1.73-4.55	
Width	Controlled	-0.62	-1.11-(-0.06)	0.223
	Uncontrolled	-0.12	-0.20-1.11	
AUC	Controlled	0.32	-0.26-0.63	0.017
	Uncontrolled	4.03	2.25-13.35	
Tonic	Controlled	-0.26	-2.28-0.07	0.968
	Uncontrolled	0.12	-0.11-0.72	
Height %	Controlled	20.86	-27.86-191.91	0.030
	Uncontrolled	217.37	151.95-432.67	
Width %	Controlled	-18.17	-2.60-36.52	0.186
	Uncontrolled	-3.89	-6.81-53.97	
AUC %	Controlled	43.68	-18.17-54.24	0.023
	Uncontrolled	213.05	78.99-1191.61)	
Tonic %	Controlled	-13.23	2.37-(-48.51)	0.797
	Uncontrolled	4.34	-6.66-34.69	

Table 22: *Overview of the Mann-Whitney-U results on the measured parameters in the sternocleidomastoid muscles at the point of lowest spirometry. The peak height, area under curve and tonic activity was found to be statistically significantly higher in uncontrolled asthma patients when compared to controlled asthma patients*

Parameter	**Diagnosis**	**Median**	**IQR**	**Significance**
Height	Controlled	0.95	0.69-1.22	<0.001
	Uncontrolled	4.90	3.09-7.08	
Width	Controlled	2.95	2.26-3.24	0.520
	Uncontrolled	2.84	2.35-3.91	
AUC	Controlled	1.40	0.96-1.59	<0.001
	Uncontrolled	7.10	4.25-17.50	
Tonic	Controlled	2.24	1.70-3.03	0.037
	Uncontrolled	3.35	2.63-4.89	

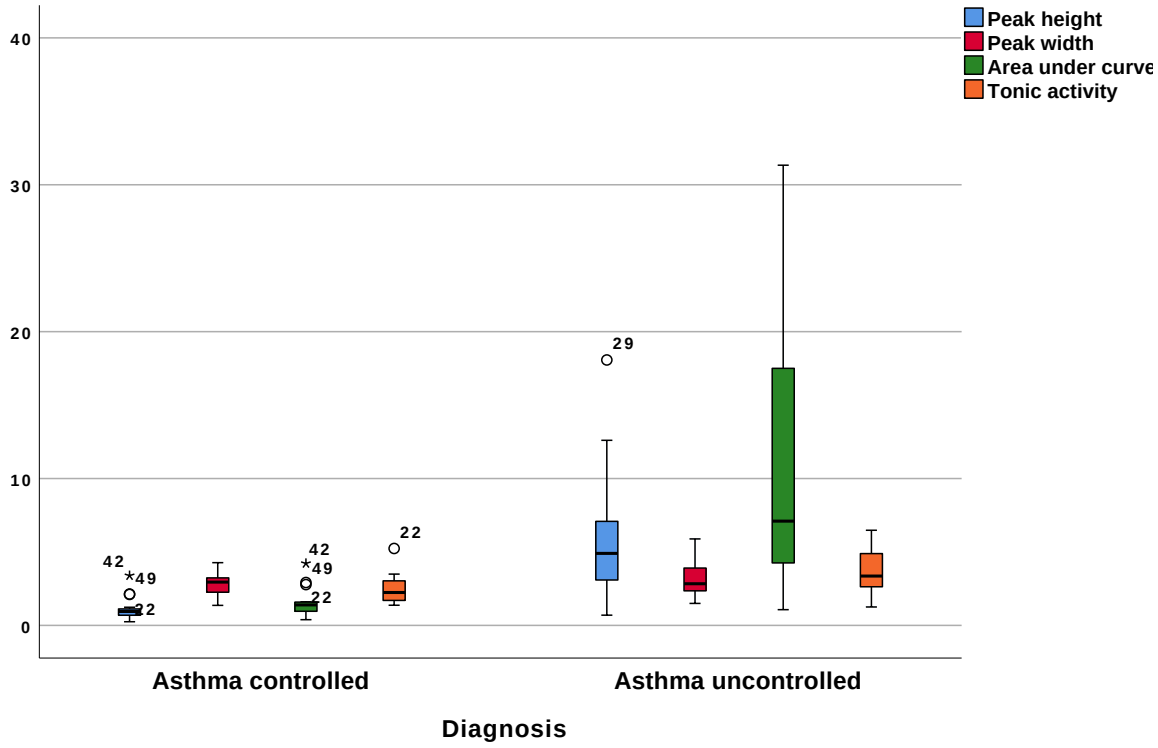

Figure 41: *Overview of parameters measured from the sternocleidomastoid muscles at the timeframe of lowest FEV_1. Outliers are displayed as circles, extreme values (Defined as 1.5 times the interquartile range) are displayed as asterisks.*

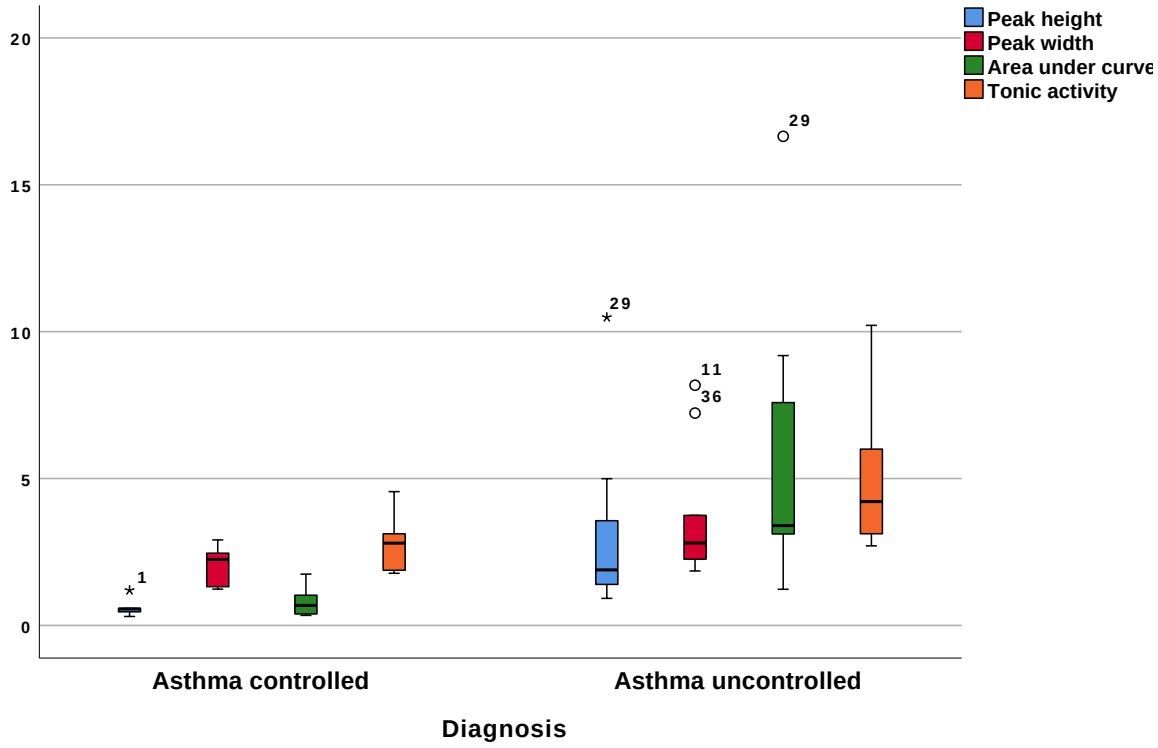

Figure 42: *Overview of parameters measured from the trapezoid muscles at the timeframe of lowest FEV_1. Outliers are displayed as circles, extreme values (Defined as 1.5 times the interquartile range) are displayed as asterisks.*

Table 23: *Overview of the Mann-Whitney-U results on the measured parameters in the trapezoid muscles at the point of lowest spirometry. The peak height, area under curve and tonic activity was found to be statistically significantly higher in uncontrolled asthma patients when compared to controlled asthma patients.*

Parameter	**Diagnosis**	**Median**	**IQR**	**Significance**
Height	Controlled	0.56	0.38-0.86	0.004
	Uncontrolled	1.89	1.26-4.28	
Width	Controlled	2.25	1.32-2.46	0.147
	Uncontrolled	2.80	2.25-3.75	
AUC	Controlled	0.68	0.39-1.03	0.002
	Uncontrolled	3.40	3.11-7.58	
Tonic	Controlled	2.80	1.88-3.12	0.032
	Uncontrolled	4.21	3.12-6.00	

Table 24: *Overview of the ideal cut-off values of the ROC curves of the changes in significant diaphragm parameters.*

Muscle group	**Parameter**	**Cut-off**	**Sens/spec**	**AUC**
Intercostal	Height	$1.69\mu V$	77.8%/90.9%	0.859
	Relative height	145.87%	88.9%/65.6%	0.828
	Area under curve	0.62	88.9%/65.6%	0.818
	Relative area under curve	73.9%	77.8%/81.8%	0.778

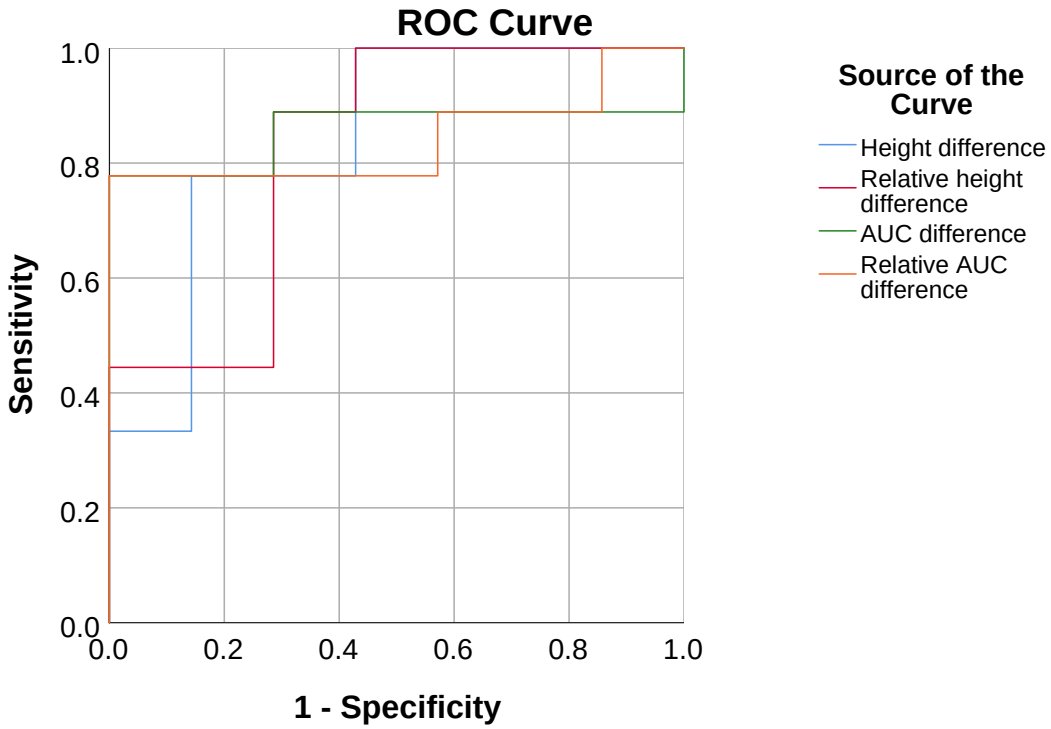

Figure 43: *Receiver operator characteristic curves of the statistically significant parameters found in the intercostal muscle measurements. The largest area under curve was found for the area under curve difference at 0.857.*

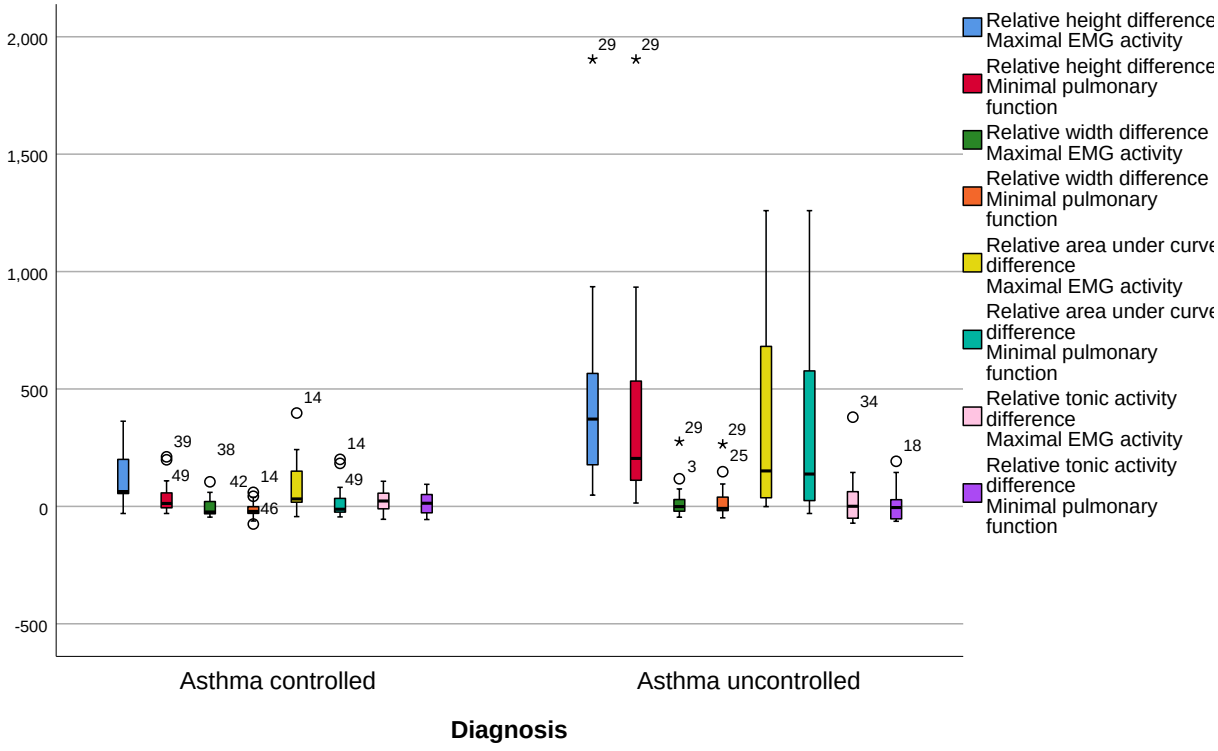

Figure 44: *Overview of the relative changes in parameters of the diaphragm activity at timeframe of maximal amplitude of the diaphragm on EMG when compared to baseline measurements. Outliers are displayed as circles, extreme values (Defined as outside 1.5 times the interquartile range) are displayed as asterisks. Extreme values of patients 23 and 29 above the 2000% range at the relative AUC difference were not displayed for readability.*

Table 25: *Overview of the Mann-Whitney-U results on the changes in diaphragm parameters at the point of maximal diaphragm amplitude on EMG. Statistically significant increases in peak height and area under the curve, both absolute and relative, were found for uncontrolled asthma patients when compared to controlled asthma patients.*

Parameter	**Diagnosis**	**Median**	**IQR**	**Significance**
Height	Controlled	1.20	0.86-2.33	<0.001
	Uncontrolled	8.29	3.96-10.60	
Width	Controlled	-0.78	-1.18-0.45	0.28
	Uncontrolled	0.03	-0.88-0.87	
AUC	Controlled	1.03	0.20-3.23	<0.001
	Uncontrolled	8.06	2.34-16.23	
Tonic	Controlled	0.34	-0.19-0.94	0.26
	Uncontrolled	-0.01	-0.96-0.96	
Height %	Controlled	63.19	-54.61-200.20	<0.001
	Uncontrolled	371.77	177.24-566.24	
Width %	Controlled	-23.29	-31.59-(-20.62)	0.14
	Uncontrolled	-0.91	-20.49-29.20	
AUC %	Controlled	31.76	17.69-150.06	0.01
	Uncontrolled	150.98	36-77-681.40	
Tonic %	Controlled	22.84	-10.33-56.18	0.29
	Uncontrolled	0.46	-50.44-62.71	

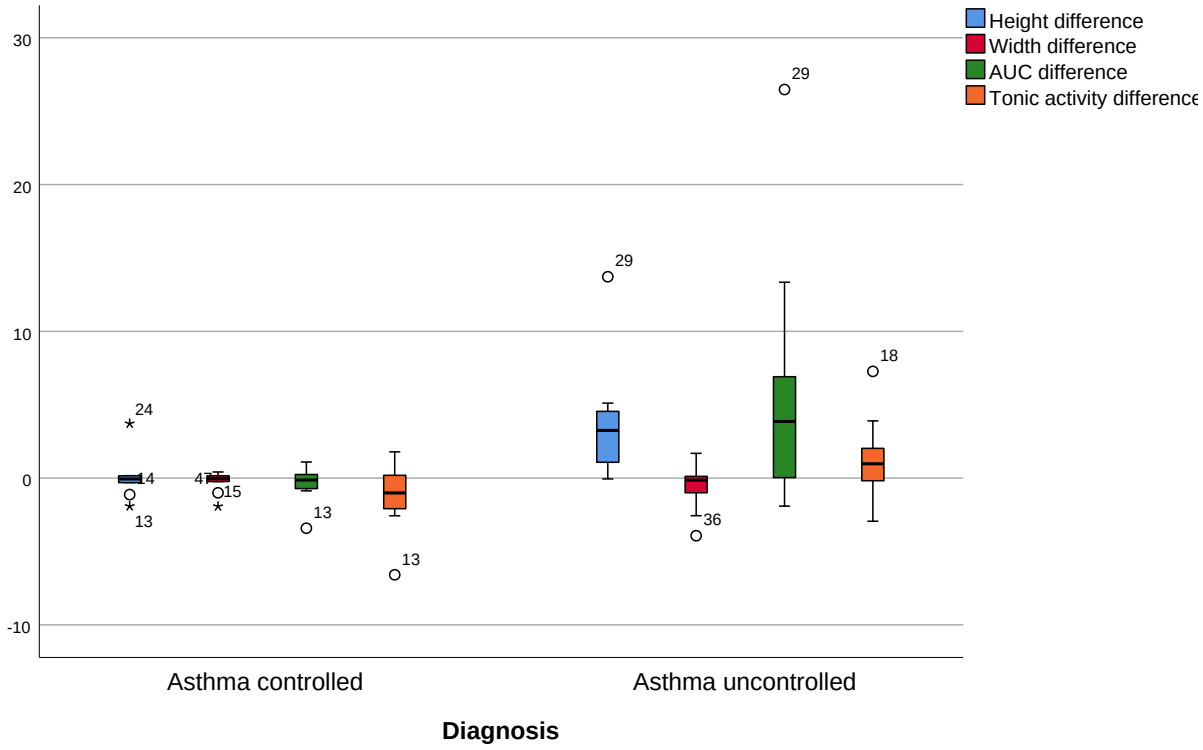

Figure 45: *Overview of changes in parameters of the intercostal muscle activity at timeframe of maximal amplitude of the diaphragm on EMG when compared to baseline measurements. Outliers are displayed as circles, extreme values (Defined as outside 1.5 times the interquartile range) are displayed as asterisks.*

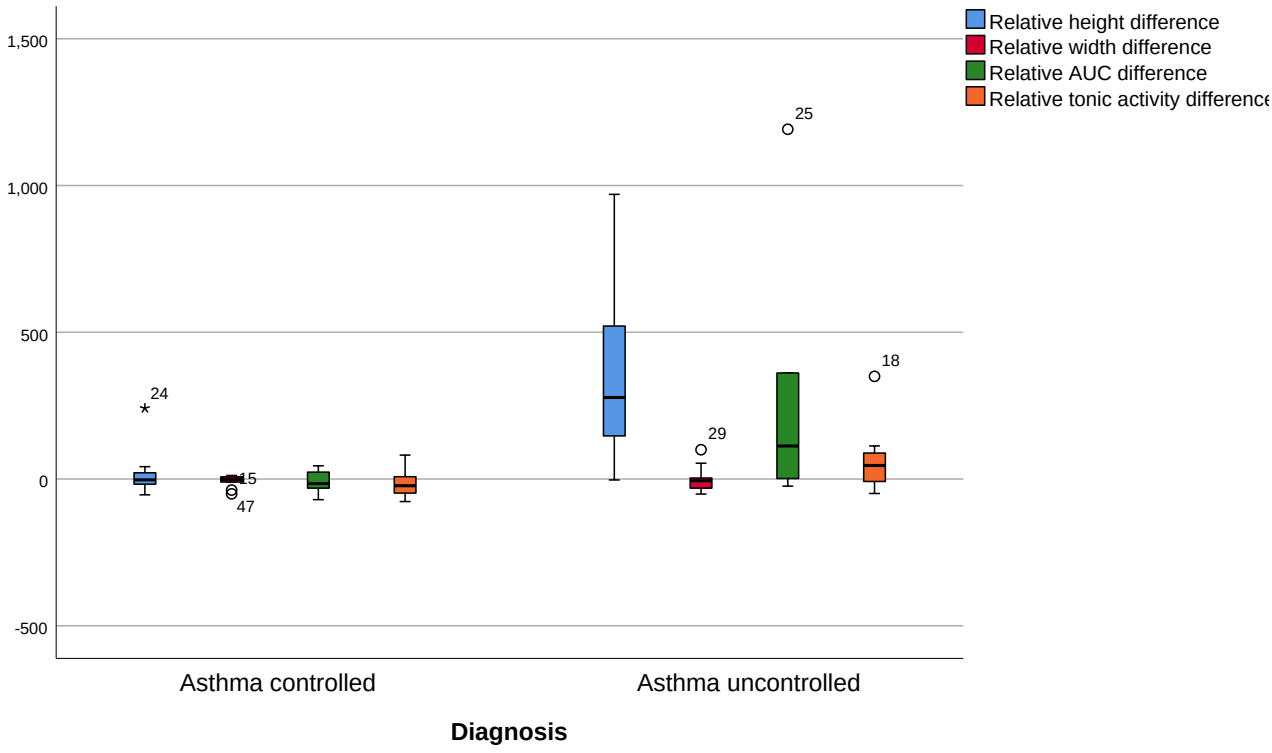

Figure 46: *Overview of the relative changes in parameters of the intercostal muscle activity at timeframe of maximal amplitude of the diaphragm on EMG when compared to baseline measurements. Outliers are displayed as circles, extreme values (Defined as outside 1.5 times the interquartile range) are displayed as asterisks. Extreme values of patient 29 above the 1500% range at the relative AUC difference were not displayed for readability.*

Table 26: *Overview of the Mann-Whitney-U results on the changes in intercostal muscle parameters at the point of maximal diaphragm amplitude on EMG. Statistically significant increases in peak height and area under the curve, both absolute and relative, were found for uncontrolled asthma patients when compared to controlled asthma patients.*

Parameter	**Diagnosis**	**Median**	**IQR**	**Significance**
Height	Controlled	-0.06	-0.31-0.15	$P < 0.01$
	Uncontrolled	3.25	1.08-4.55	
Width	Controlled	-0.04	-0.24-0.16	0.62
	Uncontrolled	-0.14	-1.00-0.12	
AUC	Controlled	-0.13	-0.72-0.25	0.02
	Uncontrolled	3.86	0.03-6.91	
Tonic	Controlled	-1.01	-2.09-0.19	0.07
	Uncontrolled	0.97	-0.18-2.03	
Height %	Controlled	-2.94	-17.60-21.29	$P < 0.01$
	Uncontrolled	277.79	146.88-521.24	
Width %	Controlled	-1.93	-10.17-7.21	0.74
	Uncontrolled	-5.94	-30.79-3.42	
AUC %	Controlled	-15.50	-30.97-23.55	0.02
	Uncontrolled	112.47	1.81-361.35	
Tonic %	Controlled	-22.84	-47.99-7.97	0.06
	Uncontrolled	46.05	-8.37-88.59	

Table 27: *Overview of the Mann-Whitney-U results on the measured parameters in the sternocleidomastoid muscles at the point of maximal EMG amplitude. The peak height and area under curve were found to be statistically significantly higher in uncontrolled asthma patients when compared to controlled asthma patients.*

Parameter	**Diagnosis**	**Median**	**IQR**	**Significance**
Height	Controlled	1.90	0.74-2.08	<0.001
	Uncontrolled	4.70	3.36-8.40	
Width	Controlled	2.81	2.20-3.17	0.160
	Uncontrolled	2.98	2.38-3.88	
AUC	Controlled	1.85	1.34-2.92	<0.001
	Uncontrolled	7.55	4.72-9.23	
Tonic	Controlled	2.28	1.80-3.71	0.063
	Uncontrolled	3.82	2.69-6.14	

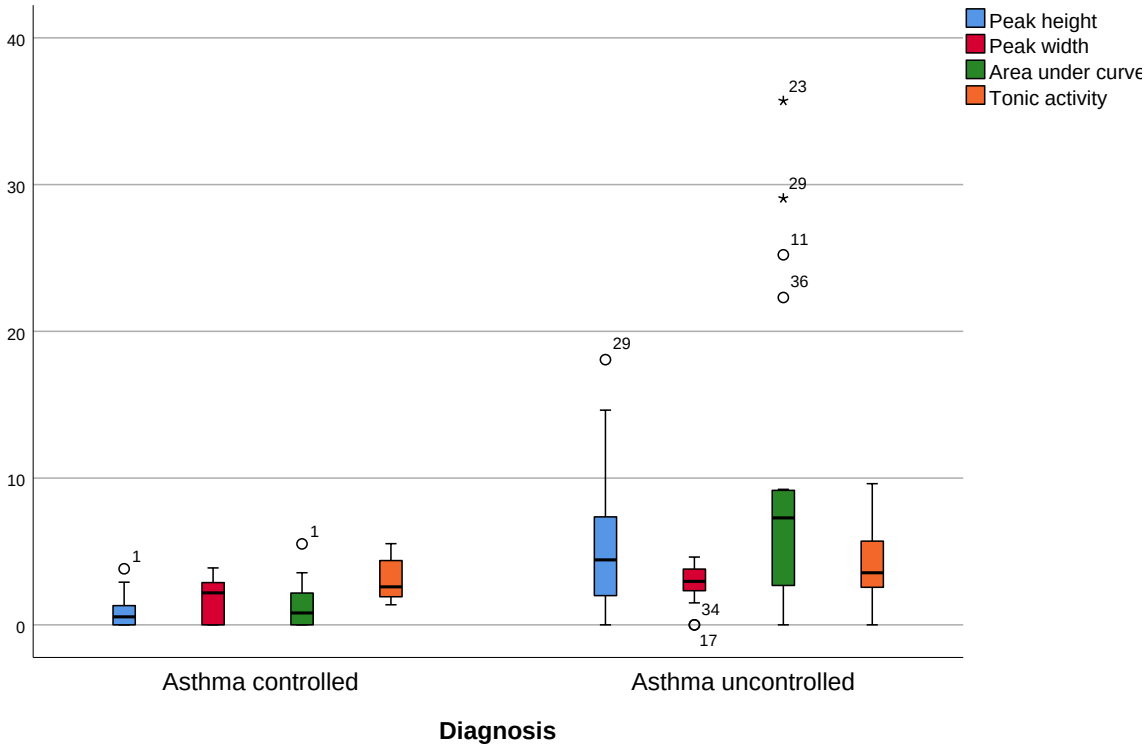

Figure 47: *Overview of the parameters measured at the sternocleidomastoid muscles at the timeframe of maximal EMG amplitude of the diaphragm. Outliers are displayed as circles, extreme values (Defined as outside 1.5 times the interquartile range) are displayed as asterisks.*

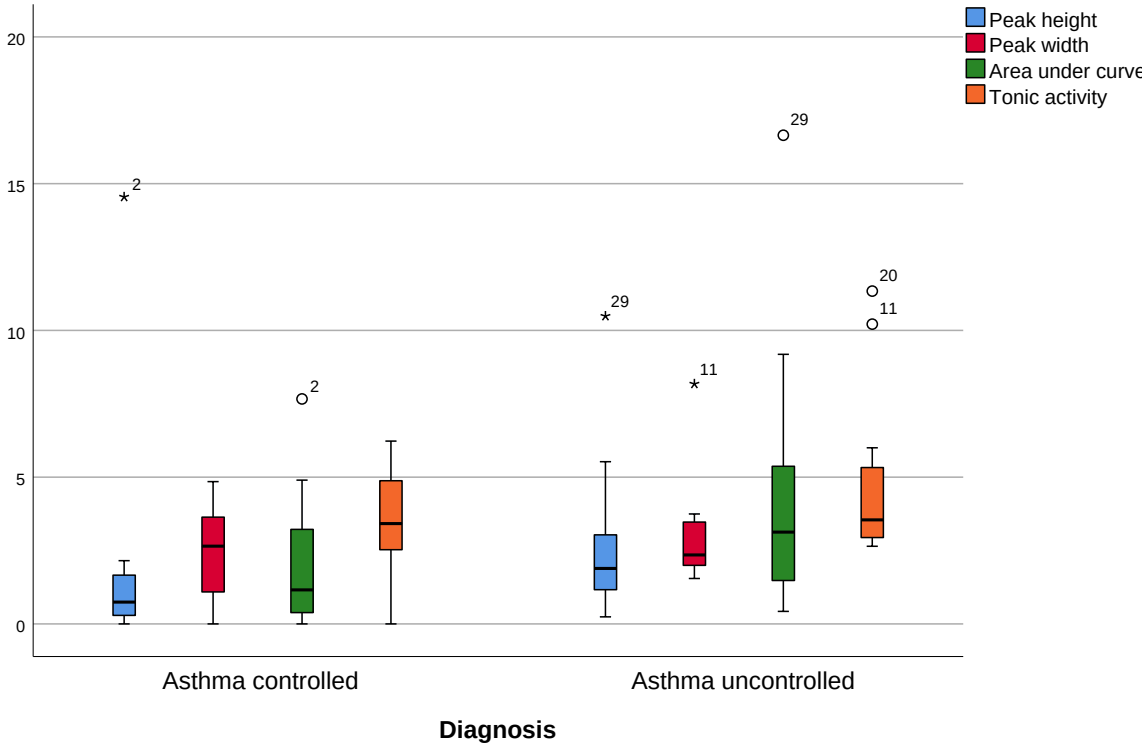

Figure 48: *Overview of the parameters measured at the trapezoid muscles at the timeframe of maximal EMG amplitude of the diaphragm. Outliers are displayed as circles, extreme values (Defined as outside 1.5 times the interquartile range) are displayed as asterisks.*

Table 28: *Overview of the Mann-Whitney-U results on the measured parameters in the trapezoid muscles at the point of maximal EMG amplitude. There area no statistically significant differences at this point.*

Parameter	**Diagnosis**	**Median**	**IQR**	**Significance**
Height	Controlled	0.74	0.29-1.66	0.07
	Uncontrolled	1.89	1.17-3.03	
Width	Controlled	2.65	1.09-3.64	0.84
	Uncontrolled	2.35	2.00-3.47	
AUC	Controlled	1.16	0.39-3.22	0.07
	Uncontrolled	3.13	1.48-5.37	
Tonic	Controlled	3.42	2.53-4.88	0.17
	Uncontrolled	3.54	2.94-5.33	

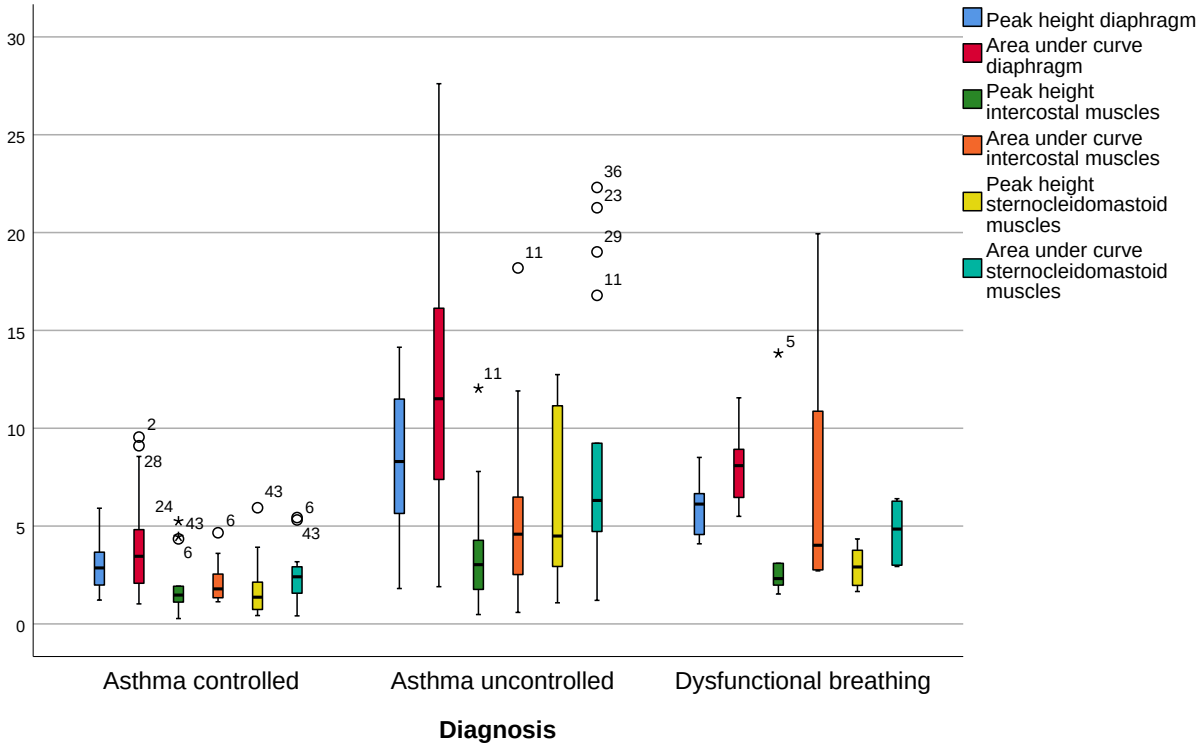

Figure 49: *Overview of the measured parameters at one minute after exercise in all three groups. Outliers are displayed as circles, extreme values (Defined as over 1.5 times the interquartile range) are displayed as asterisks.*

Table 29: *Overview of the results of the Mann-Whitney-U test one minute after exercise. The dysfunctional breathing patients statistically significantly differ from the controlled asthma patients on all measured parameters, but do not statistically significantly differ on any of the measured parameters from the uncontrolled asthma patients. The significance column overlaps in the controlled and dysfunctional group as well as in the dysfunctional and uncontrolled group, indicating two separate comparisons.*

Muscle group	**Parameter**	**Diagnosis**	**Median**	**IQR**	**Significance**
Diaphragm	Height	Controlled	2.86	1.99-3.67	< 0.01
		Dysfunctional	6.12	4.57-6.66	
		Uncontrolled	8.30	5.65-11.49	0.10
	AUC	Controlled	3.46	2.08-4.82	< 0.01
		Dysfunctional	8.09	6.46-8.92	
		Uncontrolled	11.51	7.38-16.13	0.16
Intercostal	Height	Controlled	1.47	1.11-1.93	0.03
		Dysfunctional	2.32	1.98-3.10	
		Uncontrolled	3.03	1.76-4.27	0.75
	AUC	Controlled	1.79	1.34-2.55	< 0.01
		Dysfunctional	4.02	2.76-10.87	
		Uncontrolled	4.59	2.52-6.48	0.75
Sternocleido	Height	Controlled	1.37	0.74-2.13	0.05
		Dysfunctional	2.91	1.97-3.76	
		Uncontrolled	4.49	2.94-11.15	0.16
	AUC	Controlled	2.41	1.57-2.92	< 0.01
		Dysfunctional	4.85	3.00-6.27	
		Uncontrolled	6.31	4.72-9.23	0.23

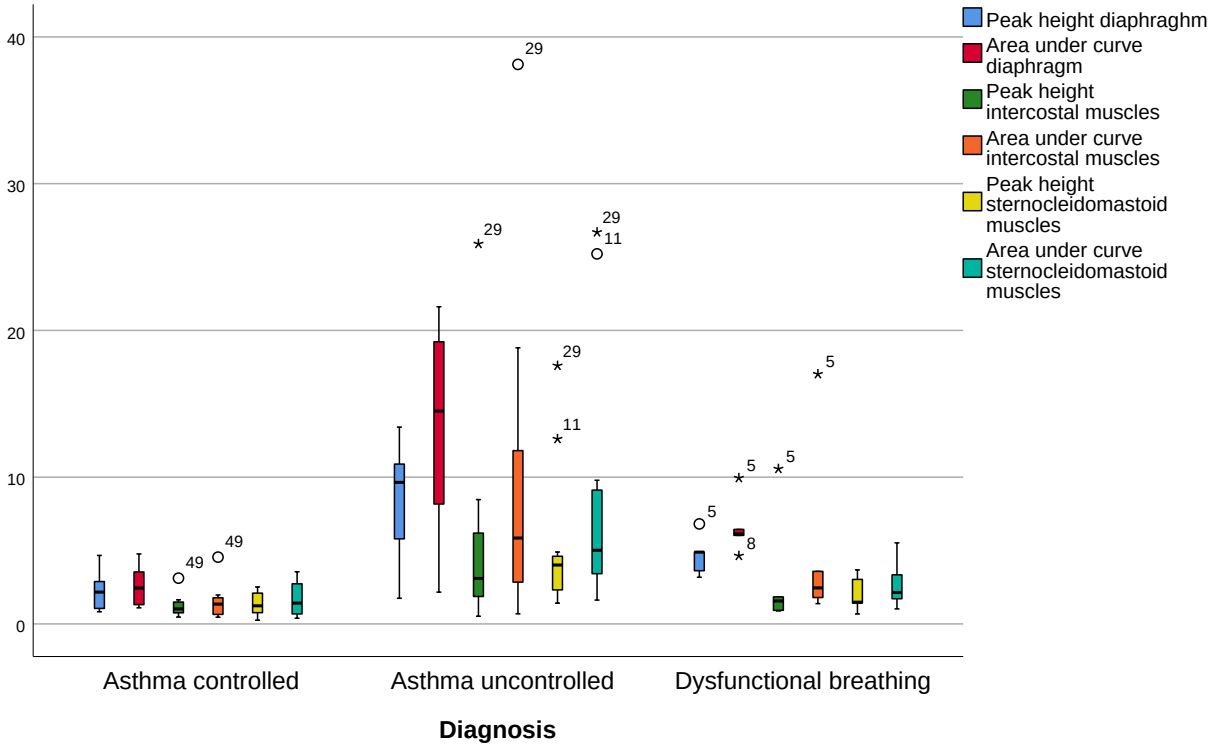

Figure 50: *Overview of the measured parameters at three minutes after exercise in all three groups. Outliers are displayed as circles, extreme values (Defined as over 1.5 times the interquartile range) are displayed as asterisks.*

Table 30: *Overview of the results of the Mann-Whitney-U test three minutes after exercise. The dysfunctional breathing patients statistically significantly differ from the controlled asthma patients at the diaphragm and in area under curve at the intercostal muscles. Dysfunctional breathing patients now also significantly differ from uncontrolled asthma patients in the parameters measured at the diaphragm and sternocleidomastoid muscles. The significance column overlaps in the controlled and dysfunctional group as well as in the dysfunctional and uncontrolled group, indicating two separate comparisons.*

Muscle group	**Parameter**	**Diagnosis**	**Median**	**IQR**	**Significance**
Diaphragm	Height	Controlled	2.59	1.75-3.24	0.03
		Dysfunctional	4.26	3.18-4.90	
					0.03
		Uncontrolled	9.28	5.76-10.89	
	AUC	Controlled	3.40	2.22-3.91	0.02
		Dysfunctional	6.08	4.64-6.44	
					0.03
		Uncontrolled	14.40	7.39-19.23	
Intercostal	Height	Controlled	0.96	0.80-1.48	0.16
		Dysfunctional	1.70	0.92-2.79	
					0.25
		Uncontrolled	3.10	1.86-4.41	
	AUC	Controlled	1.44	0.76-1.61	0.03
		Dysfunctional	3.02	1.80-4.15	
					0.25
		Uncontrolled	4.21	2.81-6.54	
Sternocleido	Height	Controlled	1.21	0.91-1.71	0.13
		Dysfunctional	1.48	1.42-3.03	
					0.05
		Uncontrolled	4.01	2.22-4.90	
	AUC	Controlled	1.38	0.84-2.37	0.13
		Dysfunctional	2.14	1.71-3.35	
					0.03
		Uncontrolled	6.60	3.66-8.45	

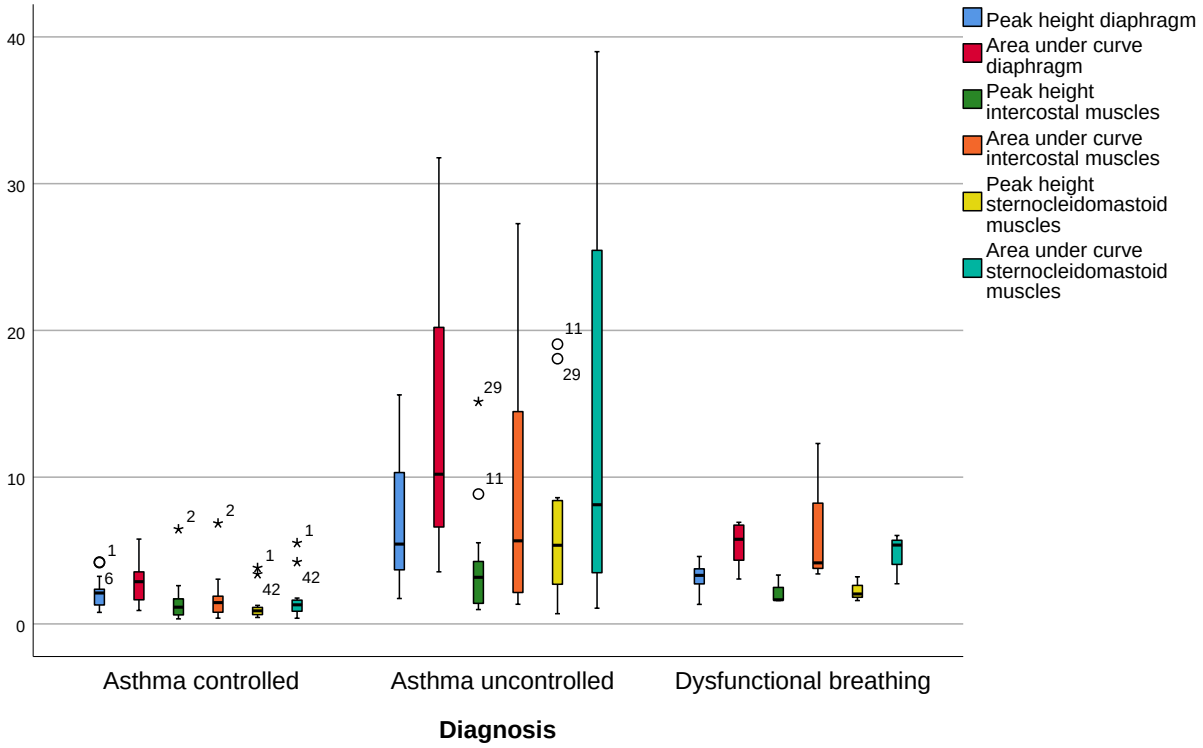

Figure 51: *Overview of the measured parameters at six minutes after exercise in all three groups. Outliers are displayed as circles, extreme values (Defined as over 1.5 times the interquartile range) are displayed as asterisks.*

Table 31: *Overview of the results of the Mann-Whitney-U test six minutes after exercise. The dysfunctional breathing patients statistically significantly differ from the controlled asthma patients for all parameters measured at the diaphragm, as well as the area under curve of the intercostal and sternocleidomastoid muscles. The dysfunctional breathing patients also statistically significantly differ from the uncontrolled asthma patients on all parameters measured at the diaphragm. The significance column overlaps in the controlled and dysfunctional group as well as in the dysfunctional and uncontrolled group, indicating two separate comparisons.*

Muscle group	**Parameter**	**Diagnosis**	**Median**	**IQR**	**Significance**
Diaphragm	Height	Controlled	2.10	1.29-2.36	0.03
		Dysfunctional	3.31	2.73-3.75	0.02
		Uncontrolled	5.44	3.69-10.31	
	AUC	Controlled	2.89	1.64-3.55	< 0.01
		Dysfunctional	5.77	4.34-6.73	0.02
		Uncontrolled	10.20	6.61-20.21	
Intercostal	Height	Controlled	1.14	0.61-1.71	0.23
		Dysfunctional	1.64	1.62-2.49	0.71
		Uncontrolled	3.18	1.40-4.26	
	AUC	Controlled	1.45	0.79-1.89	0.03
		Dysfunctional	4.16	3.78-8.22	0.71
		Uncontrolled	5.66	2.14-14.47	
Sternocleido	Height	Controlled	0.89	0.63-1.13	0.08
		Dysfunctional	2.04	1.82-2.62	0.16
		Uncontrolled	5.36	2.70-8.40	
	AUC	Controlled	1.30	0.86-1.62	0.03
		Dysfunctional	5.37	4.05-5.70	0.31
		Uncontrolled	8.12	3.49-25.46	

Table 32: *Linear regression results of the statistically significant parameters of the intercostal muscles using stepwise regression. The most accurate model was found by only integrating the relative peak height difference into the model.*

Parameter	**Pearson**	**Significance**
Peak height difference	0.41	0.186
Area under curve difference	0.47	0.949
Relative peak height difference	0.56	< 0.001
Relative area under curve difference	0.35	0.427

Table 33: *Overview of the ideal cut-off values of the ROC curves of the changes in significant intercostal muscle parameters.*

Muscle group	**Parameter**	**Cut-off**	**Sens/spec**	**AUC**
Intercostal	Height	$0.32\mu V$	90.0%/88.9%	0.90
	Relative height	48.48%	90.0%/88.9%	0.91
	Area under curve	0.01	80%/66.7%	0.78
	Relative area under curve	0.12%	80.0%/66.7%	0.81

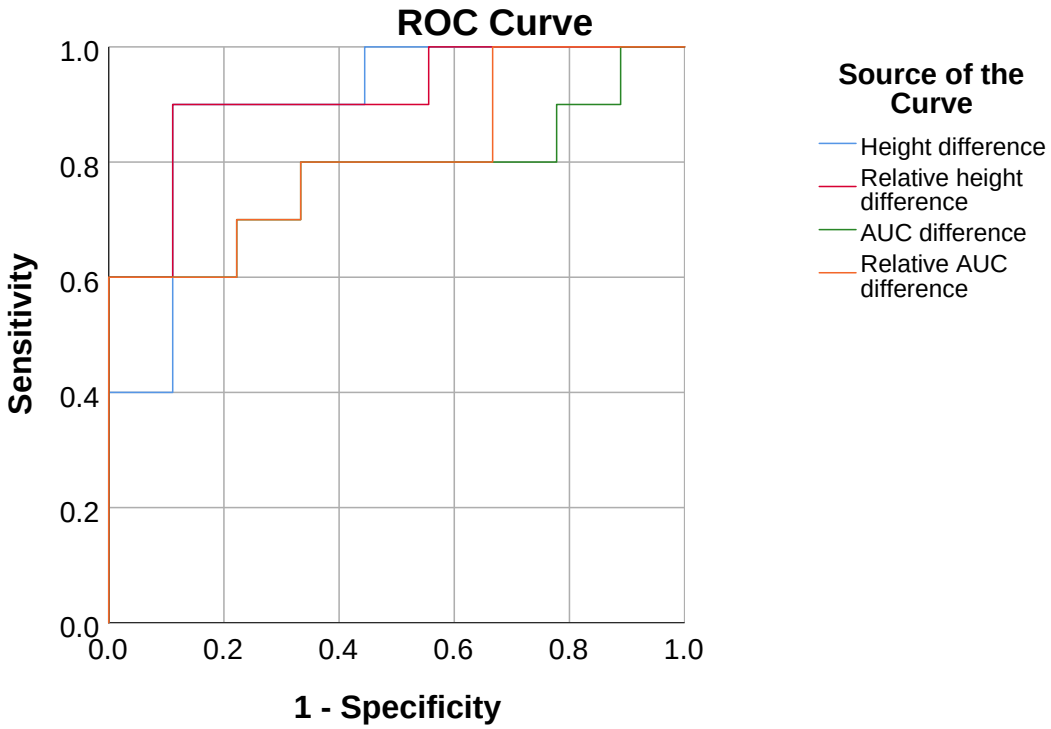

Figure 52: *Receiver operator characteristic curves of the statistically significant parameters found in the intercostal muscle measurements. The largest area under curve was found for the relative peak height difference at 0.91.*

E Patient information letters

Titel onderzoek: EMG registratie bij kinderen met astma
Informatie voor ouders/verzorgers Enschede 11-01-2018

Geachte heer/mevrouw,

De kinderarts heeft u voorgesteld dat uw zoon/dochter aan het bovengenoemde wetenschappelijk onderzoek deelneemt en heeft u al het een en ander uitgelegd. Jullie deelname moet u kunnen baseren op goede voorlichting van onze kant. Daarom ontvangt u deze schriftelijke informatie, die u rustig kunt (na/her)lezen en in uw eigen omgeving kunt bespreken. Wanneer u vragen heeft kunt u deze altijd voorleggen aan de arts en andere medewerkers aan dit onderzoek die aan het eind van deze informatiebrief vermeld staan.

Doel van het onderzoek
Astma is een lastige ziekte om te diagnosticeren. De uitgebreide inspanningstests zoals de test die uw kind krijgt zijn een zeer specifieke methode om tot een juiste diagnose te komen. In veel gevallen bestaan klachten al langere tijd en zijn deze soms (gedeeltelijk) geaccepteerd als een normale reactie bij spelen en/of sporten, waardoor het mogelijk is dat kinderen minder geïnteresseerd raken in sport en spel. Een gezonde levensstijl is erg belangrijk, zeker ook voor kinderen met astma.

Het doel van dit onderzoek is om een vaker gebruikte techniek nu op een andere manier in te zetten en tijdens de inspanningstest die uw kind krijgt een extra meting uit te voeren. Dit doen wij met een draagbaar apparaat, wat in de toekomst ook buiten het ziekenhuis ingezet zou kunnen worden. Om aan te tonen of dit potentie heeft, wordt het apparaat nu getest in het ziekenhuis en worden de resultaten van de metingen vergeleken met de uitslag die de arts geeft. De metingen worden geenszins gebruikt om een diagnose te stellen tijdens dit onderzoek.

EMG
Elektromyografie (EMG) is de techniek waarmee het mogelijk is om de activiteit van spieren in beeld te brengen. Beweging en activiteit leveren een kleine hoeveelheid elektrische energie, die door het apparaat gemeten wordt en doorgestuurd naar een computer. Het middenrif en de hulpademhalingsspieren zijn nauw betrokken bij de ademhaling en hun aandeel wordt belangrijker bij een astmatische reactie. Tijdens de meting willen wij zoveel mogelijk informatie over het aandeel van de verschillende ademhalingsspieren verzamelen.

Wat houdt het onderzoek in?
Voordat de inspanningstest begint worden er ter hoogte van het middenrif, op de borstkas en in de nek (voor en achterzijde) opplakbare elektroden aangebracht, evenals een op het borstbeen. Het meetapparaat wordt met behulp van kabeltjes aangesloten op de elektroden. Het apparaat wordt aan de broek of aan de riem gedragen tijdens het onderzoek. Vervolgens start de inspanningstest zoals gebruikelijk is en meet het apparaat gedurende de gehele test de spieractiviteit. Na afloop van de inspanningstest wordt het apparaat weer losgekoppeld en eindigt de meting. De bevindingen tijdens dit onderzoek zijn niet van invloed op de diagnose van de arts die de test uitvoert en worden niet aan u mede gedeeld.

Het onderzoek eindigt als alle deelnemers gemeten zijn. Indien gewenst wordt u op de hoogte gesteld van de uitkomst van de studie.

Mogelijke bijwerkingen/Risico's
De risico's die verbonden zijn aan deelname aan het onderzoek zijn verwaarloosbaar. Uitkomsten van deze studie zijn niet van invloed op de behandeling en/of diagnose van uw kind. Tijdens het onderzoek is altijd een arts aanwezig welke hoofdverantwoordelijk is voor het uitvoeren van de inspanningstest.

Vertrouwelijkheid
De gegevens die gedurende het onderzoek worden verzameld zullen vertrouwelijk behandeld worden volgens (inter)nationale wetten en regelgeving zoals de Gedragscode Gebruik Persoonsgegevens. Gegevens worden zodanig gecodeerd dat deze geenszins herleidbaar zijn naar individuele patiënten. Deze codering is bovendien niet gebaseerd op initialen, geboortedata of geslacht. Van de onderzoeksgegevens wordt een rapport gemaakt. Onderzoeksgegevens worden verzameld in het ZGT te Hengelo op de afdeling OCON sport. Onderzoeksgegevens worden gedurende een periode van vijf jaar beveiligd opgeslagen bij Medisch Spectrum Twente. Na deze periode zullen deze gegevens worden vernietigd.

Indien u besluit deel te nemen aan de studie geeft u toestemming voor het volgende:

- Medewerkers aan dit onderzoek en toezichthouders, waaronder de Medisch Ethische Toetsingscommissie Twente en de Inspectie voor de gezondheidszorg kunnen uw gegevens inzien. Zij zijn wettelijk verplicht deze informatie geheim te houden
- Indien u zou beslissen om uw deelname aan de studie vroegtijdig stop te zetten mogen uw gegevens die verzameld zijn vóór deze beslissing nog verwerkt worden, samen met andere gegevens, verzameld als onderdeel van het onderzoek

Onderzoeksgegevens worden gecodeerd en beschermd opgeslagen binnen het Medisch Spectrum Twente. Enkel de onderzoekers, die onderaan deze brief vermeld staan, weten welke persoon bij welke code hoort. De onderzoeker kan de gecodeerde onderzoeksgegevens van uw kind delen met andere onderzoekers en/of instellingen die betrokken zijn bij het onderzoek of belang hebben bij de onderzoeksresultaten. Hierbij zullen enkel de gecodeerde onderzoeksgegevens worden gedeeld, waarbij deze gegevens niet herleidbaar zijn naar uw kind. U heeft te allen tijde het recht om de onderzoeksgegevens in te zien. Hiervoor kunt u contact opnemen met de onderzoeker die onderaan deze brief vermeld staat.

Vrijwillige deelname
U bent vrij om deelname aan dit onderzoek toe te staan of te weigeren. Ook indien u nu toestemming geeft, kunt u te allen tijden zonder opgave van redenen deze weer intrekken. Wat u ook besluit, het zal geen enkele consequentie hebben voor de verdere behandeling van uw kind. De vrijheid om te allen tijde te stoppen met het onderzoek, zonder opgave van verdere redenen bestaat ook voor uw kind.

Ondertekening toestemmingsverklaring
Als u besluit om uw kind deel te laten nemen aan dit onderzoek, dan vragen wij u een formulier te ondertekenen. Hiermee bevestigt u uw voornemen om uw kind aan het onderzoek mee te laten doen. U blijft de vrijheid behouden om zonder opgave van redenen

de deelname van uw kind aan het onderzoek te stoppen, deze vrijheid bestaat ook voor uw kind.

Door onderstaand toestemmingsformulier te tekenen gaat u akkoord met het gebruik van de onderzoeksgegevens van uw kind. U kunt te allen tijde aangeven dat de gegevens van uw kind niet meer gebruikt mogen worden voor het onderzoek. De onderzoeker zal de gegevens van uw kind op dat moment vernietigen.

Zijn er extra kosten of krijgt u een vergoeding voor deelname aan dit onderzoek?
Er worden alleen de kosten voor de ziekenhuisbehandeling bij u of uw zorgverzekeraar in rekening gebracht. U maakt geen extra kosten wanneer uw kind deelneemt aan dit onderzoek. U krijgt geen vergoeding voor deelname aan het onderzoek.

Tenslotte
U bent gevraagd deel te nemen aan wetenschappelijk onderzoek. Dat onderzoek wordt uitgevoerd nadat goedkeuring is verkregen van de Raad van Bestuur van het Medische Spectrum Twente te Enschede. De voor dit onderzoek (inter)nationaal vastgestelde richtlijnen zullen nauwkeurig in acht worden genomen.

Verdere informatie
Mocht u na het lezen van deze brief nog nadere informatie willen ontvangen, of komen er voor of tijdens het onderzoek nog vragen bij u op, dan kunt u contact opnemen met de onderzoekers of arts via onderstaande gegevens. U heeft een bedenktijd van minimaal een week om te besluiten of u uw kind deel wilt laten nemen aan het onderzoek.

Indien u na zorgvuldige overweging besluit uw kind deel te laten nemen aan dit wetenschappelijk onderzoek, dan vragen wij u om samen met de onderzoeker het toestemmingsformulier te ondertekenen en van een datum te voorzien. Het is van belang dat beide ouders/verzorgers van het kind de toestemmingsverklaring ondertekenen.

Met vriendelijke groet,
Pascal Keijzer, stagiair onderzoek Technische Geneeskunde
Tel: 053 - 487 5709
E-mail: p.b.keijzer@student.utwente.nl

dr. B.J. Thio, kinderarts
tel. 053 - 487 2310

Toestemmingsverklaring

Titel van het onderzoek: EMG registratie bij kinderen met astma

Ik verklaar dat ik de informatiebrief heb ontvangen en gelezen en naar tevredenheid over het wetenschappelijk onderzoek geïnformeerd ben. Ik heb voldoende tijd gehad om over de deelname van mijn kind aan dit onderzoek na te denken en ben in de gelegenheid geweest om vragen te stellen. Deze vragen zijn naar tevredenheid beantwoord.

De deelname van mijn kind aan het onderzoek is vrijwillig en mijn kind en ik zijn gedurende het gehele onderzoek in de mogelijkheid om op elk moment te stoppen, zonder opgave van redenen.

Ik geef toestemming om de van mijn kind verzamelde gegevens te gebruiken voor het beschreven doeleinde van het onderzoek en om deze gegevens op de onderzoekslocaties (Medisch Spectrum Twente & Ziekenhuisgroep Twente Hengelo) op te slaan voor een periode van vijftien jaar.

Ik geef toestemming dat leden van de Medisch Ethische Toetsingscommissie en bevoegde autoriteiten inzage kunnen krijgen in de medische gegevens van mijn kind en onderzoeksgegevens.

Ik geef toestemming om de gegevens van mijn kind te gebruiken voor de doelen die in de informatiebrief beschreven staan.

Ik geef toestemming om deze gegevens gedurende vijf jaar na afloop van dit onderzoek te bewaren.

Door dit formulier te tekenen geeft ik toestemming voor deelname van mijn kind aan bovengenoemd wetenschappelijk onderzoek.

Naam kind waarvoor toestemming wordt gegeven

_____

Naam ouder	Plaats en datum	Handtekening
_____	_____	_____
Naam ouder	Plaats en datum	Handtekening
_____	_____	_____

Ik verklaar hierbij dat ik de deelnemer en ouders/verzorgers van de deelnemer volledig heb geïnformeerd over het genoemde onderzoek. Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de deelnemer en/of ouders/verzorgers van de deelnemer zou kunnen beïnvloeden, dan breng ik deze daarvan tijdig op de hoogte.

Naam onderzoeker	Plaats en datum	Handtekening
_____	_____	_____

Verklaring behandelend arts
Zowel schriftelijk als mondeling is de bovengenoemde ouder geïnformeerd ten aanzien van het onderzoek “EMG registratie bij kinderen met astma”. De ouder heeft toegestemd zijn/haar kind te willen laten participeren binnen dit onderzoek. De behandelend arts verklaart dat een vroegtijdige beëindiging van de deelname geen invloed heeft op de zorg die hem of haar toekomst.

Naam behandelend arts	Plaats en datum	Handtekening
_____	_____	_____

Een kopie van het ondertekend toestemmingsformulier en de informatiebrief wordt meegegeven.

Titel onderzoek: EMG registratie bij kinderen met astma
Informatie voor deelnemer Enschede 11-01-2018

Beste [Naam Kind],

De kinderarts heeft voorgesteld dat je aan het bovengenoemde wetenschappelijk onderzoek deelneemt en heeft je al het een en ander uitgelegd. Jouw deelname moet je kunnen baseren op goede voorlichting van onze kant. Daarom ontvang je deze informatiebrief, die je rustig kunt (na/her)lezen met je ouders en/of vrienden kunt bespreken. Wanneer je vragen hebt kan je deze altijd stellen aan de arts en andere medewerkers aan dit onderzoek die aan het eind van deze informatiebrief vermeld staan.

Doel van het onderzoek
Astma is een lastige ziekte om te diagnosticeren. De uitgebreide inspanningstests zoals de test die jij krijgt zijn een zeer specifieke methode om tot een juiste diagnose te komen. In veel gevallen bestaan klachten al langere tijd en zijn deze soms (gedeeltelijk) geaccepteerd als een normale reactie bij spelen en/of sporten. Hierdoor kan het gebeuren dat kinderen minder geïnteresseerd raken in sporten en buiten spelen. Een gezonde levensstijl is erg belangrijk, zeker ook voor kinderen met astma.

Het doel van dit onderzoek is om een vaker gebruikte techniek nu op een andere manier in te zetten. Dit doen wij door tijdens de inspanningstest die jij krijgt een extra apparaat te gebruiken. Dit doen wij met een draagbaar apparaat, wat in de toekomst ook buiten het ziekenhuis gebruikt zou kunnen worden. Om aan te tonen of dit werkt, wordt het apparaat nu getest in het ziekenhuis en worden de resultaten van de metingen vergeleken met de uitslag die de arts geeft. De metingen worden niet gebruikt om een diagnose te stellen tijdens dit onderzoek.

EMG
Elektromyografie (EMG) is de techniek waarmee het mogelijk is om de activiteit van spieren in beeld te brengen. Beweging en activiteit leveren een kleine hoeveelheid elektrische energie, die door het apparaat gemeten wordt en doorgestuurd naar een computer. Het middenrif en de hulpademhalingsspieren zijn nauw betrokken bij de ademhaling en hun aandeel wordt belangrijker bij een astmatische reactie. Tijdens de meting willen wij zoveel mogelijk informatie over het aandeel van de verschillende ademhalingsspieren verzamelen.

Wat houdt het onderzoek in?
Voordat de inspanningstest begint worden er ter hoogte van het middenrif, op de borstkas en in de nek (voor en achterkant) opplakbare elektroden aangebracht, evenals een op het borstbeen. Het meetapparaat wordt met behulp van kabeltjes aangesloten op de elektroden. Het apparaat wordt aan de broek of aan de riem gedragen tijdens het onderzoek. Vervolgens start de inspanningstest zoals gebruikelijk is en meet het apparaat gedurende de gehele test de spieractiviteit. Na afloop van de inspanningstest wordt het apparaat weer losgekoppeld en eindigt de meting. De bevindingen tijdens dit onderzoek zijn niet van invloed op de diagnose van de arts die de test uitvoert en worden niet aan je mede gedeeld.

Het onderzoek eindigt als alle deelnemers gemeten zijn. Als je de uitkomst van het onderzoek graag wilt weten kun je dit aangeven.

Mogelijke bijwerkingen/Risico's
De risico's die verbonden zijn aan deelname aan het onderzoek zijn verwaarloosbaar. Uitkomsten van het onderzoek zijn niet van invloed op jouw behandeling en/of diagnose. Tijdens het onderzoek is altijd een arts aanwezig welke hoofdverantwoordelijk is voor het uitvoeren van de inspanningstest.

Vertrouwelijkheid
De gegevens die gedurende het onderzoek worden verzameld zullen vertrouwelijk behandeld worden volgens (inter)nationale wetten en regelgeving zoals de Gedragscode Gebruik Persoonsgegevens. Gegevens worden zodanig gecodeerd dat deze niet op jou terug te leiden zijn. Van de gegevens wordt een rapport gemaakt. Deze codering is bovendien niet gebaseerd op initialen, geboortedata of geslacht. Onderzoeksgegevens worden verzameld in het ZGT te Hengelo op de afdeling OCON sport. Onderzoeksgegevens worden gedurende een periode van vijf jaar beveiligd opgeslagen bij Medisch Spectrum Twente. Na deze tijd worden de gegevens vernietigd.

Indien je besluit deel te nemen aan de studie geef je toestemming voor het volgende:

- Medewerkers aan dit onderzoek en toezichthouders, waaronder de Medisch Ethische Toetsingscommissie Twente en de Inspectie voor de gezondheidszorg kunnen jouw gegevens inzien. Zij zijn wettelijk verplicht deze informatie geheim te houden
- Indien je zou beslissen om je deelname aan de studie vroegtijdig stop te zetten mogen jouw gegevens die verzameld zijn vóór deze beslissing nog verwerkt worden, samen met andere gegevens, verzameld als onderdeel van het onderzoek

Onderzoeksgegevens worden gecodeerd en beschermd opgeslagen binnen het Medisch Spectrum Twente. Alleen de onderzoekers, die onderaan deze brief vermeld staan, weten welke persoon bij welke code hoort. De onderzoeker kan de gecodeerde onderzoeksgegevens delen met andere onderzoekers en/of instellingen die betrokken zijn bij het onderzoek of belang hebben bij de onderzoeksresultaten. Hierbij worden alleen de gecodeerde onderzoeksgegevens worden gedeeld, waarbij deze gegevens niet dus niet naar jou terug te leiden zijn. Je hebt zelf altijd het recht om de onderzoeksgegevens in te zien. Hiervoor kan je contact opnemen met de onderzoeker die onderaan deze brief vermeld staat.

Vrijwillige deelname
Je bent vrij om deelname aan dit onderzoek toe te staan of te weigeren. Ook als je nu toestemming geeft, kan je altijd zonder opgave van redenen stoppen met het onderzoek. Wat je ook besluit, het zal geen enkele consequentie hebben voor de verdere behandeling.

Ondertekening toestemmingsverklaring
Als je besluit om deel te nemen aan dit onderzoek, dan vragen wij je een formulier te ondertekenen. Hiermee bevestig jij dat je aan het onderzoek mee wilt doen. Je blijft de vrijheid behouden om zonder reden je deelname aan het onderzoek te stoppen.

Door het formulier onderaan deze brief te tekenen ga je akkoord met het gebruik van jouw onderzoeksgegevens. Je kunt altijd aangeven dat jouw gegevens niet meer gebruikt mogen worden voor het onderzoek. De onderzoeker zal jouw gegevens op dat moment vernietigen.

Zijn er extra kosten of krijg ik een vergoeding voor dit onderzoek?
Er worden alleen de kosten voor jouw behandeling in het ziekenhuis gemaakt bij de verzekering van jouw ouders. Deelname aan het onderzoek kost niets. Je krijgt geen vergoeding voor deelname.

Tenslotte
Je bent gevraagd deel te nemen aan wetenschappelijk onderzoek. Dat onderzoek wordt uitgevoerd nadat goedkeuring is verkregen van de Raad van Bestuur van het Medische Spectrum Twente te Enschede. De voor dit onderzoek (inter)nationaal vastgestelde richtlijnen zullen nauwkeurig in acht worden genomen.

Verdere informatie
Mocht je na het lezen van deze brief nog nadere informatie willen ontvangen, of komen er voor of tijdens het onderzoek nog vragen bij je op, dan kan je contact opnemen met de onderzoekers of arts via onderstaande gegevens.

Met vriendelijke groet,
Pascal Keijzer, stagiair onderzoek Technische Geneeskunde
Tel: 053 - 487 5214
E-mail: p.b.keijzer@student.utwente.nl

dr. B.J. Thio, kinderarts
tel. 053 - 487 2310

Toestemmingsverklaring

Titel van het onderzoek: EMG registratie bij kinderen met astma

Ik verklaar dat ik de informatiebrief heb ontvangen en gelezen en genoeg informatie over het onderzoek heb ontvangen. Ik heb voldoende tijd gehad om over mijn deelname na te denken en heb vragen mogen stellen over het onderzoek. De vragen die ik had zijn goed beantwoord.

Mijn deelname aan het onderzoek is vrijwillig en ik mag altijd stoppen zonder daar een reden voor te geven.

Ik geef toestemming om mijn verzamelde gegevens te gebruiken voor het beschreven onderzoek en om mijn gegevens op de onderzoekslocaties (Medisch Spectrum Twente & Ziekenhuisgroep Twente Hengelo) vijf jaar op te slaan.

Ik geef toestemming dat leden van de Medisch Ethische Toetsingscommissie en bevoegde autoriteiten inzage kunnen krijgen in mijn medische gegevens en onderzoeksgegevens.

Door dit formulier te tekenen geeft ik toestemming voor deelname aan bovengenoemd wetenschappelijk onderzoek

Naam deelnemer	Plaats en datum	Handtekening
_____	_____	_____

Ik verklaar hierbij dat ik de deelnemer en indien noodzakelijk ouders/verzorgers van de deelnemer volledig heb geïnformeerd over het genoemde onderzoek. Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de deelnemer en/of ouders/verzorgers van de deelnemer zou kunnen beïnvloeden, dan breng ik deze daarvan tijdig op de hoogte.

Naam onderzoeker	Plaats en datum	Handtekening
_____	_____	_____

Verklaring behandelend arts
Zowel schriftelijk als mondeling is de bovengenoemde deelnemer geïnformeerd ten aanzien van het onderzoek “EMG registratie bij kinderen met astma”. De deelnemer heeft toegestemd te willen participeren binnen dit onderzoek. De behandelend arts verklaart dat een vroegtijdige beëindiging van de deelname geen invloed heeft op de zorg die hem of haar toekomst.

Naam behandelend arts	Plaats en datum	Handtekening
_____	_____	_____

Een kopie van het ondertekend toestemmingsformulier en de informatiebrief wordt meegegeven.

INFORMATIE OVER DEELNAME AAN EEN WETENSCHAPPELIJK ONDERZOEK

Titel onderzoek: EMG registratie bij kinderen met astma

Beste [naam kind],

Leuk dat je misschien wilt meedoen aan dit onderzoek. Voordat je echt beslist om mee te doen, is het belangrijk om te weten waar je precies aan mee gaat doen. Lees deze informatiebrief rustig door en praat er over met je ouders of vrienden en familie. Heb je na het lezen van de brief nog vragen? Dan kun je altijd contact opnemen met ons, ons telefoonnummer en e-mail adres staan onderaan deze brief.

Waarom doen we dit onderzoek?

Astma is een veel voorkomende ziekte waar kinderen heel veel last van kunnen hebben. Om dat te voorkomen geeft een dokter soms medicijnen, zoals bijvoorbeeld pufjes. Het is soms voor kinderen, maar ook voor ouders en de dokter moeilijk in te schatten hoe het nu precies gaat met je astma. En ook of kinderen eigenlijk nog wel astma hebben. Hiervoor hebben we een uitgebreide test in het ziekenhuis, maar eigenlijk willen we deze het liefste wat makkelijker maken. Zo kunnen we deze test later misschien ook buiten het ziekenhuis doen.

Wat houdt het onderzoek in?

Binnenkort ga je naar het ziekenhuis in Hengelo om een test te doen waarmee wij kijken hoe het gaat met jouw benauwdheid. Tijdens die test willen wij graag een extra meting gaan doen met een nieuw apparaat. Dit apparaat meet jouw spieren die je gebruikt bij het ademhalen Hiervoor gebruiken we:

1. Een kastje
   Hiernaast zie je het kastje dat wij gebruiken. Dit is het meet apparaat. Het is een klein kastje en deze draag je aan je broek(riem) tijdens het onderzoek.
2. Plakkers
   Onder het kastje zie je de plakkers. Dit zijn een

soort stickers die we bij jou op je huid plakken. Er zitten speciale knopjes op waar we de kabeltjes die uit het kastje komen aan vast maken.

Wat moet ik verder nog doen?
Voor dit onderzoek hoef jij niets extra te doen. Het onderzoek gebeurt tegelijkertijd met de test waarvoor de kinderarts jou naar Hengelo heeft verwezen. Voor deze test heb je een aparte brief thuisgestuurd gekregen. De test waarvoor de kinderarts je naar Hengelo heeft verwezen is speciaal om te kijken hoe het gaat met je benauwdheid.

Wat als ik niet (meer) mee wil doen aan dit onderzoek?
Als je niet mee wil doen aan het onderzoek met het kastje hoef je verder niks te doen en dat vindt niemand erg. Ook als je tijdens het onderzoek wil stoppen mag dat en hoef je het alleen maar te zeggen. Je mag tijdens het onderzoek altijd stoppen zonder reden.

Wil je verder nog iets weten?
Als je nog vragen hebt over het onderzoek, kunnen jij of je ouders altijd contact opnemen met Pascal Keijzer (Tel 053 - 487 5214, e-mail p.b.keijzer@student.utwente.nl).

Groetjes van Pascal en dr. Thio