Ventilatory pattern efficiency in different physiologic and pathologic conditions

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PhD candidate
MSc Mandolesi Gaia

Supervisor
Professor Cogo Annalisa

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INTRODUCTION

The respiratory system consists primarily of the lungs, whose main function is to ensure gas exchanges with the environment, and the thoracic wall, which moves as a result of continual muscle action sustained by ventilatory drive. Between the components that make possible the breathing, a fundamental role is insured by the thoraco-abdominal area composed by the rib cage and abdomen wall that are separated by the diaphragm. Thus, normal thoraco-abdominal motion consists of expansion and retraction of these compartments during inspiration and expiration, respectively. Although the rib cage and abdomen move in unison, each of the compartments has independence of movement. When the displacement between the compartments is harmonious, the thoraco-abdominal motion is synchronous.

The ventilatory efficiency is defined as the amount of ventilation, composed by the tidal volume ($V_T$) and the breathing frequency (RR), required to achieve a given level of oxygen saturation under spontaneous breathing [1]. The efficiency of breathing is given by the thoraco and abdominal contributions to the minute ventilation (VE): a higher coordination between two sections corresponds to a higher efficiency [2]. Another aspect that contributes to the breathing efficiency is the ventilatory pattern represented by the ratio $VE/V_T$. As a fact it has been demonstrated in COPD patients that a deeper and lower ventilation is more efficient in terms of gas exchange, because there is a smaller fraction of anatomic dead space that is rebreathed in each breath [3].

A more efficient respiratory pattern, as the slow yoga breathing, characterized by a lower respiratory rate and a higher tidal volume, looks like to maintain a satisfactory oxygen transport. This has been seen both in healthy subjects during exposure to high altitude, in which a good oxygen saturation has been maintained without the need of marked increases in ventilation and ventilatory drive [1,4] and chronic obstructive pulmonary disease (COPD) patients [5]. Also in subjects suffering of chronic heart failure it has been demonstrated that a slow respiratory rate reduces the dyspnoea improving the resting pulmonary gas exchange and exercise performances [6].

Breathing pattern and thoraco-abdominal motion may be influenced by several factors, such as the individual’s positioning, age, sex, respiratory overload, neuromuscular diseases, lung diseases associated with increased airway resistance and chronic obstructive pulmonary disease [7].
Data on breathing pattern and thoraco-abdominal synchrony are important sources of information on ventilatory efficiency and represent an important tool in functional evaluations of athlete performances (i.e. endurance-trained runners) and of subjects suffering of respiratory diseases (i.e. asthma and COPD), especially in evaluation of exercise training programs.

The ventilatory pattern can be analysed by a spirometer with the use of a mouth piece or a mask. But this modality of measure can influence the breathing pattern. To overcome this problem we can use an unobtrusive monitoring technique that evaluates both the breathing pattern and the thoraco-abdominal motion, the inductive plethysmography. The portable respiratory inductive plethysmography measures the displacement of thoraco-abdominal compartments, the changes in time and in pulmonary volumes and accurately estimates the ventilation during exercise. It allows therefore to identify the differences in breathing patterns among healthy subjects and patients with pulmonary or cardiac diseases [8].

To the best of our knowledge, despite the importance of these aspects there are few available studies on breathing pattern and thoraco-abdominal motion among healthy adults [9, 10, 11].

Our group performed a pilot study on elite climbers at high altitude that evidenced a reduction of thoraco-abdominal coordination associated to an oxygen desaturation with increasing of ground slope during exercise. To discriminate if this reduction in breathing coordination was due simply to exercise or also to hypoxic condition we conducted a study at sea level on trained volunteers performing a similar exercise. The results show a decrease of thoraco-abdominal coordination associated to an increase in treadmill’s slope during intense incremental exercise at sea level (max slope reached: 25%), then we hypothesized that an higher slope may have prompted subjects to change their posture, leading to a thoraco-abdominal asynchrony.

This was the start point of the design of Study 1 [12].

Especially for what concerns the ventilatory pattern we found that obesity is a para-physiological condition that could modify the breathing efficiency at rest and during exercise. In fact obesity has a profound effect on the physiology of breathing: tidal volumes are often reduced in severe obesity and breathing follow a rapid, shallow pattern both at rest as well as during an exercise. This implies a limited ventilatory efficiency. Having the opportunity to study asthmatics subjects, and being obesity a risk factor of asthma, we decided in
Study 2 to investigate if the presence of obesity together with the bronchial obstruction could have had a further influence on the ventilatory pattern and breathing efficiency.

In conclusion the present research aims to:

- analyse the breathing coordination and ventilatory parameters in elite athletes (skyrunners) during an heavy-intensity exercise at altitude to verify if a better thoraco-abdominal coordination is associated to a more efficient breathing pattern and endurance performance. (Study 1)

- describe the breathing pattern at rest and during exercise in subjects with a different body mass index (BMI), both healthy and asthmatics in order to identify the influence of bronchial obstruction and elevated BMI on ventilation and exercise capacity. (Study 2)

The first study is composed by two parts: a descriptive research on retrospective pulmonary function data of asthmatic patients with the purpose to identify a possible role of obesity on the airflow severity, and a randomized non-blinded parallel case-control designed as an observational research that compares matched asthmatic and healthy control subjects to highlight the differences in breathing efficiency, exercise capacity and functional health-related lifestyle and quality of life parameters.

The second study is an observational study in which evaluations during heavy intensity exercises were performed to analyse the breathing pattern efficiency and thoraco-abdominal synchrony related to exercise performance at altitude of elite athletes.

Ethical approval by the Committee of the Ethics of the University Hospital of Ferrara, and informed consent by patients and subjects evaluated were obtained.
1. RESPIRATORY MECHANICS

The chest wall is formed by structures that protect the lungs: the rib cage, sternum, vertebrae, muscles and connective tissues. Chest wall muscles responsible for breathing are the diaphragm that separates the thoracic from the abdominal cavity and the internal and external intercostal, inserted on the coasts. Inspiration and expiration are driven by a pressure gradient that causes the movement of the air from high pressure areas to low pressure areas. Inspiration occurs when the atmospheric pressure is greater than the alveolar pressure, resulting in a pressure gradient that moves the air inside of the alveoli; expiration occurs when the atmospheric pressure is less than the alveolar one [13]. These air flows determined by breathing muscles change the volume of the lungs.

The relationship governing pressure and volume of a gas follows *Boyle’s law* which states that given a certain amount of gas within a container, the pressure is inversely proportional to the volume of the container. So if the lung volume increases, the air pressure decreases [14]. When the lungs are at rest and all respiratory muscles are relaxed, the alveoli contain a volume of air called residual functional capacity (FRC) and the pressure is equal to the atmospheric pressure. At the beginning of inspiration the lungs expand as a result of the inspiratory muscles contraction. This contraction causes an increase in the volume of the alveoli and then a decrease of the pressure inside them: for this reason, thanks to the pressure gradient the air is conveyed in the lungs. During expiration the opposite occurs: the thorax and lungs tend to return to the rest position, for the elastic recoil, whereby the air leaves the lungs when the pressure is greater in the alveoli. Volume changes in the alveoli take place thanks to the change in volume in the chest cavity, by means of respiratory muscles.

The lung’s elastic behavior is the tendency of the lungs to return to its resting volume after distension. One factor responsible of the elastic recoil is the elastic tissue of lungs constituted of fibers of elastin and collagen present in the alveolar walls and around vessels and bronchi. The elastic recoil decreases with age and in respiratory diseases (i.e emphysema), this change is caused by changes in this elastic tissue.
Lung volumes

The conducting airways (bronchi up to terminal bronchiole) represent the anatomic dead space. This leads into the gas-exchanging region of the lung, which is bounded by the blood-gas interface and the pulmonary capillary blood. With each inspiration, about 500 ml of air enters the lung (tidal volume, $V_T$). The anatomic dead space represents a small proportion of the total lung volume as the volume of capillary blood is very small compared with that of alveolar gas.

The static volumes of the lung can be measured with a spirometer. During quiet respiration the normal breathing can be seen ($V_T$). Next, the subject is asked to take a maximal inspiration followed by a maximal expiration. The total volume is called the vital capacity (VC). However, some gas remains in the lung after a maximal expiration; this is the residual volume (RV). The volume of gas in the lung after a normal expiration is the FRC. When a forced inspiration and expiration is performed (FVC) the forced expiratory volume in the first second (FEV$_1$) can be measured, which represents a dynamic measurement of lung function. The ratio FEV$_1$/VC indicates the pulmonary airflow capacity and the presence of airway obstruction. [15]

As with many anatomic and physiologic measures, lung volumes vary with age, gender, height and body size. Common practice evaluates lung volumes in relation to established standards that consider these factors.

2. VENTILATION

The primary function of the lung is the gas exchange. In order to transfer gases from the lung in an efficient manner, blood and air must be brought into close proximity in the lung. Ventilation is the movement of fresh air from the outside to the alveoli for gas exchange, along with the subsequent movement of alveolar air back to the outside. The total ventilation or minute ventilation ($VE = \text{volume exhaled per minute, L/min}$) can be determined multiplying the volume of gas exhaled during one normal respiratory cycle (tidal volume ($V_T$)) by the breathing frequency:

$$VE = V_T \times RR$$
The dynamic VE depends from the maximum air volume (VC) and the speed of the moving a volume of air (RR). In turn, the airflow velocity depends on the airflow pulmonary resistance and by the lung compliance, the stiffness imposed by the mechanical properties of the chest and lung tissue to a change in shape during breathing.

**Alveolar ventilation**

A gas exchange occurs in the alveolar acinus when fresh air comes in close proximity to capillary blood. However, not all the air inspired reaches the alveoli to participate in gas exchange. The conducting airways (nose, mouth, pharynx, larynx, trachea, bronchi and bronchioles) conduct air from atmosphere to alveoli but they do not participate in gas exchange since they contain no alveoli. At the end of inspiration, the volume of air remaining in the conducting airways is called the anatomic dead space. In addition to the conducting airways any alveoli that are ventilated with air but not perfused with blood do not participate in gas exchange. The volume of ventilation going to these alveoli also acts as dead-space ventilation and is called alveolar dead space. The sum of anatomic and alveolar dead space makes up the physiologic dead space. The volume of air that does participate in gas exchange because it is on contact with perfused alveoli is the alveolar ventilation (Vₘ). [16]

The ventilatory efficiency is very important for the gas exchange since the body’s carbon dioxide (CO₂) production is eliminated only by ventilation and the level of alveolar O₂ reflects a balance of two processes: the oxygen delivery to the alveoli by ventilation and the oxygen removal from the alveoli by capillary blood. A representation of lung volumes and flows is in the Figure 1. [15]
Control of breathing

The normal automatic process of breathing originates in impulses that come from the brainstem. The central pattern generator that comprises groups of neurons located in the pons and medulla is responsible for generating the rhythmic pattern of inspiration and expiration and it receives the input from chemoreceptors, lung and other receptors, and the cortex. The cortex can override these centers if voluntary control is desired. These complex nervous mechanism regulates the respiratory rhythm in order to maintain normal levels of the partial pressure of $O_2$ and $CO_2$ in the arterial blood, in spite of widely differing demands for $O_2$ uptake and $CO_2$ output made by the body in different conditions. The nervous stimulation of respiratory muscles occurs through the release of acetylcholine from motoneurons in the neuromuscular junction. [16]

Unlike all other processes essential for life, breathing is a semi-automatic and semi-voluntary activity: normally occurs without conscious participation and autonomously, but we can step in with a conscious action to change its rhythm and depth. It, through the forced ventilation, can be enhanced further by recruiting other muscles voluntarily. At this stage of hyperventilation is highlighted even more the work of the internal and external intercostal muscles, aided by other muscle groups. During this work the shoulder blades are stabilized by trapezius and elevator of scapula and rhomboid muscles; the small pectoral and serratus anterior raise the coasts; upper limbs can be stabilized through the use of the pectoralis major.

Ventilatory Response to Carbon Dioxide (CO$_2$)

The most important factor in the control of ventilation under normal conditions is the partial pressure of CO$_2$ of the arterial blood (PaCO$_2$). Arterial PCO$_2$ is the most important stimulus to ventilation under most conditions and is normally tightly controlled: most of the stimulus comes from the central chemoreceptors, but the peripheral chemoreceptors also contribute and the response is magnified if the arterial PO$_2$ is lowered. The ventilatory response to CO$_2$ is reduced by sleep, increasing age, and genetic. Trained athletes tend to have a low CO$_2$ sensitivity. The ventilatory response to CO$_2$ is also reduced if the work of breathing is increased. [15]
The reduced ventilatory response to CO$_2$ and the consequent CO$_2$ retention in some patients with lung disease can also be partly explained by an increasing in work of breathing. The main stimulus to increase ventilation when the arterial PCO$_2$ rises comes from the central chemoreceptors, which respond to the increased H+ concentration of the brain extracellular fluid near the receptors. An additional stimulus comes from the peripheral chemoreceptors, because of both the rise in arterial PCO$_2$ and the fall in pH.

**Ventilatory Response to Oxygen (O$_2$)**

Raising the PaCO$_2$ increases the ventilation at any PaO$_2$. When the PaCO$_2$ is increased, a reduction in PaO$_2$ below 100 mmHg causes some stimulation of ventilation, unlike the situation in which the PaCO$_2$ is normal. Thus, the combined effects of both stimuli exceed the sum of each stimulus given separately; this is referred to as interaction between the high CO$_2$ and low O$_2$ stimuli. Large differences in response occur between individual subjects. Because in healthy subjects at sea level the PaO$_2$ can normally be reduced so far without evoking a ventilatory response, the role of this hypoxic stimulus in the day-to-day control of ventilation is small. [15]

However, in the presence of low PaO$_2$ (i.e. on ascent to high altitude or as a consequence of respiratory and cardiac diseases), a large increase in ventilation occurs in response to the hypoxia. Hypoxemia reflex stimulates ventilation by its action on the carotid and aortic body chemoreceptors. It has no action on the central chemoreceptors; however, prolonged hypoxemia can cause mild cerebral acidosis, which, in turn, can stimulate ventilation.

**Respiratory muscles**

The respiratory muscles are morphologically and functionally skeletal muscle, and their primary task is to displace the chest wall rhythmically to pump gas in and out of the lung. The actions of diaphragm, the muscles of rib cage and abdominal muscles normally are simultaneous and coordinated. Rib cage and abdomen, the two compartments that compose the chest wall are mechanically arranged in parallel and are separated from each other by a thin musculotendinous structure, the diaphragm. [16]

The *diaphragm* is the most important muscle of *inspiration*. It is supplied by the phrenic nerves from cervical segments. During inspiration the diaphragm
contracts and its dome descends. This motion expands the thoracic cavity, causing a fall in the pleural pressure and an increase in the lung volumes, and displaces the abdominal visceral mass downward and forward increasing the abdominal pressure. The action of diaphragm increases the vertical dimension of thoracic cavity. In addition, the rib margins are lifted and moved out, causing an increase in the transverse diameter of the thorax. The contraction of external intercostal muscles increases in both the lateral and the anteroposterior diameters of the thorax by a lifting and rotating effects on the ribs. The intercostal muscles are supplied by intercostal nerves that come off the spinal cord at the same level. The accessory muscles of inspiration include the scalene muscles, which elevate the first two ribs, and the sternomastoids, which raise the sternum. There is little, if any, activity in these muscles during quiet breathing, but during exercise, they may contract vigorously. When the lungs expands the alveolar pressure decrease below the atmospheric pressure level and the air flows in the alveoli until the two pressures reaches the same level.

The expiration is a passive process during quiet breathing. The lung and chest wall are elastic and tend to return to their equilibrium positions after being actively expanded during inspiration. During exercise and voluntary hyperventilation, expiration becomes active. The most important muscles of expiration are those of the abdominal wall, including the rectus abdominis, internal and external oblique muscles, and transversus abdominis. When these muscles contract, intra-abdominal pressure raises, and the diaphragm is pushed upward. The internal intercostal muscles assist active expiration by pulling the ribs downward and inward (opposite to the action of the external intercostal muscles), thus decreasing the thoracic volume. This causes an increase of alveolar pressure that becomes higher than atmospheric pressure and assure the air movement out of the lungs. Thus, moving the chest wall during breathing is a complex, integrated process that involves many muscles. The control mechanism that promote coordinated use of these different muscles are critically important to maintaining both the work of breathing and the \( V_A \) within acceptable limits. The regulation of gas exchange is made possible by the carefully control of the level of ventilation.
**Work of breathing**

Work is required to move the lung and chest wall. During inspiration, the work done on the lung is given by the work required to overcome the elastic forces and the work overcoming viscous (airway and tissue) resistance. The higher the airway resistance or the inspiratory flow rate, the more negative would be the intrapleural pressure excursion. On expiration, the work is required to overcome airway and tissue resistance and this work can be accomplished by the energy stored in the expanded elastic structures and released during a passive expiration. There is also a little work dissipated as heat.

The total work done moving the lung and chest wall (Total work of breathing) can be calculated by measuring the O₂ cost of breathing and assuming a figure for the efficiency as given by:

\[
\text{Efficiency} \% = \frac{\text{Useful work}}{\text{Total energy expended (or O}_2\text{ cost)}} \times 100
\]

The efficiency is believed to be about 5% to 10%. The O₂ cost of quiet breathing is extremely small, being less than 5% of the total resting O₂ consumption. With voluntary hyperventilation, it is possible to increase this to 30%. In patients with obstructive lung disease, the O₂ cost of breathing may limit their exercise ability. [15]

Concerning the breathing pattern, the higher the respiratory rate, the faster the flow rates and the larger is the viscous work. On the other hand, the larger the tidal volume, the larger is the elastic work. When pulmonary compliance is reduced (stiff lungs), breaths tend to be small rapid, whereas in presence of severe airway obstruction sometimes breath is slow and these patterns tend to reduce the work done on the lungs.
3. VENTILATORY RESPONSE TO EXERCISE

Adaptations in the pulmonary system during exercise

The lung has a primary role in the ability to perform exercise. The respiratory system represents, together with musculoskeletal and cardiovascular systems, the integrated structure that enables the execution of the exercise. The role of the respiratory system is basically to provide supplies and diffusion of O₂ and CO₂ elimination. [9]

During exercise, the increased demands of O₂ by the muscle and the need to eliminate the CO₂ produced increase the ventilation. In addition, during heavy exercise, higher levels of lactic acid are produced by anaerobic glycolysis, and additional CO₂ is therefore eliminated from bicarbonate. The increased CO₂ elimination because the increased H⁺ concentration stimulates the peripheral chemoreceptors, thus further increasing ventilation.

The gas exchange demands of the lung are then enormously increased by exercise. Typically, the resting oxygen consumptions of 300 ml/min can rise to about 3000 ml/min in a moderately fit subject (and as high as 6000 ml/min in a top level athlete). Similarly, the resting CO₂ output of 240 ml/min increases to about 3000 ml/min.

Essential to meeting these tasks is an increase in breathing, specifically an increase in Vₐ. The increase in pulmonary ventilation required to meet these needs must be achieved efficiently with minimal oxygen consumption (VO₂) by the respiratory muscles. As the work rate (or power) is increased, ventilation increases linearly initially, but at high VO₂ values, it increases more rapidly because lactic acid is liberated, and this increases the ventilatory stimulus. Unfit subjects produce lactate at relatively low work levels, and they have an earlier ventilation increase, whereas well trained subjects can reach fairly high work levels before substantial anaerobic glycolysis occurs.

During a maximal exercise, the increase of metabolic requests, in particular the oxygen request, from the muscles involved in the effort can be considerable: in untrained healthy subjects oxygen consumption can increase about 10 times compared to the measured value in rest condition, and in trained individuals and athletes can increase by more than 20 times. The increased oxygen demand by the skeletal muscles leads to a progressive
increase in ventilation. This increase in healthy subjects is initially obtained by an increase in the depth of breathing (V₁), through the use of both a portion of the expiratory reserve volume and inspiratory reserve volume. Afterwards, it will occur even an increase in RR through the respiratory muscle capacity (inspiratory and expiratory) to increase its activity. [17] Ventilation cannot increase indefinitely. The maximum ventilation that a subject can produce is described as maximum voluntary ventilation (MVV). Its measurement is carried out asking to the subject to ventilate at maximum speed and depth for 12 seconds. An healthy subject during quiet breathing (at V₁ level at rest), has a wide ventilatory reserve, defined as the difference between the maximum predicted ventilation and the maximum ventilation reached during a maximal exercise. During an exercise the VE never reaches the ventilatory capacity in healthy subjects; in fact generally the exercise is stopped for muscular exhaustion or for the achievement of maximum heart rate. At the end of the exercise we can then highlight the ventilatory reserve. The possible ventilatory limit to effort is generally determined by the ventilatory reserve: it states that when the ventilatory reserve is at least 15 l/min, the ventilation system is not the limiting element to exercise. The maximum theoretical ventilation can be obtained directly through the manoeuvre of MVV or indirectly by multiplying the FEV₁ by 0.35 to 0.40. During an exercise the ventilatory pattern analysis, the analysis of the prevalence of RR and/or V₁ and of the movements of the chest and abdominal compartment and their coordination are very important. Greater respiratory coordination is in fact associated to a greater ventilatory efficiency. [9, 18, 19, 10]

Moreover, the oxygen dissociation curve of hemoglobin moves to the right in exercising muscles because of the increase in PCO₂, H+ concentration, and temperature. This assists the unloading of oxygen to the muscles. When the blood returns to the lung, the temperature of the blood falls a little and the curve shifts leftward somewhat. The arterial PO₂, PCO₂, and pH are poorly affected by moderate exercise whereas at very high work levels, PCO₂ often falls, while PO₂ rises, and pH falls because of lactic acidosis.

Many other functions of the respiratory system change in response to exercise. The diffusing capacity of the lung increases because of increases in both the diffusing capacity of the membrane and the volume of blood in the pulmonary capillaries. These changes are brought about by recruitment and distension of pulmonary capillaries, particularly in the upper parts of the lung. Nevertheless,
some elite athletes at extremely high work levels show a fall in arterial PO$_2$ caused by diffusion limitation because of the reduced time available for the loading of oxygen in the pulmonary capillary. The cardiac output increases approximately linearly with the work level, this implies an increase in pulmonary arterial and venous pressures, which account for the recruitment and distension of pulmonary capillaries and a pulmonary vascular resistance falls. However there is a much larger increase in VE than blood flow and the change in cardiac output is only about a quarter of the increase in VE.

**Respiratory system causes of exercise performance limitation**

Three are the mechanism primarily under the control of respiratory system that contribute to exercise limitation: the respiratory muscle work and fatigue, the arterial oxygen desaturation and cyclical fluctuations in intrathoracic pressure. [20, 21]

Heavy intensity sustained exercise can cause a time dependent arterial oxygen desaturation in arterial blood which can be evident in some elite athletes (see above). This is also due to a rightward shift in the oxygen dissociation curve because of a progressive metabolic acidosis and a rise in blood temperature which occurs to varying extents in all subjects. This implies an increase in peripheral fatigue and in the rate of perception of limb discomfort with a decrease in exercise time to exhaustion.

At the same time, the hyperventilation intensity dependent, that occurs during sustained high intensity exercise, requires the progressive recruitment of inspiratory and expiratory muscles. If the exercise intensity exceeds 80% of the maximum (and is sustained for a long time), a significant diaphragm and expiratory muscle fatigue can occur.

This exercise induced respiratory muscle fatigue does not limit the hyperventilatory response throughout exercise. However, according to Dempsey [22] it might trigger a metaboreflex from the fatiguing diaphragm which in turn causes sympathoexcitation and vasoconstriction of the vasculature of the exercise limb, resulting in a reduced limb flow. In Figure 2 is shown as during exercise at intensities greater than 80% of maximal oxygen consumption (VO$_2$max) the diaphragm shows a significant fatigue, in part due to the high levels of diaphragmatic work and in part because it must compete with the locomotor muscles for the available blood flow during heavy intensity
exercise. This promotes an inadequate oxygen transport and an higher fatigue of the diaphragm. The consequences of a fatiguing diaphragm and other respiratory accessory muscles (inspiratory and expiratory), is that the fatiguing contractions and accumulation of metabolites in the inspiratory and expiratory muscles activates type IV phrenic afferents, which in turn increases sympathetic vasoconstrictor activity via a supra-spinal reflex. The consequence is a gradual increase in limb muscle sympathetic nerve activity and a reduction in vascular conductance and blood flow in the resting limb.

![Figure 2](image)

A decreased respiratory muscle work affects the performance through a relief of dyspnea perceptions and a reduction of peripheral locomotor muscle fatigue via augmented limb blood flow and O₂ transport. [23]

4. **PHYSIOLOGICAL SETTING: THE HYPOXIC ENVIRONMENT**

Hypoxia, is a pathological condition in which the body as a whole (generalized hypoxia) or a region of the body (tissue hypoxia) is deprived of adequate oxygen supply.

At high altitude, differences in barometric pressure result in insufficient oxygen in the air, thereby causing hypoxia. People at high-altitude for short periods of time, who are not adapted to that environment, are at increased risk for acute altitude sickness involving pulmonary and cerebral edema. Newcomers to high altitude frequently complain of headache, fatigue, dizziness, palpitations,
insomnia, loss of appetite, and nausea. This is known as acute mountain sickness (AMS) and is attributable to the hypoxemia and alkalosis.

The more important responses of the organism to hypoxia are those implemented to prevent tissue hypoxia. These include changes in ventilation, heart rate, pH and hematocrit and hemoglobin concentration. All the beneficial changes implemented in response to hypoxia at high altitude take the name of acclimatization.

Variations in arterial oxygen concentrations can be also part of the normal physiology, for example, during strenuous physical exercise. A mismatch between oxygen supply and its demand at the cellular level may result in a hypoxic condition.

Mountain medicine distinguishes five height zones based on various limits on the acclimatization and exercise. [24]

- **sea level** (0-500 m): no effect on fit
- **low altitude** (500-2000 m): no effect of altitude on fit, but possible reductions in athletic performance completely reversible with acclimatization.
- **moderate altitude** (2000-3000 m): possible symptoms of altitude sickness, after a period of acclimatization the exercise capacity turns back to previous levels of exposure to altitude.
- **high altitude** (3000-5500 m): altitude sickness is common; rare manifestations of pulmonary and cerebral edema. Despite a good acclimatization is achieved, athletic performances are reduced.
- **extreme altitude** (over 5500 m): altitude-related disorders are numerous; the total acclimatization above 5400 m is considered impossible.

**Ventilatory response in hypoxic conditions**

Altitude’s physiologic challenge comes from the decreased PO$_2$ and air density progressively with the ascent above sea level. The PO$_2$ falls as the gas moves from the atmosphere in which we live to the mitochondria where it is utilized. The PO$_2$ of air is 20.93% of the total dry gas pressure. At sea level, the barometric pressure is 760 mmHg, and at the body temperature of 37°C, the water vapor pressure of most inspired gas (which is fully saturated with water vapor) is 47 mmHg. Thus, the PO$_2$ of inspired air at sea level is (760 – 47) x 20.93, or 150 mmHg. The barometric pressure decreases with distance above
the earth’s surface in an approximately exponential manner. At the summit of Mount Everest (8848 m), the inspired PO$_2$ is only 43 mm Hg. A remarkable degree of acclimatization occurs when humans ascend to these altitudes; indeed, climbers have lived for several days at altitudes that would cause unconsciousness within a few seconds in the absence of acclimatization.

At altitude we can reach very high ventilations (up to 200 L/min), especially during exercise, due to the lower density of the air and to the increase of the maximum breathing capacity. The maximum O$_2$ uptake (VO$_{2\text{max}}$) declines starting at about 1200 m; at 1800 m it is about 10% and it progressively loss the 10% each 1000 m of altitude. It can change depending on individual acclimatization level, training and ethnicity. The hypoxic ventilatory response (HVR) is defined as the increase of ventilation caused by hypoxic stimulus. As it is well known, the main stimulus to ventilation is an increase in PaCO$_2$ detected at the level of the aortic and carotid bulbs. These stimulate breathing so that the PaCO$_2$ is maintained within very narrow limits (variations of 2-3%); outside these values the system gain is very high and breathing is strongly inhibited or stimulated. The hypoxic stimulus causes an increase in ventilation only when the PaO$_2$ drops below 60 mmHg, a variation of as much as 40% compared to normal value 100 mmHg. This apparently too wide margin is actually appropriate, since it operates around the values of PaO$_2$ whereby hemoglobin dissociation curve becomes steeper.

The reduction in PaCO$_2$ caused by increased ventilation, following the hypoxic stimulus, constitutes an inhibitory stimulus on the breath, partially masking the ventilatory response to hypoxia either directly or because of the increase in blood pH due to depletion of CO$_2$. Ventilatory response to hypoxia is not quantitatively equal in all subjects. The individual variations are important, especially in the early days of exposure to high altitude. In particular categories, such as athletes trained at sea level and elderly, there is a minor HVR. The subjects exposed to intermittent hypoxia show a sort of basic acclimation to hypoxia with an increase of HVR. In high mountain populations the values of PaO$_2$ to which breathing is stimulated can be extremely low, probably due to some degree of tissue tolerance to hypoxia; the fact that babies born at altitude show a HVR equal to that of the habitants to sea level suggests that the phenomenon is mainly due to an individual acclimatization, and only secondarily to genetic factors. Even in individuals born at low
altitudes not belonged to high mountain populations, in fact, it can be seen a
decrease of HVR after decades of residence, also not catching up the local
values, whose physique has some adaptations not yet clarified. The return at
low altitude of subjects acclimated shows a rapid increase in PaCO₂: ventilation
decreases to values between the values at high altitudes and those in
normoxia conditions. The fact that ventilation remains high is partly a
consequence of the lowering of the set-point of peripheral chemoreceptors of
CO₂, which persists for a few days after the removal of the hypoxic stimulus.

Exercise in hypoxic environment intensifies the hyperventilatory response and
the work of breathing and diaphragm fatigue accordingly. Since it is recognized
that the respiratory muscle strength is reduced during the first days of
exposition at altitudes above 4000 m, we cannot exclude a role of the
respiratory muscles in exercise limitation. [25]

**The hemoglobin affinity for oxygen and oxygen dissociation curve**

Under hypoxic conditions despite the impediment to the release of O₂ to tissue
level, an increase in the affinity of hemoglobin for oxygen has beneficial
effects, especially during exercises. In conditions of limited diffusion a greater
oxygen affinity of hemoglobin increases O₂ extraction by alveolar air more
than it prevents the release, increasing the tissue oxygenation.

O₂ in fact forms an easily reversible combination with hemoglobin (Hb) to give
oxyhemoglobin: O₂ + Hb = Hb O₂. The maximum amount of O₂ that can be
combined with Hb is called the O₂ *capacity*. This is when all the available
binding sites are occupied by O₂. The O₂ saturation of Hb is the percentage of
the available binding sites that have O₂ attached and is given by:

\[
\frac{O_2 \text{ combined with Hb}}{O_2 \text{ capacity}} \times 100
\]

At sea level in normal conditions, the O₂ saturation of arterial blood (SpO₂)
with PO₂ of 100 mm Hg is about 97.5%, whereas that of mixed venous blood
with a PO₂ of 40 mm Hg is about 75%. The curved shape of the O₂ dissociation
curve has several physiological advantages (Figure 3). [15]
The flat upper portion means that even if the PO\textsubscript{2} in alveolar gas falls somewhat, loading of O\textsubscript{2} will be little affected. The steep lower part of the dissociation curve means that the peripheral tissues can withdraw large amounts of O\textsubscript{2} for only a small drop in capillary PO\textsubscript{2}.

![Figure 3](image)

During exercise the O\textsubscript{2} dissociation curve is shifted to the right, that is, the O\textsubscript{2} affinity of Hb is reduced, due to an increase in H\textsuperscript{+} concentration, PCO\textsubscript{2} (Bohr effect) and temperature. A rightward shift means more unloading of O\textsubscript{2} at a given PO\textsubscript{2} in a tissue capillary. An exercising muscle is acid, hypercarbic, and hot, and it benefits from increased unloading of O\textsubscript{2} from its capillaries.

In hypoxic conditions, at moderate altitudes (2000-3000 m), there is a rightward shift of the O\textsubscript{2} dissociation curve that results in a better unloading of O\textsubscript{2} in venous blood at a given PO\textsubscript{2}. The cause of the shift is an increase in concentration of 2,3-diphosphoglycerate (DPG), an end product of red cell metabolism that occurs in chronic hypoxia, which develops primarily because of the respiratory alkalosis. At higher altitudes, there is a leftward shift in the dissociation curve caused by the respiratory alkalosis, and this assists in the loading of O\textsubscript{2} in the pulmonary capillaries. The number of capillaries per unit volume in peripheral tissues increases, and changes occur in the oxidative enzymes inside the cells.

**Hemocrit and plasma hemoglobin concentration**

The amount of oxygen carried depends for the most part by the saturation of hemoglobin and its concentration; to the portion carried by red blood cells
must be added the proportion of oxygen dissolved in plasma. Normally, the latter contributes to arterial \( \text{O}_2 \) content only for 1.5%. The hypoxic stimulus induces the synthesis of erythropoietin through the activation of the hypoxia inducible factor (HIF-1 gene), and possibly through other mechanisms. In subjects fully acclimatized to altitudes above 5000 m oxygen content is the same as at sea level (≈200 ml/L) due to the increase in the concentration of hemoglobin. In the first weeks of exposure to high altitude the hemoglobin concentration grows rapidly because of changes in plasma volume. The plasma volume decreases significantly secondarily to an increase in diuresis, remaining below the normal values even during definitively acclimatization, especially in subjects that do not exhibit symptoms of acute mountain sickness. The effects of reduced plasma volume on total blood volume are partially offset by an increase of the mass of erythrocytes.

**Other Physiological Changes at High Altitude**

Pulmonary vasoconstriction occurs in response to alveolar hypoxia. This increases the pulmonary arterial pressure and the work done by the right heart. The pulmonary hypertension is further increased by the polycythemia, which raises the viscosity of the blood. There is no physiological advantage in this response, except that the topographical distribution of blood flow becomes more uniform with an improvement of \( \text{VE/Qc} \) ratio. The pulmonary hypertension is sometimes associated with pulmonary edema, although the pulmonary venous pressure is normal. The probable mechanism is that the arteriolar vasoconstriction is uneven, and leakage occurs in unprotected, damaged capillaries. The edema fluid has a high protein concentration, indicating that the permeability of the capillaries is increased.
5. PHATOLOGICAL SETTING: ASTHMA AND OBESITY

5.1 ASTHMA

Definition of Asthma

Asthma is a common complex chronic disorder of the airways characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. The interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment. Asthma is defined by its clinical, physiological, and pathological characteristics. The predominant feature of the clinical history is episodic shortness of breath often accompanied by non-productive cough. Wheezing appreciated on auscultation of the chest is the most common physical finding.

The dominant pathological feature is airway inflammation, sometimes associated with airway structural changes. Asthma has significant genetic and environmental components, but since its pathogenesis is not clear, much of its definition is descriptive.

Based on the functional consequences of airway inflammation, an operational description of asthma is: “Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.”

There is now good evidence that the clinical manifestations of asthma symptoms, sleep disturbances, limitations of daily activity, impairment of lung function, and use of rescue medications, can be controlled with appropriate treatment. When asthma is controlled, there should be no more than occasional recurrence of symptoms and severe exacerbations should be rare. [26, 27]

Pathophysiology of Asthma

Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway. These include:
• **Bronchoconstriction**
In asthma, the dominant physiological event leading to clinical symptoms is airway narrowing and a subsequent interference with airflow. In acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens or irritants. In addition, other stimuli (including exercise, cold air, and irritants) can cause acute airflow obstruction. The mechanisms regulating the airway response to these factors are less well defined, but the intensity of the response appears related to the level of underlying airway inflammation.

• **Airway edema**
As the disease becomes more persistent and inflammation more progressive, other factors further limit airflow. These include edema, inflammation, mucus hypersecretion with the formation of inspissated mucus plugs, as well as structural changes including hypertrophy and hyperplasia of the airway smooth muscle.

• **Airway hyperresponsiveness**
Airway hyperresponsiveness is an exaggerated bronchoconstrictor response to a wide variety of stimuli, and it is a major, but not necessarily unique, feature of asthma. The degree to which airway hyperresponsiveness can be defined by contractile responses to challenges with methacholine correlates with the clinical severity of asthma. The mechanisms influencing airway hyperresponsiveness are multiple and include inflammation, dysfunctional neuroregulation, and structural changes. Inflammation appears to be a major factor in determining the degree of airway hyperresponsiveness and it has a central role in the pathophysiology of asthma. Airway inflammation involves an interaction of many cell types and multiple mediators with the airways that eventually results in the characteristic pathophysiological features of the disease: bronchial inflammation and airflow limitation that result in recurrent episodes of cough, wheeze, and shortness of breath. The processes by which these events occur and lead to clinical asthma are still under investigation. Treatment directed toward reducing inflammation can reduce airway hyperresponsiveness and improve asthma control.

• **Airway remodeling**
In some persons with asthma, airflow limitation may be only partially reversible. Permanent structural changes can occur in the airway and these
are associated with a progressive loss of lung function that is not prevented by or fully reversible by current therapy. Airway remodeling involves an activation of many of the structural cells, with consequent permanent changes in the airway that increase airflow obstruction and airway responsiveness and render the patient less responsive to therapy. These structural changes can include thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and hypersecretion.

**Pathogenesis of asthma**

Factors that influence the risk of asthma can be divided into those causing the development of asthma and those triggering asthma symptoms; some have both effects. The former include host factors (which are primarily genetic) while the latter are usually environmental factors. However, the mechanisms whereby they influence the development and expression of asthma are complex and interactive. In addition, developmental aspects, such as the maturation of the immune response and the timing of infectious exposures during the first years of life, are emerging as important factors modifying the risk of asthma in the genetically susceptible person.

**Host Factors**

**Genetic:** It is well recognized that asthma has an inheritable component to its expression, but the genetics involved in the eventual development of asthma remain a complex and incomplete picture.

**Obesity:** Asthma is more frequently observed in obese subjects (Body Mass Index > 30 kg/m²) and is more difficult to control. Obese people with asthma have lower lung function and more co-morbidities compared with normal weight people with asthma131. The use of systemic glucocorticosteroids and a sedentary lifestyle may promote obesity in severe asthma patients, but in most instances, obesity precedes the development of asthma. How obesity promotes the development of asthma is still uncertain but it may result from the combined effects of various factors. It has been proposed that obesity could influence airway function due to its effect on lung mechanics, development of a pro-inflammatory state, in addition to genetic, developmental, hormonal or neurogenic influences. In this regard, obese
patients have a reduced expiratory reserve volume, a pattern of breathing that may possibly alter airway smooth muscle plasticity and airway function. In fact, to overcome the reduced total respiratory compliance and respiratory muscle inefficiency associated to obesity, obese subjects may breathe rapidly and shallowly. This pattern of breathing is similar to that seen among patients with neuromuscular and musculoskeletal disorders. This pattern of breathing is also associated with increased oxygen cost of breathing (Sood 2009).

Furthermore, the release by adipocytes of various pro-inflammatory cytokines and mediators (i.e. interleukin-6, tumor necrosis factor (TNF)-α, leptin) combined with a lower level of anti-inflammatory adipokines in obese subjects can favor a systemic inflammatory state although it is unknown how this could influence airway function.

**Sex**: In early life, the prevalence of asthma is higher in boys. At puberty, however, the sex ratio shifts, and asthma appears predominantly in women.

**Environmental Factors**

**Allergens**: Sensitization and exposure to house-dust mite and Alternaria are important factors in the development of asthma in children. Early studies showed that animal dander, particularly dog and cat, were associated with the development of asthma. Exposure to cockroach allergen, for example, a major allergen in inner-city dwellings, is an important cause of allergen sensitization and is a risk factor for the development of asthma. In addition, allergen exposure can promote the persistence of airway inflammation and likelihood of an asthma exacerbation.

**Infections**. During infancy, a number of respiratory viruses have been associated with the inception or development of the asthma. In early life, respiratory virus and parainfluenza virus in particular, cause bronchiolitis that parallels many features of childhood asthma. Symptomatic rhinovirus infections in early life also are emerging as risk factors for recurrent wheezing.

**Other environmental exposures**. Tobacco smoke, air pollution, occupations, and diet have also been associated with an increased risk for the onset of asthma, although the association has not been as clearly established as with allergens and respiratory infections.
Measures of asthma assessment and monitoring

Diagnosing a patient as having asthma is the first step in reducing the symptoms, functional limitations, impairment in quality of life, and risk of adverse events that are associated with the disease. The ultimate goal of treatment is to enable a patient to live with none of these manifestations of asthma, and an initial assessment of the severity of the disease allows an estimate of the type and intensity of treatment needed. An important point linking asthma severity, control, and responsiveness is that the goals are identical for all levels of baseline asthma severity: in well-controlled asthma, the manifestations of asthma are minimized by therapeutic intervention.

Diagnosis of asthma

To establish a diagnosis of asthma, the clinician should determine that:
- Episodic symptoms of airflow obstruction or airway hyperresponsiveness are present.
- Airflow obstruction is at least partially reversible.
- Alternative diagnoses are excluded.

Recommended methods to establish the diagnosis are:
- Detailed medical history.
- Physical exam focusing on the upper respiratory tract, chest, and skin.
- Spirometry to demonstrate obstruction and assess reversibility. Reversibility is determined by an increase in FEV₁ of both ≥12 percent from baseline and ≥ 200mL after inhalation of a short-acting bronchodilator.

Pulmonary function testing (spirometry)

The gold standard for the diagnosis of asthma is spirometry, particularly the demonstration of reversibility of bronchial obstruction. Usually a forced expiration curve is performed with the measurement of forced expiratory volume in the first second (FEV₁) and forced vital capacity (FVC), FEV₁, FVC, FEV₁/FVC measurements are recommended before and after the patient inhales a short-acting bronchodilator. These measurements help to determine whether there is airflow obstruction, its severity, and whether it is reversible over the short term. Patients’ perception of airflow obstruction is
highly variable, and spirometry sometimes reveals obstruction much more severe than would have been estimated from the history and physical examination. Spirometry typically measures the maximal volume of air exhaled from the point of maximal inhalation (FVC) and the volume of air exhaled during the first second of this maneuver (FEV₁).

Airflow obstruction is indicated by a reduction in the values for both the FEV₁ and the FEV₁/FVC relative to reference or predicted values. Predicted values of FEV₁, FVC, and PEF based on age, sex, and height have been obtained from population studies. They are useful for judging whether a given value is abnormal or not.

*Significant reversibility* is indicated by ATS standards as an increase in FEV₁ of >200 mL and ≥12 percent from the baseline measure after inhalation of a short-acting bronchodilator (e.g., albuterol, 2–4 puffs of 90 mcg/puff).

A reduced ratio of FEV₁/FVC (<88% in M and 89% in F or below the 5th percentile) indicates the presence of obstruction to the flow of air from the lungs, whereas a proportionately reduced FVC with a normal or increased FEV₁/FVC ratio suggests a restrictive pattern. The severity of abnormality of spirometric measurements is evaluated by comparison of the patient’s results with reference values based on age, height, sex, and race.

Spirometry should be performed using equipment and techniques that meet standards developed by the American Thoracic Society (ATS) [28]. Correct technique, calibration methods, and maintenance of equipment are necessary to achieve consistently accurate test results. Maximal effort by the patient in performing the test is required to avoid important errors in diagnosis and management.

5.2 OBESITY

**Definition of obesity**

Obesity is a complex multifactorial chronic disease that develops from an interaction of genotype and the environment. The development of obesity involves the integration of social, behavioral, cultural, physiological, metabolic and genetic factors. Obesity is generally acknowledged as a global phenomenon that increases morbidity and reduces life expectancy.
This disease is a major risk factor for many acute and chronic disorders, including cardiovascular and cerebrovascular disease, and diabetes. Higher body weights are also associated with increases in all-cause mortality. Most observational studies have shown a U- or J-shaped relationship between BMI and mortality, with individuals at very low and very high weights at increased risk, after adjusting for confounding factors such as smoking or preexisting illness. The number of overweight and obese men and women has risen since 1960; in the last decade the percentage of people in these categories has increased to 54.9% of adults age 20 years or older.

**Obesity classification**

The primary classification of obesity is based on the measurement of BMI. This classification is designed to relate BMI to risk of disease. The BMI, which describes relative weight for height, is significantly correlated with total body fat content. The relation between BMI and disease risk varies among individuals and among different populations. In addition, susceptibility to risk factors at a given weight varies among individuals. Some individuals may have multiple risk factors with mild obesity, whereas others may have fewer risk factors with more severe obesity. BMI is a practical indicator of the severity of obesity, and it can be calculated from existing tables (Figure 4). [29]

BMI is a direct calculation based on height and weight, regardless of gender. The relationship between BMI and body fat content varies somewhat with age, sex, and possibly ethnicity because of differences in factors such as composition of lean tissue, sitting height, and hydration state. The limitations of BMI as a measure of total body fat, nonetheless, must be recognized. The BMI is calculated as follows:

\[
\text{BMI} = \frac{\text{weight (kg)}}{\text{height squared (m}^2)}
\]

---

*Classification of Overweight and Obesity by BMI*

<table>
<thead>
<tr>
<th>Obesity Class</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
</tr>
<tr>
<td>I Obesity</td>
<td>30.0 – 34.9</td>
</tr>
<tr>
<td>II Obesity</td>
<td>35.0 – 39.9</td>
</tr>
<tr>
<td>III Extreme Obesity</td>
<td>≥ 40</td>
</tr>
</tbody>
</table>

The patient’s risk status is assessed by determining the degree of overweight or obesity based on BMI, the presence of abdominal obesity based on waist circumference, and the presence of concomitant cardiovascular diseases risk factors or comorbidities. Some obesity-associated diseases and risk factors place patients in a very high risk category for subsequent mortality. Obesity also has an aggravating influence on several cardiovascular risk factors.

**Effects of obesity on lung functions**

Obesity has a profound effect on the physiology of breathing. [30, 31, 32] Obese people are at increased risk of respiratory symptoms, such as breathlessness, particularly during exercise, even if they have no obvious respiratory illness. Obesity has a clear potential to have a direct effect on respiratory well-being, since it increases oxygen consumption (VO$_2$) and carbon dioxide production (VCO$_2$), while at the same time it stiffens the respiratory system and increases the mechanical work of breathing. The effects of obesity and being overweight on the control of breathing, pulmonary mechanics and their consequences on lung function tests and symptoms are discussed hereafter.

- **LUNG VOLUMES**

The most consistently reported effect of obesity on lung function is a reduction in the functional residual capacity (FRC). This effect reflects a shift in the balance of inflationary and deflationary pressures on the lung due to the mass load of adipose tissue around the rib cage and abdomen and in the visceral cavity. There is an exponential relationship between BMI and FRC with a reduction in FRC detectable even in overweight individuals. However, the effects of obesity on total lung capacity (TLC) and RV, are modest: TLC is usually maintained above the lower limit of normal, and the RV is usually well preserved. The reduction in FRC is manifested by an increase in inspiratory capacity (IC) and a very marked decrease in the expiratory reserve volume (ERV) [33] (Figure 5). The reasons for the reduction in TLC are not known, but it is probably due to a mechanical effect of the adipose tissue.
- **FAT DISTRIBUTION AND BODY COMPOSITION**

Abdominal and thoracic fat are likely to have direct effects on the downward movement of the diaphragm and on chest wall properties, while fat on the hips and thighs would be unlikely to have any direct mechanical effect on the lungs. Both abdominal fat and thoracic or upper body fat are associated with reductions in lung volumes.

- **RESPIRATORY SYSTEM MECHANICS**

An important respiratory abnormality in obesity is a decrease in total respiratory system compliance. Obesity is indeed characterized by a stiffening of the total respiratory system, which is presumed to be due to a combination of effects on lung and chest wall compliance. The reduction in lung compliance in obese individuals, exponentially related to BMI, is likely to be the result of decreased lung volumes while the decrease in chest-wall compliance is associated with the obese individual’s accumulation of fat in and around the ribs, the diaphragm and the abdomen. Both respiratory resistance and airway resistance rose significantly with the level of obesity, which appeared to be inversely related to changes in FRC. Although considerable energy may be spent in overcoming the reduction in chest wall compliance, it accounts for only one-third of the increased work of breathing and the remaining increase is likely due to an increase in non-elastic work,
performed to overcome the air flow limitation and the airway resistance that are increased, or an inefficiency of the respiratory muscles.

- **AIRWAY FUNCTION**
  Spirometric variables, such as FEV$_1$ and FVC, tend to decrease with increasing BMI. However, the effect is small, and the values usually within the normal range in healthy, obese adults and children. The FEV$_1$/FVC ratio is usually well preserved and this implies that the major effect of obesity is on lung volumes, with no direct effect on airway obstruction (Figure 6) [34]. Respiratory resistance is increased in the obese, indicating that airway caliber is reduced and this apparent reduction is attributable to the reduction in lung volumes rather than to airway obstruction.

![Figure 6](image)

**Figure 6**

- **RESPIRATORY MUSCLES**
  Obese individual’s respiratory muscles must work constantly against a less compliant chest wall and higher airway resistance, and their MVV is reduced (especially in severe obesity). This may result from diaphragm dysfunction due to increased abdominal and visceral adipose tissue deposition. It has been suggested that the additional load causes a length-tension disadvantage for the diaphragm due to fiber overstretching. Obese subjects may demonstrate inefficiency of respiratory muscles, particularly the diaphragm. Reduced respiratory muscle strength and endurance, as suggested by static maximal inspiratory pressure (MIP) values of 60-70% of normal subjects. Recent
studies have confirmed that obese subjects are at greater risk for inspiratory muscle fatigue both at rest and with exercise [35]. A possible cause of impaired respiratory muscle function in obesity includes increased elastic load which the respiratory muscles are required to overcome during inspiration. An overstretched diaphragm would place this respiratory muscle at a mechanical disadvantage, leading to decreased inspiratory muscle strength and efficiency.

- BREATHING PATTERN

At rest:
Tidal volumes are often reduced in severe obesity, and breathing is characterized by a rapid, shallow pattern. This pattern is likely to be a response to the increased stiffness of the respiratory system associated to increased elastic loads. Despite the reduction in \( V_T \), the increase in RR is such that VE is significantly increased and was shown to be 11 L/min or greater in most studies [31]. However, in mild-moderate obesity, tidal volumes at rest are often in the normal range, and the frequency and magnitude of regular sighs and deep inspirations appear similar to those in normal weight subjects [32].

Breathlessness at rest may also be reported by obese individuals but it is unclear if this is due entirely to obesity.

During exercise:
The breathing pattern observed during exercise is similar to that at rest, with a rapid, shallow breathing pattern. Obese subjects preferentially increase their breathing frequency more, and \( V_T \) less, than non-obese subjects [36, 32]. This is predominantly due to the mechanical constraints (increased elastic load) placed on the chest wall from excessive adipose tissue deposition. Since obese individuals have a higher basal metabolic rate than lean subjects, it is not surprising that they have a higher oxygen consumption during exercise for any given work rate. Obese subjects increase their oxygen intake during exercise by increasing their \( V_T \) and RR similar to normal-weight subjects, however, as they burn more \( O_2 \), they need to augment their VE to an even greater extent than normal-weight subjects. This is achieved mainly through a higher RR, as their \( V_T \) are not generally greater. This could probably be related to body fat distribution leading to impaired diaphragmatic excursion, and therefore an inability to augment \( V_T \) during exercise any further.
In obese subjects the oxygen cost of breathing is increased, since the oxygen cost of breathing increases parabolically with breathing frequency and the relative dead space \((V_D/V_T)\) increases: rapid breathing ultimately is uneconomical. Morbidly obese patients dedicate a disproportionately high percentage of total \(\text{VO}_2\) for respiratory work, even during quiet breathing. This relative inefficiency would suggest a decreased ventilatory reserve, since their breathing reaches earlier the maximum level of ventilation and a predisposition to respiratory failure in the setting of even mild pulmonary or systemic insults [30]. Anyway, despite the abnormalities imposed on the respiratory system, it is unusual for obese individuals to demonstrate ventilatory limitation based on traditional measures used to determine ventilatory reserve. Ventilatory reserve is the difference between maximum voluntary ventilation (MVV) and the VE achieved at peak exercise. It can be directly measured or predicted from the forced expiratory volume in 1 sec (FEV\(_1\)) multiplied for 35 or 40. The ventilatory reserve normally ranges from 20 to 60 L/min, with an extreme lower limit of normal of 11 L/min, although caution should be applied to this measure given the unreliability of calculated MVV.

**DYSPNOEA**

Breathlessness during exercise is a common complaint among morbidly obese individuals (BMI > 35), almost 80% of subjects, and obesity has long been thought to be a cause of dyspnoea, but data supporting this have been scarce and the mechanisms that drive these symptoms are not well defined. In severely obese subjects, Dempsey et al. [36] found that even during maximal exercise on a cycle ergometer these subjects were able to increase their ventilation sufficiently to avoid hypercapnia. [37] showed that during cycle exercise \(\text{VO}_2\) and VE are greater in obese subjects than normal weight at all work rates and that the relationships between breathlessness scores and these two values is not different in two groups. The implication of this finding is that the determinants of breathlessness were similar in obese and normal weight subjects, and that respiratory mechanical factors related to obesity did not contribute to breathlessness in the obese subjects. Concerning the walk exercise Hulens [38] showed that morbidly obese were more exerted and complained more frequently of dyspnea than obese and lean subjects during the six minute walking test (6MWT). In COPD patients during 6MWT obese
patients seem to show higher dyspnea than lean subjects [39] also if this result is not confirmed by other studies [40].

If we look to the origins of obesity-related dyspnea the data in this regard are inconclusive, and given the complex mechanisms underlying dyspnoea the cause is likely to be multifactorial. Many potential causes have been investigated. Some studies showed that subjects with severe dyspnoea had significantly lower TLC, FRC and ERV values and tended to have a higher respiratory drive than subjects with mild to moderate dyspnoea. Other studies have shown that dyspnoea in obese subjects is related to respiratory muscle performance or rib cage muscle activity and further supporting the idea that increased respiratory muscle work leads to dyspnoea in these patients is the observation that they also have an increased oxygen cost of breathing [31].

5.3 INTERACTION BETWEEN ASTHMA AND OBESITY

Obesity has recently been identified as one of the major risk factor for the development of asthma. Asthma in obese individuals tends to be more severe, does not respond as well to treatment, and is becoming a major public health issue in many countries. Several prospective studies, both in children and adults, indicate that obesity antedates asthma, and that the relative risk of incident asthma increases with BMI [41, 42, 43, 44]. Sin et al. [34] using data from the Third National Health and Nutrition Examination Survey, demonstrated a dose-dependent relationship between self-report of asthma and BMI, independent of many confounding factors. Longitudinal cohort studies of asthma and obesity determined causation in the relationship between the two. In the Danish Twin Registry Study, Thomsen et al. [45] reported that the incidence of new cases of self-reported asthma over 8 years was 4.3% in Danish adults aged 20–40 years, with a linear relationship between baseline BMI and incident asthma in both men and women. Nystad et al. [46], using data from a population-based study of 135 000 Norwegians who were followed for 21 years found, that on average for every one unit increase in BMI above 20, the risk of self-reported asthma increased by 10% in men and 7% in women. Beuther and Sutherland [47] performed a meta-analysis of these prospective epidemiological studies and reported that, in aggregate, these studies demonstrated a dose-dependent relationship between BMI and the incidence of asthma with overweight
increasing the odds of incident asthma by 38% and obesity increasing the odds by 92% compared with normal body weight. Higher BMI is also associated with worse asthma control and quality of life independently of age, sex and asthma severity [48]. The association between obesity and asthma has raised new concerns about whether the mechanical effects of obesity on the respiratory system contribute to airway dysfunction that could induce or worsen asthma. The mechanisms relating obesity and asthma are likely to include mechanical factors, inflammatory mediators, and immune responses that are all altered in the obese state. In obesity, lung volume and tidal volume are reduced, events that promote airway narrowing. Obesity also leads to a state of low-grade systemic inflammation that may act on the lung to exacerbate asthma. Obesity related changes in adipose-derived hormones, including leptin and adiponectin, may participate in these events. Moreover comorbidities of obesity, such as dyslipidemia, gastroesophageal reflux, sleep-disordered breathing, type 2 diabetes, or hypertension may provoke or worsen asthma. Finally, obesity and asthma may share a common etiology, such as common genetics, common in utero conditions, or common predisposing dietary factors. [49, 50, 51]. Nicolacakis et al. [52] suggest that obesity and asthma have additive, rather than synergistic effects and that asthma and obesity appear to influence the respiratory system through different processes. It remains unclear whether there is any association between obesity and airway hyperresponsiveness, a characteristic feature of the pathophysiology of asthma. However, the reduction in operating lung volume in the obese has the potential to modify the effects of bronchoconstriction and increases the occurrence of expiratory flow limitation.

Bronchoconstriction in the obese is associated with increased airway closure compared with non-obese and thus could increase gas trapping and alter ventilation distribution, but no published data are available about the effect of bronchoconstriction on ventilation distribution in the obese. Bronchoconstriction causes greater hyperinflation (an abnormal increase in FRC) in obese subjects, which may increase the severity of dyspnea. [32] The occurrence of additional elastic loads during bronchoconstriction might explain why some obese asthmatic subjects have more severe symptoms than their lean counterparts, despite similar spirometry.
Exercise in asthmatics and obese

Lifestyle, including physical inactivity in daily life, plays an important role in terms of disability and mortality. Regular physical activity may prevent or delay the onset or progress of different chronic diseases. The assessment of the amount and intensity of physical activity in daily life is considered very important due to the close relationship between activity levels and health. Physical activity is considered “any bodily movement produced by skeletal muscles that result in energy expenditure”. Therefore, physical activity in daily life can be considered “the totality of voluntary movement produced by skeletal muscles during every day functioning”.

Asthma is a chronic inflammatory respiratory disease that may be characterized by the presence of exercise induced bronchospasm (EIB). EIB is a term typically assigned to symptoms induced by a submaximal, prolonged exercise and is estimated to affect, to varying degrees, 80% to 90% of those with asthma. Thus, many asthmatic patients avoid physical activity, especially exercise, because they are afraid that it will exacerbate their asthma. For those with well-controlled asthma, exercise is recommended at the same level as for the general population because in addition to cardiovascular benefits, exercise aids long-term respiratory function. On the other hand, the absence of exercise and the adoption of a sedentary lifestyle can lead to respiratory deconditioning and to lower thresholds for exercise-induced symptoms. Such deconditioning can further discourage patients from exercising, thus perpetuating a vicious cycle of inactivity and worsening asthma symptoms. Compounding the problem, lack of physical activity can contribute to obesity, which is a well-known correlate of poor asthma outcomes. In addition obesity itself is a well-known obstacle to physical activity and exercise. Reasons may include difficulty performing exercises and fear of musculoskeletal injuries, which occur more frequently and can be more serious in obese individuals. A study on the exercise habits and obesity of asthmatics indicated that patients with well controlled asthma were more likely to exercise. [53] Rasmussen et al. [54] supported the hypothesis that decreased physical fitness in childhood was significantly correlated with the development of adolescent asthma. Physical inactivity is known to affect many important asthma outcomes. For example, a large United States population-based study on risk factors for asthma demonstrated that physical inactivity was associated with a higher
number of emergency room visits, inability to go to work, asthma symptoms, sleep problems, use of medication and inhalers [55].

A literature review [56] of exercising patients with pulmonary disease concluded that asthmatic subjects can improve cardiopulmonary fitness with exercise conditioning. In addition to decrease risks of cardiovascular disease and diabetes, the benefits of conditioning on asthma are both subjective (increased participation in activities, improved emotional status, higher quality of life, and decreased intensity of wheezing attacks) and objective (improved running performance and increased aerobic fitness). The training programs in asthmatics vary with respect to mode, frequency, duration, and intensity, but almost universally the clinical studies have shown major improvement in exercise performance in patients after participation in rehabilitation programs. [57] However, it is unclear whether improved fitness influences the severity of underlying asthma. A study on effects of 10-weeks of rehabilitation program on asthmatics demonstrated that there were improvements in cardiovascular conditioning, walking distance, FEV₁ and asthma symptoms [58, 59]. Exercise rehabilitation improves aerobic fitness in both asthmatic and non-asthmatic participants of a 10-week aerobic fitness program. Additional benefits are the improved ventilatory capacity and decreased breathing frequency during exercise in patients with mild asthma.

Moreover it has been demonstrated that a 12-week supervised aerobic exercise leads to improvements in asthma control and quality of life in partially controlled asthmatics motivated to exercise. These improvements are maintained after the training, while aerobic fitness and perceived asthma control significantly improved over an additional 12 weeks of self-administered exercise [60].
6. STUDY 1: VENTILATORY EFFICIENCY IN SKYRUNNERS DURING A RACE SIMULATION AT ALTITUDE

Background

Starting from a study conducted on climbers at 5200 m that evidenced during a standardized exercise a reduction of thoraco-abdominal coordination significantly related to the ground slope and the decrease in oxygen saturation [61] we decided to further investigate the relationship between thoraco-abdominal coordination and ground slope in normoxic conditions. We reasoned that hypoxic exposure could have a role in the results. The new study was performed in the Biomedical Sport Studies Center of the University of Ferrara where 7 age-matched trained volunteers, all males, were analyzed. They performed two incremental tests to exhaustion on a treadmill at sea level (Conconi test and Balke test) wearing an inductive plethysmography system (Life shirt). In the Conconi test the intensity increase is due to a speed increase (0.3 Km/h every 30 seconds until exhaustion) at constant slope; in the Balke test the slope increases of 1% every minute at constant speed (5.3 Km/h). To compare an equivalent number of breaths for each subject, regardless of the variation in the duration of the exercise, we analysed four periods of 20 breaths during the four stages of test. Results (Table 1A) have shown that VE and PhAng, an index of thoraco-abdominal coordination, have an significantly higher increase in Balke test. This increase in PhAng, evidenced in the Balke means a reduced synchrony between the abdominal and thoracic compartments [12].

<table>
<thead>
<tr>
<th>Exercise Intensity</th>
<th>BALKE test</th>
<th>CONCONI test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>VE</td>
</tr>
<tr>
<td>Low</td>
<td>100.9±8.6*</td>
<td>25.8±17.7</td>
</tr>
<tr>
<td>Int</td>
<td>123.6±5.8</td>
<td>38.7±29.2</td>
</tr>
<tr>
<td>Sub</td>
<td>156.9±16</td>
<td>54.4±36.5</td>
</tr>
<tr>
<td>Max</td>
<td>173.4±12.1</td>
<td>70.3±48.7</td>
</tr>
</tbody>
</table>

means values ± SD, * p<0.05 Low vs Max

The results of this study show that a decrease of thoraco-abdominal coordination occurs also at sea level and is associated to the increase in
treadmill’s slope that is present in the Balke test but not in the Conconi test (max slope reached: 25%).
We hypothesized that the slope increase may have prompted subjects to move their center of gravity forward to counteract the treadmill slope, leading to a thoraco-abdominal asynchrony.
On the basis of these results we decided to further investigate the ventilation (included thoraco-abdominal coordination), the ventilatory pattern and oxygen saturation during different field exercise.
The first project regards a study on elite skyrunners athletes during a simulated race at increasing altitude with different ground slopes.

**Introduction**

Skyrunning is a new sport attracting an ever increasing number of people: it involves running on mountain trails at altitudes between 2000 and 4000 m with ground slopes that can exceed 30%. Heavy-intensity exercise in these environmental conditions requires important physiological engagement from the body, in particular from the respiratory and cardiovascular systems. The respiratory adaptations during exercise represent a key constituent of endurance performance; the oxygen desaturation, respiratory muscle work and inspiratory and expiratory intrathoracic pressures, are well-established to contribute to performance limitation [21, 62]. During heavy-intensity exercise at altitude the ventilatory need increases further because of the combined effect of exercise and hypoxia. At altitudes > 2000-2500 m the activation of the ventilatory system is higher than at sea level since the minute ventilation (VE) augments in consequence of the increase in the hypoxic ventilatory drive [63, 64, 65]. It is also well known that a deeper and lower VE is more efficient in terms of gas exchange, because there is a smaller fraction of anatomic dead space [3, 6]. In hypoxic conditions a more efficient breathing pattern implies a decreased effect of hypoxia and the maintenance of a satisfactory oxygen transport without the need of a marked increase in VE and in ventilatory drive [1, 4, 5].
Therefore it could be expected that during exercise in hypoxic conditions at moderate altitude (2000-2800 m) a better respiratory efficiency is associated to a better exercise performance by reducing the factors limiting the exercise. The efficiency of breathing is given by the thoraco and abdominal contributions
to the VE: a higher coordination between two sections corresponds to a higher efficiency [66, 10].

Although one study [11] on healthy subjects during quiet breathing evidenced that a progressively increased inclination of the trunk determines a progressive reduction of rib cage displacement, tidal volume, and minute ventilation at rest, no studies on pulmonary volumes changes with dynamic position were conducted.

The present study was conducted then in order to test the effect of ground slope on thoraco-abdominal coordination and to prove the hypothesis that during exercise at moderate-high altitude a better thoraco-abdominal coordination is associated to a more efficient breathing pattern, characterized by a higher tidal volume ($V_T$) and lower breathing rate (RR), and to a higher arterial oxygen saturation ($\text{SpO}_2$) influencing the factors acting on the endurance performance. For these purposes, we evaluated the VE, the thoraco-abdominal coordination and the arterial oxygen saturation ($\text{SpO}_2$) in relation to ground slope in elite skyrunners (SKY) during a race simulation at altitudes above 2000 m.

**Materials and methods**

Fifteen endurance-trained skyrunners (13 males, 2 females) were recruited for the study with the contribution of the International Skyrunning Federation (ISF). All were current athletes participating in skyrunning races with positions in the first half of final results tables, and their speciality competitive events included the Vertical Kilometer: a race with a drop of 1000 m and an ascent ground slope of >30% over distances between 3.5-6 km.

Exclusion criteria included injury or illness that impaired normal training and racing before the study. Data were collected in two different sessions during the summer of 2012. All subjects gave written informed consent to the protocol approved by the ethics committee of the University of Ferrara. This study was part of a larger research project also covering cardiovascular evaluation of athletes.

Anthropometric data, medical history and habitual training at altitude information were collected by a questionnaire administered by an operator. All subjects were asked to run the “vertical kilometer trail” from Cervinia, Italy
(2030 m) to Rifugio Orioni (2804 m) simulating a skyracing race. The trail was tracked by an expert of the ISF the first day of the study.

Lung volumes, vital capacity (VC), forced expiratory volume in the first second (FEV\textsubscript{1}) and FEV\textsubscript{1}/VC were evaluated at rest at 2030 m before and after the race using a portable spirometer (Spiropalm Cosmed, Italy). Muscle inspiratory strength was evaluated at the same time using a respiratory pressure meter (MicroRPM Carefusion, USA). During the race athletes wore a portable respiratory inductive pletysmography (RIP) system (Lifeshirt VivoMetrics; Ventura, CA) equipped with a finger pulse-oxymeter, and a GPS (Garmin Edge 305, USA) positioned on the arm. The RIP system consists of a snugly fitting, elastic garment incorporating a rib cage and abdominal inductance sensors, containing shielded electrical conductors. Sensors were placed by one of the investigators and were connected to a portable battery-powered device incorporating the RIP, pulse oxymetry, ECG, three accelerometers and a signal-processing and recording unit for continuous data collection over ≥24h [8]. (Figure 7)

![Figure 7. Schematic drawing of the portable RIP system.](image)

Data recording changes in the breathing pattern (VE, V\textsubscript{T}, VE/V\textsubscript{T}) and thoraco-abdominal coordination, expressed by the phase angle index (PhA), were measured breath by breath by the RIP sensors.

PhA is an index of thoraco-abdominal coordination, representing the delay between thoracic and abdominal excursion and it is calculated by the analysis of Konno-Mead curves on the basis of a single breath. It is expressed in grades: 0° represents the perfect synchrony, 180° the total asynchrony of rib
cage and abdomen movements. PhA was assessed by computing the rib cage contribution to \( V_T \) and the phase shift between rib cage and abdominal excursion. \( \text{SpO}_2 \) and heart rate data were collected respectively from the pulse-oxymeter and ECG incorporated in the portable RIP recorder. The RIP system was calibrated for each subject at rest before the race, following the calibration procedure: subjects were asked to breath rapidly into a calibration bag of fixed volume for seven cycles emptying and filling the bag with each breath. This procedure was repeated four times alternating between the sitting and upright position in order to evaluate the contribution of rib cage and abdomen to the tidal volume in the different body positions. The study was conducted in line with the Helsinki principles and was approved by the Ethics and Research Committee of the Medical School of the University of Ferrara. The study was performed in between June and September 2012.

**Data and Statistical analysis**

Data of VE, PhA, \( \text{SpO}_2 \) and HR were analysed by a dedicated software (VivoLogic, VivoMetrics). The artifact of movement during exercise was removed from the collected data. To do this, the minimum acceptable value of \( V_T \), settled for the assessment of breath, has been modified from 25% of basal value to 75%: a decrease <75% of basal value was not considered a breath.

Data of breathing pattern, PhA and \( \text{SpO}_2 \) were averaged for one minute intervals and integrated with the data from the GPS. For the respiratory and anthropometric parameters, mean values \( \pm \) standard deviation (SD) were calculated. All variables analysed during the race have been normalized. Data are summarized as mean \( \pm \) SD.

The difference between means for each parameter were evaluated by the paired Student’s \( t \) test. The normal distribution was verified with the Kolmogorov-Smirnov test. Correlations were analysed by the Pearson correlation coefficient for dependent variables. The level of significance was set at \( p<0.05 \) for all statistical comparisons.

All computations were done using a statistical software package (SPSS version 20.0.0).
Results

15 SKY (13M, 2F) with an age between 34 and 60 years (42±8.8) and a body mass index (BMI) of 21.7±2.9 participate to the Vertical Kilometer race simulation. The SKY were well comparable for anthropometric characteristics (Table 1).

Table 1. Anthropometric data of 15 SKY

<table>
<thead>
<tr>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Weight (Kg)</th>
<th>Height (m)</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>M</td>
<td>63.3</td>
<td>1.74</td>
<td>20.91</td>
</tr>
<tr>
<td>38</td>
<td>M</td>
<td>62.8</td>
<td>1.72</td>
<td>21.23</td>
</tr>
<tr>
<td>50</td>
<td>M</td>
<td>55.9</td>
<td>1.68</td>
<td>19.81</td>
</tr>
<tr>
<td>46</td>
<td>M</td>
<td>66.6</td>
<td>1.83</td>
<td>19.89</td>
</tr>
<tr>
<td>56</td>
<td>F</td>
<td>57.4</td>
<td>1.65</td>
<td>21.08</td>
</tr>
<tr>
<td>60</td>
<td>M</td>
<td>71.2</td>
<td>1.74</td>
<td>23.52</td>
</tr>
<tr>
<td>34</td>
<td>M</td>
<td>59.7</td>
<td>1.70</td>
<td>20.66</td>
</tr>
<tr>
<td>36</td>
<td>M</td>
<td>80.0</td>
<td>1.88</td>
<td>22.63</td>
</tr>
<tr>
<td>42</td>
<td>M</td>
<td>85.4</td>
<td>1.80</td>
<td>26.36</td>
</tr>
<tr>
<td>34</td>
<td>M</td>
<td>70.5</td>
<td>1.88</td>
<td>19.95</td>
</tr>
<tr>
<td>35</td>
<td>M</td>
<td>63.9</td>
<td>1.72</td>
<td>21.63</td>
</tr>
<tr>
<td>34</td>
<td>M</td>
<td>78.0</td>
<td>1.77</td>
<td>24.90</td>
</tr>
<tr>
<td>33</td>
<td>F</td>
<td>49.9</td>
<td>1.60</td>
<td>19.53</td>
</tr>
<tr>
<td>37</td>
<td>M</td>
<td>76.9</td>
<td>1.75</td>
<td>25.14</td>
</tr>
<tr>
<td>35</td>
<td>M</td>
<td>55.0</td>
<td>1.71</td>
<td>18.81</td>
</tr>
</tbody>
</table>

The SKY had a mean weekly training of 107 Km with a mean difference in height of 3500 meters. Subjects run 6.0 Km±1.3 (ascent), with mean speed of 1.6±0.3 (m/sec) in 65.2±14.1 minutes.

All subjects presented normal spirometric values and PImax at rest before the race. Reference values used are in referred to ATS/ERS [67] guidelines. The VC expressed both as absolute value and in % of predicted, as well as the maximal inspiratory pressure values (MIP), are significantly reduced after the race (p<0.05) (Table 2).

Table 2. Spirometric data of 15 SKY pre and post race

<table>
<thead>
<tr>
<th></th>
<th>PRE race</th>
<th>POST race</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (L)</td>
<td>5.46±0.7</td>
<td>5.32±0.7 *</td>
</tr>
<tr>
<td>VC %</td>
<td>117.2±14.2</td>
<td>114.5±16.5 *</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>4.07±0.6</td>
<td>4.09±0.5</td>
</tr>
<tr>
<td>FEV1%</td>
<td>109.5±8.4</td>
<td>109.7±10.5</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>76.6±11.9</td>
<td>75.26±7.6</td>
</tr>
<tr>
<td>FEV1/VC %</td>
<td>92.6±11.7</td>
<td>93.86±8.9</td>
</tr>
<tr>
<td>MIP (cmH2O)</td>
<td>115±22</td>
<td>110±23*</td>
</tr>
</tbody>
</table>
Data are expressed as mean±SD. VC: vital capacity; FEV$_1$: forced expiratory volume in the first second; MIP: maximal inspiratory pressure. % is the percentage of predicted values (ERS 1995) *P<0.05

One male and one female were excluded from the RIP analysis for illegible data. Data of ventilatory pattern (VE, VT, VE/VT), PhAng, ground slope (S) and SpO$_2$ at rest and during the race of the remaining 13 SKY (12M, 1F) with BMI 21.9±2.3, are reported in Table 3.

**Table 3. Data of ventilation, thoraco abdominal coordination, ground slope, SpO$_2$ at rest and during the race (mean±SD) of 13 SKY**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE (L/min)</td>
<td>20.5±4.4</td>
<td>131.1±28.8 *</td>
</tr>
<tr>
<td>VT (L)</td>
<td>0.9±0.1</td>
<td>2.5±0.5 *</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>24.3±4.5</td>
<td>52.8±9.2 *</td>
</tr>
<tr>
<td>VE/VT</td>
<td>22.5±4.0</td>
<td>51.8±8.5 *</td>
</tr>
<tr>
<td>PhAng (°)</td>
<td>11.9±4.3</td>
<td>12.5±1.8</td>
</tr>
<tr>
<td>S (%)</td>
<td>-</td>
<td>18.8±5.7</td>
</tr>
<tr>
<td>SpO$_2$ (%)</td>
<td>94.6±1.1</td>
<td>85.2±3.1 *</td>
</tr>
</tbody>
</table>

VE: minute ventilation, VT: tidal volume, f: breathing rate, PhAng: phase angle, S: ground slope; SpO$_2$: arterial oxygen saturation, *P<0.001

For the analysis we decided to take into account the slopes between 0% and 40% since the negative slopes during the ascent were numerically irrelevant and slopes >40% needed climbing activity with the use of hands that implied unavoidable changes in the posture.

For better representation of data we grouped in four classes the values of S (0-10%; 10-20%; 20-30%; 30-40%) associating to each class of S the mean value of PhA.

The better interpolation of these points is represented by a quadratic curve (for S>0%) Y= 12.897-0.773 x+0.301 x$^2$ (Figure 8).
We can observe that when $S$ increases over the 30% a significant increase in PhA is observed ($p<0.01$), representing a worse thoraco-abdominal coordination. The increase in PhA is significantly related to a decrease in $\text{SpO}_2$ ($r=-0.26; \ p<0.001$) (Figure 9) and to an increase in $\text{VE}/\text{V}_T$ ($r=0.19; \ p<0.001$) (Figure 10). We grouped PhA in four classes (0-10; 10-13; 13-16; >16) considering the mean values of $\text{VE}/\text{V}_T$ for each class. Data are well evaluated by a linear model ($R^2 = 0.98$).
The relationship between the breathing pattern and thoraco abdominal coordination become stronger if we consider a S between 20% and 40% \((r=0.34; \ p<0.001)\).

Considering a S between 0% and 40%, the increase in \(\text{VE/VT}\) in turn significantly affects the \(\text{SpO}_2\): an higher fall of \(\text{SpO}_2\) is associated to an higher ratio of \(\text{VE/VT}\) \((r=-0.69; \ p<0.01)\) (Figure 11).

To evaluate the performance we use the mean race speed since it was the most comparable parameter between SKY. A low \(\text{SpO}_2\) is associated to a lower race speed (mean 1.6±0.3 m/sec.): both for 20% \(\leq S \leq 40\%\) \((r= 0.33; \ p<0.01)\) and for 0% \(\leq S \leq 20\%\) \((r= 0.4; \ p<0.01)\) (Figure 12).
Discussion

We hypothesized that during exercise the ground slope has effects on the thoraco-abdominal coordination of breathing and this fact could modify the ventilatory pattern with possible consequences on gas exchange (oxygen saturation) and athlete’s performance. We studied a group of athletes well trained in mountain running, during a simulated race between 2000 m and 3000 m, altitudes at which hypoxia also plays a role on the respiratory system.

The main finding of our investigation is that in elite skyrunners, during heavy endurance exercise at moderate altitude, the ground slope negatively influences the thoraco-abdominal coordination with a worsening as shown by the increase in the angle representing the excursions of the two compartments (Figure 8). This phenomenon, more evident when slope is >30%, confirms the reduced synchrony between rib cage and abdomen with increasing slope that we found in a previous study at sea level during exercise on a treadmill at slopes between 0% and 25% (personal, unpublished data).

The reduction of breathing synchrony in skyrunners corresponds to a change in ventilatory pattern represented by a higher respiratory rate for the same amount of ventilation (higher ratio VE/V̇T) (Figure 10). It is well known that this ventilatory pattern is less efficient for the gas exchange [3]: in fact a breathing pattern characterized by low respiratory rate and high tidal volume is associated to the preservation of a satisfactory oxygen transport (SpO₂) and
is therefore considered more efficient. This has been proved both for healthy subjects during exposure to altitude [1, 4] and COPD patients [5]. In fact, in our study the change in ventilatory pattern turned out to be associated to a decrease in SpO$_2$ (Figure 11) with a stronger relationship for slopes >20%.

In the present study the higher decrease in SpO$_2$ appears to negatively influence the performance: athletes with a higher level of desaturation during the race have a lower race speed, and hence a reduced exercise performance (Figure 12). This significant relationship between the decrease in SpO$_2$ and the speed performance during the race at 2000-3000 m confirms the role of arterial oxygen desaturation in the decline in endurance race performance at altitudes, as reported by Chapman et al. [68] in highly trained distance runners in simulated hypoxia (2100m).

To the best of our knowledge, this is the first study investigating the breathing coordination during exercise in the field (i.e. with continuous changes in ground slope) and there are few data in the literature with which to confront.

We think that the change in breathing pattern towards a less efficient condition associated to the slope increasing and to the consequent reduction in thoraco-abdominal coordination that we found could be one of the factors that negatively influence the performance. As a matter of fact, we suppose that the reduced thoraco-abdominal coordination consequent to the slope increase is dependant from a change in posture towards a higher inclination of the trunk with an ahead displacement of barycentre in order to contrast the increasing slope. Few studies on thoraco-abdominal kinematics [11, 69] have reported that a higher inclination of the trunk is associated to a reduction in rib cage displacement causing a disequilibrium of the two compartments. This might explain our results. In this way the increased thoraco-abdominal asynchrony could play also an important role in the reduction of SpO$_2$ and in the consequent drop of endurance performance.

In addition, we cannot exclude also a role of the respiratory muscles on the performance, since it well known that they can give a significant contribute to performance limitations [22, 70, 71]. Unfortunately we have not data of respiratory muscles work and oxygen consumption; anyway the reduction of VC and MIP that we found at the end of the race is an indication going in this way.
Some limitations to the present study are represented by the management of variable slopes during exercise in the field, different from a standardized exercise at treadmill, and the absence of oxygen consumption and respiratory muscles work data. Finally we have also to consider the influence of ventilatory determinants to the altitude’s response.

Future investigations of the posture, such as a specific study during exercise on treadmill at different slopes, conducted both at sea level and at simulated hypoxia, should give more informations about the role of the posture on breathing pattern. It could also help to better identify the influence of the level of hypoxemia (duration and severity of oxygen desaturation) on racing performance.

Not less important it would be the exploration of possible strategies for the enhancement of the posture, as i.e the respiratory muscles training. Indeed breathing involves also the back and abdominal muscles that contribute to posture control. Therefore the respiratory muscle training could be a method to improve the posture and the thoraco-abdominal coordination.

A study conducted on swimmers [72] supports this hypothesis displaying that four weeks of respiratory muscle training strains the spine, leading to better posture control and an increase in pulmonary volumes (VC and FEV$_1$).

Turner et al. [73] evidenced also that the inspiratory muscle training significantly reduces the oxygen cost of breathing during exercise suggesting that this reduction of oxygen requirement of the respiratory muscles may facilitate the increased O$_2$ availability to the active muscles. Furthermore it is demonstrated that the respiratory muscle endurance training improves the respiratory muscle endurance as well as the resistance performance reducing the perception of breathlessness [74, 75].

We conclude that in elite athletes during heavy exercise the increase of ground slope leads to a reduced thoraco-abdominal synchrony that is associated to a less efficient breathing pattern and tissue oxygenation, more evident for slopes superior to 20-30%. The athletic performance is negatively influenced by these changes.

Acknowledgment
This study was performed in the framework of a project including other respiratory and cardiovascular evaluations. The study has been carried out with the collaboration of the ISF and thanks to a contribution of EV-K$^2$-CNR.
7. STUDY 2: VENTILATORY PATTERN AND EXERCISE CAPACITY IN ASTHMATICS AND NON-ASTHMATICS IN RELATIONSHIP TO BMI

Background

Obesity (Body mass index or BMI $\geq 30$ kg/m$^2$) is the most common metabolic disease in the world and its prevalence is raising worldwide. Respiratory function is impaired in obesity and the magnitude of impairment is more clearly demonstrable in cases of severe obesity (BMI$>40$). Several epidemiological studies confirm that obesity precedes and predicts the onset of asthma with a time effect, and that increased obesity leads to more severe asthma with a dose-response effect. Obesity increases the prevalence and incidence of asthma [44]. A cohort study on 135,000 Norwegian evidenced that the risk of asthma increases steadily with BMI, from a BMI of 20 and 22 in men and women respectively [46]. Asthma incidence is increased by 50% in overweight/obese individuals with a dose-response relationship, with no differences of gender [47]. Higher BMI is also associated with worse asthma control and the quality of life independently of age, sex and asthma severity [48]. The obesity is a modifiable risk factor of asthma and regular exercise is associated to better asthma control [60]. Nevertheless not very much is known about the exercise capacity and physical activity in obese asthmatics.

The relationship between asthma and exercise is mainly characterized by two aspects: in most asthmatics (60-80%) exercise can provoke an increase in airways resistance inducing the so called “exercise-induced bronchospasm; on the other hand, regular physical activity and participation in sports are considered to be important components in the overall management of asthma. A number of studies [76, 77] have reported asthmatics to have lower cardiorespiratory fitness than their peers and physical inactivity has been associated with a higher number of hospital admissions, reduced absenteeism from work, asthma symptoms and use of medication [55]. In people with asthma, physical training can improve cardiopulmonary fitness without changing lung function. It is not yet clear whether improved fitness is translated into improved quality of life [78].

The aim of the first part of the study is addressed to the analysis of the relationship between BMI and airflow obstruction in asthmatic subjects and to identify and confirm a possible role of obesity on the airflow severity.
In the second part of the study we have recruited two groups: one of asthmatic and the second of non-asthmatic subjects with the aim to analyse their ventilatory pattern and exercise capacity during a standardized exercise in relationship with different body mass indexes (BMI) and severity of obstruction. We also analyzed the physical activity level and quality of life to well understand the incidence of obesity and airflow limitation on these factors.

**Materials and methods**

**Subjects**

In the first part of the study, spirometric and anthropometric data of 280 asthmatic subjects regularly visited at the Asthma Center of the University Hospital in Ferrara have been retrospectively analyzed and evaluated. In the second part we have studied 55 asthmatic patients selected from the group analyzed in the first part. Patients were progressively recruited with a phone interview by explaining them the aim and the protocol of the study. Patients were considered eligible if they had a diagnosis of asthma [26] and a stability in the respiratory disease for at least 8 weeks. The age range of this group spanned between 18 and 80 years; in all patients there was no clinical contraindication to exercise testing and no presence of any osteoarticular and cardiovascular diseases. The control group instead was composed by 37 matched non-asthmatics subjects participating in an exercise program at the Medical Sport Center “Fausto Coppi” of Ferrara, with a BMI between 18.5-43 kg/m². Evaluations were executed at the Laboratory of Respiratory Pathophysiology of the University Hospital of Ferrara and at the Medical Sport Center “Fausto Coppi”. Data from each participant included age, gender, height, weight, smoking history, medication use, medical history, physical examination. All participants accepted to provide informed consent prior to the testing. The study protocol was approved by the Committee of the Ethics of University Hospital of Ferrara.

The two groups were matched by age, gender, BMI and the asthmatics group by spirometric severity categories, European Respiratory Society (ERS) criterion [79].
Study design
The first part of the project was an observational study on anthropometric and pulmonary function data analysis of asthmatic patients regularly followed at the Asthma Center of the University Hospital in Ferrara. Data of the last visit and pulmonary function test were analysed. The second part was a non-blinded parallel observational study comparing the physical activity level, quality of life and the physiologic responses during exercise in matched asthmatics and non-asthmatics subjects. Hereafter are the methods of the second study.

Six Minute Walking Test (6MWT)
The 6MWT was performed for all participants. Subjects were instructed to walk as fast as they could along an even, 23-meters hospital corridor marked every 5 m and the last bit for 3 m. The operator used a lap counter system and the total distance walked during 6 min was measured using a tape measure from the nearest marker on the floor. For this test, patients were instructed to walk as far as possible along the corridor for 6 min. Rest periods were allowed and standardized encouragement was offered every minute, according to ATS Statement [80]. Borg ratings of dyspnea and leg fatigue were assessed on the modified Borg’s scale 0-10 before the test and at test completion. A practice test was not given. Chest pain, severe dyspnea, physical exhaustion, muscle cramps, sudden gait instability or other signs of severe distresses were the criteria used for stopping the test. The distance covered in 6 min by each subject was used as variable for the analysis. During the test, the measurements of heart rate (HR), tidal volume (Vt), respiratory rate (RR) and oxygen arterial saturation (SpO₂) were determined with a portable device (Spiropalm, Cosmed IT).

Assessment of physical activity
Daily physical activity was measured using a multisensor Armband (SenseWear Pro armband; BodyMedia, Inc., Pittsburgh, PA, USA) which was worn on the upper right arm over the triceps muscle. This metabolic holter incorporates a biaxial accelerometer (longitudinal and transverse) and other physiological information sensors that detect the cutaneous temperature, the warm dissipated and the cutaneous galvanic response. The informations recorded are elaborated by an algorithm that provides reproducible
measurements of total energy expenditure (Kcal), active energy expenditure and energy expenditure at rest (Kcal), METs (Kcal/Kg/h), total number of steps, time spent in physical activity and duration of sleep. Patients were told to wear the Armband 24 h/day with the exception of the time spent on personal hygiene, for 7 days. The wearing time was recorded by the instrument. The first and last days were not used for the analysis because they were considered an incomplete daily measurement and a bias since the patients had to visit the Clinic at the University Hospital. At the end, measured data from 5 days (3 weekdays plus Saturday and Sunday) were available for most patients. For a valid day of activity measurement, the threshold was set at 90% wearing time per day. Days below that threshold were excluded from analysis. The energy expenditure was expressed in metabolic equivalent tax (METs), the ratio of work metabolic rate to resting metabolic rate (1METs = 3.5 mL/VO2/Kg or 1 Kcal/Kg/h). The physical activity level was calculated by dividing the total daily energy expenditure by whole-night sleeping energy expenditure. A physical activity level above of 1.6 METs defines an active person, 1.40–1.59 METs defines a moderately active, 1.2-1.39 defines a low active person and a person with a physical activity level below 1.2 is a sedentary person [81]. Since the weight has a not negligible influence in the METs calculation we decide to collect and analyze data not only of mean daily energy expenditure but also of mean weekly steeps.

**Pulmonary function test**

Pulmonary function tests were performed at baseline, with measurements of forced expiratory volume in the first second (FEV1), vital capacity (VC) and FEV1/VC with Spiropalm, Cosmed. Pulmonary function testing followed American Thoracic Society performance criteria. Spirometry was performed using equipment and techniques that meet standards developed by the American Thoracic Society (ATS) [28]. Severity of pulmonary obstruction was defined according to the ERS criterion (Figure 13) [79].
Quality of life assessment

The Asthma Quality of Life Questionnaire (AQLQ) [82] and Medical Outcomes Study short-form (SF-12) [83] were administered respectively to asthmatics and non-asthmatics group to assess the health related quality of life of participants.

The AQLQ is an asthma-specific questionnaire composed of 32 items which comprise four domains: Symptoms, Activity limitations, Emotional Functioning and Environmental Stimuli. Each domain can be scored from 1 (worst health) to 7 (best health). A total score can be obtained as the sum of scores on the four domains. Asthma-related quality-of-life questionnaire assesses the impact of asthma symptoms on the patient’s daily activities as well as the patient’s perspective on the overall effectiveness of asthma therapy.

The AQLQ is related to likelihood of exacerbations in asthma and it has demonstrated good reliability, construct validity and responsiveness of the questionnaire.

The SF-12 is a standardized generic measure, and has been used widely in research interested in the impairment associated with physiological and psychological health conditions. The 12 items contribute to 2 weighted scales, a Physical Component Summary Scale (PCS) and a Mental Component Summary Scale (MCS). Higher scores indicate higher levels of functioning.

Items on the PCS assess how health is perceived to limit everyday physical activities, how physical health is perceived to limit social functioning and productivity in work and other roles, and the extent to which pain is experienced. Items on the MCS assess how emotional health is perceived to limit social functioning and productivity in work and other roles, and the extent to which participants feel anxious, depressed, and lethargic.
Dyspnea
The dyspnea during the daily life activities was assessed by the Modified Medical Research Council (MMRC) dyspnea scale index [84]. The MMRC, has been shown to be a simple method categorizing patients with obstructive disease in terms of their disability. Levels of dyspnea are graded as follows:
Grade 0: “I only get breathless with strenuous exercise”
Grade 1: “I get short of breath when hurrying on the level or up a slight hill”
Grade 2: “I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level”
Grade 3: “I stop for breath after walking 100 yards or after a few minutes on the level”
Grade 4: “I am too breathless to leave the house”.

Obesity
Height and weight were measured by an operator, with the subject wearing no shoes and only lighting clothing. The height was measured with a wall-mounted stadiometer. Weight and height were then used to calculate the BMI. The international standard definition of obesity was used [29]. Subjects were classified as normal if BMI was <25 (NW); overweight if their BMI was ≥25 <30 (OW); and obese (OB) if BMI was ≥30. Subjects with BMI >35 were considered extremely obese (EOB).

Data and Statistical analysis
Data of HR, V_T, RR and SpO_2 were measured at rest and each 15 seconds during the 6MWT with Spiropalm system and averaged for one minute intervals. Student’s t test for unpaired data was used to evaluate differences in baseline characteristics of two groups of asthmatics and non-asthmatics. The normal distribution was verified with the Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) was used to test differences between four subgroups of EB, OB, OW and NW in both asthmatics and non-asthmatics groups. Correlations were analyzed by the Pearson correlation coefficient for dependent variables. The level of significance was set at p<0.05 for all
statistical comparisons. All computations were done using a statistical software package (GraphPad Prism 5; GraphPad Software; San Diego, CA).

Results

First part of the study

Spirometric and anthropometric values of 280 asthmatics (154 females, 126 males), with age between 18 and 89 years, are reported in Table 4. Subjects were divided in three categories: extreme obese, obese, overweight and normal weight on the obesity classification.

Table 4. Anthropometric and spirometric data of 280 asthmatics

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>EOB (3.5%)</th>
<th>OB (14.3%)</th>
<th>OW (32.5%)</th>
<th>NW (50.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects N</td>
<td>280 (100%)</td>
<td>10 (3.5%)</td>
<td>40 (14.3%)</td>
<td>91 (32.5%)</td>
<td>141 (50.3%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.2±16.7</td>
<td>49.6±13</td>
<td>52.8±17</td>
<td>53.7±17.4</td>
<td>41.9±14.3</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
<td>25.5±4.8</td>
<td>39.1±6*</td>
<td>33.5±4.5*</td>
<td>27.2±1.4*</td>
<td>21.8±1.7*</td>
</tr>
<tr>
<td>FEV1%</td>
<td>85.2±18</td>
<td>82.2±20.8</td>
<td>83.2±18.8</td>
<td>82.4 ±19.2</td>
<td>87.9±16.2</td>
</tr>
<tr>
<td>VC %</td>
<td>102.3±15</td>
<td>100.3±19.4</td>
<td>101.6±16.2</td>
<td>100.3±17.7</td>
<td>104.3±14.4</td>
</tr>
<tr>
<td>FEV1/VC %</td>
<td>85.6±13</td>
<td>89.6±12.1</td>
<td>85.1±15.8</td>
<td>83.2±12.3</td>
<td>87±12.1</td>
</tr>
</tbody>
</table>

3.5% (5M,5F) were EOB; 14.3% (20M,20F) were OB; 32.5% (50M,41F) were OW; 50.35% (54M,87F) were NW and 2.8% (2M,6F) were underweight. The prevalence of obesity and overweight was higher in males than females (respectively 15.9% vs 13% and 39.7% vs 26.6%). The same was evidenced for the severity of obstruction. In Table 5 subjects were matched for the severity of obstruction: mild (FEV1%>70), moderate (69>FEV1%>60), severe (FEV1%<59).

Table 5. Severity of bronchial obstruction

<table>
<thead>
<tr>
<th></th>
<th>Mild obstruction</th>
<th>Moderate obstruction</th>
<th>Severe obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tot. N (%)</td>
<td>187 (66.79)</td>
<td>66 (23.57)</td>
<td>27 (9.64)</td>
</tr>
<tr>
<td>Males N (%)</td>
<td>76 (60.32)</td>
<td>35 (27.78)</td>
<td>15 (11.90)</td>
</tr>
<tr>
<td>Females N (%)</td>
<td>111 (72.08)</td>
<td>31 (20.13)</td>
<td>12 (7.79)</td>
</tr>
</tbody>
</table>

In males the difference in FEV1% between OB, OW and NW is more evident
than in females (OB: 76.9%, OW: 78.2%, NW: 85.9%).

For a better analysis we defined two different groups: one with BMI $\geq 25$ and the other with BMI $< 25$ (Table 6).

<table>
<thead>
<tr>
<th>Table 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>BMI $&lt; 25$</td>
</tr>
<tr>
<td>BMI $\geq 25$</td>
</tr>
</tbody>
</table>

Mean ± standard deviation
* p 0.02

The relationship between obstruction severity (ERS 2005) and BMI evidenced a FEV$_1$% significantly lower in subjects with a BMI $\geq 25$ as compared to subjects with a BMI $< 25$ (p $<$ 0.05) (Figure 14). No differences in vital capacity between two groups.

There is not significant correlation between BMI and FEV1%.

**Second part of the study**

The two groups (asthmatic and non-asthmatic subjects) were subdivided in four categories EOB, OB, OW, NW. Characteristics of 55 asthmatic patients are reported in Table 7. Twenty four subjects were obese (6M, 18F), 11 extremely obese (2M, 9F), nineteen overweight (9M 10F) and twelve normal weight (4M,
There were no differences in the baseline characteristics and in lung function measurements, expressed in terms of FEV$_1$/VC% and FEV$_1$%, between asthmatics EOB, OB, OW and NW. Neither the presence nor the severity of obstruction resulted related to BMI.

**Table 7. Asthmatics characteristics**

<table>
<thead>
<tr>
<th></th>
<th>E OB</th>
<th>OB</th>
<th>OW</th>
<th>NW</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>11 (2)</td>
<td>24 (43.6)</td>
<td>19 (34.5)</td>
<td>12 (21.8)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>56.2±13.2</td>
<td>57.7±11.6</td>
<td>58.4±13.1</td>
<td>54.7±7.5</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (Kg/m$^2$)</td>
<td>37.8±2.7</td>
<td>35±3.4</td>
<td>27.3±1.3</td>
<td>23.4±1.3</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>FEV$_1$ %</td>
<td>80.6±17.6</td>
<td>80.1±19.1</td>
<td>85.5±20.8</td>
<td>84±14.5</td>
<td>ns</td>
</tr>
<tr>
<td>VC %</td>
<td>98±17.6</td>
<td>98.7±15.7</td>
<td>100.3±15.9</td>
<td>94.6±16.1</td>
<td>ns</td>
</tr>
<tr>
<td>FEV$_1$/VC %</td>
<td>86±14</td>
<td>84.2±14.6</td>
<td>88.±15.5</td>
<td>88.9±8.1</td>
<td>ns</td>
</tr>
<tr>
<td>FEV$_1$/VC</td>
<td>67.1±10.5</td>
<td>65.5±11.8</td>
<td>68.26±12.5</td>
<td>69.4±6.2</td>
<td>ns</td>
</tr>
<tr>
<td>SpO$_2$ % rest</td>
<td>96.6±1</td>
<td>96.3±1.4</td>
<td>96.5±1.3</td>
<td>98±0.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

Characteristics of 37 non-asthmatic subjects (control group) are reported in Table 8. Subjects were 9 EOB (3M, 6F), 15 OB (8M, 7F), 14 OW (10 M, 4 F), 8 NW (3M, 5F).

There was a difference in FEV$_1$% between OB and EOB vs OW in non-asthmatics group.

**Table 8. Non-asthmatics characteristics**

<table>
<thead>
<tr>
<th></th>
<th>E OB</th>
<th>OB</th>
<th>OW</th>
<th>NW</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>9 (4%)</td>
<td>15 (40)</td>
<td>14 (37.8)</td>
<td>8 (21.6)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>50.8±8.3</td>
<td>55.3±9.5</td>
<td>53.1±7.5</td>
<td>50.1±5.9</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (Kg/m$^2$)</td>
<td>38±2.2</td>
<td>38.5±3.2</td>
<td>28.1±1.8</td>
<td>22±1.3</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>FEV$_1$ %</td>
<td>98.5±6.5*</td>
<td>100.74±8.6**</td>
<td>114±10.02</td>
<td>103.8±19.6</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>VC %</td>
<td>104.7±11.1</td>
<td>105±9.7</td>
<td>115.1±9.1</td>
<td>115.3±23.5</td>
<td>ns</td>
</tr>
<tr>
<td>FEV$_1$/VC %</td>
<td>104.2±6.9</td>
<td>99.6±7.7</td>
<td>102.9±6.4</td>
<td>94.9±7.6</td>
<td>ns</td>
</tr>
<tr>
<td>SpO$_2$ % rest</td>
<td>97.3±0.9</td>
<td>97.0±1</td>
<td>97.1±1.1</td>
<td>97.2±0.7</td>
<td>ns</td>
</tr>
</tbody>
</table>

**OB vs OW; * EOB vs OW**
As expected the two groups of asthmatics and non-asthmatics differed significantly for lung function. Asthmatics had a reduced ratio FEV<sub>1</sub>/VC% and a reduced FEV<sub>1</sub>% compared with corresponding non-asthmatics categories (p<0.001) (Table 9).

**Table 9. Lung function values of Asthmatics vs Non-asthmatics**

<table>
<thead>
<tr>
<th></th>
<th>E OB</th>
<th>OB</th>
<th>OW</th>
<th>NW</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; %</td>
<td>80.6±17.6</td>
<td>80.1±19.1</td>
<td>85.5±20.8</td>
<td>84±14.5</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/VC %</td>
<td>86±14</td>
<td>84.2±14.6</td>
<td>88.±15.5</td>
<td>88.9±8.1</td>
</tr>
</tbody>
</table>

\* p< 0.001 asthmatics vs non-asthmatics

In both groups of asthmatics and non-asthmatics the MMRC dyspnea score in OB and EOB resulted higher than in NW. Comparing asthmatics with non-asthmatics, in all four categories asthmatics showed a higher dyspnea score (Table 10).

**Table 10. MMRC dyspnea score in asthmatics vs non-asthmatics**

<table>
<thead>
<tr>
<th></th>
<th>E OB</th>
<th>OB</th>
<th>OW</th>
<th>NW</th>
<th>* p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>asthmatics</td>
<td>1.6±0.9</td>
<td>1.4±0.8</td>
<td>1.0±0.7</td>
<td>0.8±0.5</td>
<td>* P&lt;0.001</td>
</tr>
<tr>
<td>non-asthmatics</td>
<td>0.7±0.4</td>
<td>0.7±0.4</td>
<td>0.1±0.3</td>
<td>0.1±0.3</td>
<td>* P&lt;0.001</td>
</tr>
</tbody>
</table>

\* p< 0.001 asthmatics vs non-asthmatics;

**Physical activity**

There is a trend to a lower physical activity in subjects with a higher BMI in both groups of asthmatics and non-asthmatics. In asthmatics it is independent from the presence and the severity of obstruction (r 0.07, ns; r -0.04, ns, respectively). Data that we collected demonstrate a great variability and despite there is a statistical significance, the elevated value of the standard deviation it does not permit to get definitively conclusions.

**Quality of Life**

We did not find significant differences in quality of life between different BMI
categories both in asthmatics group (AQLQ total score: OB 5.3±0.7; OW 5.4±1.0; NW 5.6±0.8) and non-asthmatics group (SF-12 total score: OB 92.8±18.8; OW 98.4±14.6; NW 101.1±11). Since the questionnaires used for two groups were different and had different score computing, we could not compare asthmatic and non-asthmatic groups between them.

**Exercise Capacity**
During 6MWT, OB showed reduced exercise capacity than NW (Table 11 and Table 12), as is represented by the significant inverse correlation between BMI and six minute walking distance both in asthmatics (r=-0.4, p 0.004) and non-asthmatics (r=-0.6, p 0.0001) (Figure 15).
The Borg index for the final dyspnea and leg fatigue is always < 3 in both groups.

**Table 11. Exercise capacity in asthmatics (6MWT)**

<table>
<thead>
<tr>
<th></th>
<th>EOB</th>
<th>OB</th>
<th>OW</th>
<th>NW</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meters</td>
<td>419±92</td>
<td>436.1±89.8 *</td>
<td>484.4±77.9</td>
<td>548.4±52.5 *</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Dyspnea (Borg)</td>
<td>2.6±1.5</td>
<td>2.6±2.1</td>
<td>2.3±2.1</td>
<td>1.2±1.3</td>
<td></td>
</tr>
</tbody>
</table>

**Table 12. Exercise capacity in non-asthmatics (6MWT)**

<table>
<thead>
<tr>
<th></th>
<th>EOB</th>
<th>OB</th>
<th>OW</th>
<th>NW</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meters</td>
<td>497±55 *</td>
<td>513.8±55.1 *</td>
<td>571±47.4</td>
<td>599.8±34.5 *</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Dyspnea (Borg)</td>
<td>2.5±0.9</td>
<td>1.8±1.3</td>
<td>2.1±1.1</td>
<td>1.1±0.8</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 15**

![Figure 15](image-url)
Comparing the two groups, non-asthmatics showed a higher 6 minute walking distance than asthmatics independently from the obesity classification (Figure 16).

**Ventilatory analysis:**
During exercise (6MWT) we found a difference in the ventilation increase between OB (EOB) and NW only in the asthmatics group (Table 13, Figure 17). This was independent from the level of obstruction. Both in asthmatics and non-asthmatics the VE increase was mainly due to the increase in $V_T$ rather than in RR.

![6MW Distance](image)

**Figure 16**

<table>
<thead>
<tr>
<th>Table 13. Ventilatory parameters during exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthmatics</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Increase VE (%)</td>
</tr>
<tr>
<td>Increase $V_T$ (%)</td>
</tr>
<tr>
<td>Increase RR (%)</td>
</tr>
<tr>
<td><strong>Non Asthmatics</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Increase VE (%)</td>
</tr>
<tr>
<td>Increase $V_T$ (%)</td>
</tr>
<tr>
<td>Increase RR (%)</td>
</tr>
</tbody>
</table>
In asthmatics there were differences in ventilatory reserve between OB and NW: 35.8±19.1 vs 63.5±24.3 (L/min), 48.2±12.9 vs 36.2±10.7 (%MVV), while these differences were not present in non-asthmatics group.

![VE increase (%) 6MWT](image)

**Discussion**

The first part of the study aimed to identify the role of increased BMI on airflow obstruction severity in asthmatic subjects. Results of this study draw to the conclusion that obesity (BMI >30) leads to a more severe asthma. In fact there is a significant difference in FEV₁% between the groups of normal weight (BMI<25) and overweight/obese subjects (BMI<25). These results are in accord with the literature [85] founding a reduction in FEV₁ and FVC according to the BMI increase and a negative relationship between BMI and FEV₁/FVC in asthmatics. One possible explanation of these findings could be the mechanical factor: an excess of fatty tissue compressing the thoracic cage and a fatty infiltration of chest wall might contribute to determine a reduction in lung volumes for a mechanical effect. This could lead to a reduction in airway peripheral diameter, and over time to an increase of airway obstruction.

The second part of the study was designed to better understand the influence of obesity and different level of airway obstruction, on exercise capacity, ventilatory pattern, physical activity level and quality of life.

This part of the study has been done on a limited sample of population (55
asthmatics and 37 non-asthmatics) which cannot be representative of a general asthmatics population, anyway we can observe a trend (not statistically significant) of greater severity of obstruction (lower FEV₁%) in obese as regard as normal weight asthmatics. The first important result is that obesity is associated to a lower exercise capacity both in asthmatics and non-asthmatics: in fact BMI is significantly and inversely correlated to a reduced walking distance covered during the six minute walking test. The presence of asthma constitutes and additional limitation to the reduction of exercise capacity as shown by the lower distance walked by asthmatics as compared to non-asthmatics in all BMI categories. We find the same trend in the dyspnea score (MMRC): obese subjects always have a greater perception of the symptom in daily activities as compared to NW with higher score in asthmatics. This is probably due to the presence of bronchial obstruction. These data, as reported by recent literature, confirm that exercise capacity in obese is frequently affected by the sensation of dyspnea, that may originate from an increased work of breathing and by discomfort due to increased load on the feet and joints [86]. Moreover obesity seems to have a negative influence on the daily physical activity independently from the presence of asthma, also if the great variability in our data does not allow to get definitively conclusions.

The second relevant result regards the influence of asthma on ventilation during exercise. During exercise the influence of obesity seems to be relevant only if associated to the presence of asthma. In fact obese asthmatics have a significantly greater increase in ventilation as compared to normal weight while no differences were found in non-asthmatics showing a smaller ventilatory reserve. This could explain the reduced exercise capacity of obese asthmatics and it is probably the direct result of the functional impairment of the bronchial obstruction associated to the greater metabolic energy exchange required by the increased body mass. The ventilatory increase in both groups is mainly due to an increase in tidal volume rather than in respiratory rate, as expected [31]. It could be due to the modality of exercise: the 6MWT is not an incremental maximal test and a great increase in tidal volume rather than in respiratory rate is a normal ventilatory answer to a submaximal constant exercise.
In summary we found that obesity has a negative effect on exercise capacity. The presence of asthma worse the exercise capacity and influences also the lung function and the ventilation during exercise. An investigation on the role of an elevated BMI on the breathing pattern at different exercises mode (continuous and incremental workload) and the repetition of the same protocol after a significant weight loss in obese and overweight subject.
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