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# Effects of the supine position on respiratory mechanics assessed by the forced oscillation technique in chronic obstructive pulmonary disease (COPD) and normal subjects

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# EFFECTS OF THE SUPINE POSITION ON RESPIRATORY MECHANICS ASSESSED BY THE FORCED OSCILLATION TECHNIQUE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND NORMAL SUBJECTS

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# EFFECTS OF THE SUPINE POSITION ON RESPIRATORY MECHANICS ASSESSED BY THE FORCED OSCILLATION TECHNIQUE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND NORMAL SUBJECTS

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is due to chronic inflammation of the airways and lung parenchyma leading to either chronic airway obstruction, emphysema or both. It is mostly seen in smokers or former smokers but exposition to occupational or domestic noxious gases can also be a cause. It is treatable but not curable and currently is the fourth leading cause of death worldwide. The most disabling symptom is dyspnea, occurring at exercise or even at rest in severe disease. Some patients also complain of orthopnea, the occurrence or increase of breathlessness in the supine posture. Although it is a common symptom, the cause of orthopnea in COPD remains elusive and is poorly describe in literature.

This study aims to assess the changes in respiratory mechanics occurring when switching from the sitting to the supine posture. Two techniques were used: the forced oscillation technique (FOT) and spirometry. Spirometry is the most commonly used technique in the clinic to measure lung function. The FOT consists in sinusoidal soundwaves sent by a loudspeaker into the airways in order to measure the respiratory system resistance and reactance. FOT was used to measure parameters related to respiratory resistance ($R_5$, $R_{20}$ and $R_{5-20}$) and reactance ($\Delta X_5$, $X_5$, $X_{5in}$, $X_{5ex}$ and AX) and spirometry for the assessment of mobilized lung volumes and flows. These tests were performed in both position in 20 normal subjects (control group), and 45 stable COPD subjects with variable disease severity, of whom 25 reported orthopnea.

This study showed significant differences between the COPD and control groups for both FOT and spirometry parameters in both the sitting and the supine postures with more significant increase in small airways related parameters when adopting the supine position. FOT suggests the occurrence or increase in expiratory flow limitation since $\Delta X_5$ and $X_{5ex}$ were increased in the supine posture, particularly in the orthopneic group. Importantly, we observed a significant decrease in inspiratory capacity (IC) in COPD subjects while it increased in supine position in the control group, suggesting an increased functional residual capacity (FRC) in the COPD group as opposed to a decrease in the control group. In the COPD group, these changes were more pronounced in orthopneic patients. We also observed a correlation between changes in dyspnea and changes in AX, $\Delta X_5$, $X_5$ and $X_{5ex}$ between sitting and supine.

In conclusion, this study showed that the adoption of the supine position is associated with profound changes in small airway function in patients with COPD. These changes are more pronounced in orthopneic subjects and suggest that they are responsible for the occurrence or increase in expiratory flow limitation and dynamic lung hyperinflation which play a critical role in the genesis of dyspnea in COPD.

**Keywords**: Chronic Obstructive Pulmonary Disease, Forced Oscillation, Spirometry, Supine position, Orthopnea

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# Table of content

**List of abbreviations**

ANOVA: analysis of variance

AX: area under the reactance-frequency curve

BF: breath frequency

BMI: body mass index

cm $H_2O$: centimetre of water

COPD: chronic obstructive pulmonary disease

DH: dynamic hyperinflation

EELV: end expiratory lung volume

EFL: expiratory flow limitation

EVC: expiratory vital capacity

$FEV_1$/FVC: Tiffeneau index

$FEV_1$: forced expiratory volume in one second

FOT: forced oscillation technique

FRC: functional residual capacity

$FRC_{pleth}$: functional residual capacity measured by body plethysmography

Fres: resonant frequency measure by the forced oscillation technique

FVC: forced vital capacity

GOLD: global initiative for chronic obstructive lung disease

IC: inspiratory capacity

kg: kilogram

L: litre

MRC: medical research council

PEEP: positive end expiratory alveolar pressure

PV: pressure-volume

$R_{20}$: resistance measured at 20 Hz by the forced oscillation technique

$R_5$: resistance measured at 5Hz by the forced oscillation technique

$R_{5-20}$: resistance measured at 5 Hz minus resistance measured at 20 Hz by the forced oscilla-

tion technique

$R_{aw}$: airways resistance

$R_{rs}$: respiratory system resistance

RV: residual volume

s: second or seconds

SD: standard deviation

$SpO_2$: arterial oxygen saturation

${}_sR_{aw}$: specific airway resistance

TLC: total lung capacity

VAS: visual analogue scale

VC: vital capacity

VE: minute ventilation

$V_T$: tidal volume

WHO: world health organization

$X_5$: reactance measured at 5 Hz by the forced oscillation technique

$X_{5ex}$: expiratory reactance measured at 5 Hz by the forced oscillation technique

$X_{5in}$: inspiratory reactance measured at 5 Hz by the forced oscillation technique

$X_{rs}$: respiratory system reactance

y: years

$\Delta X_5$: difference between inspiratory and expiratory reactance measured at 5 Hz by the forced oscillation technique

# 1. Introduction

## 1.1. COPD

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent diseases worldwide. According to the World Health Organisation (WHO), 251 million cases were reported around the world in 2016 and it was responsible for 3.17 million deaths in 2015. COPD was the fifth leading cause of death in 2002 [1], became the fourth in 2015, and the WHO anticipates that it will become the third cause of death worldwide before 2020 [2].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) (an international panel aiming at disseminating guidelines about COPD) defines COPD as a common disease characterised by permanent airflow obstruction as measured by spirometry and the presence of persistent respiratory symptoms.

COPD is considered as a non-reversible disease due to chronic inflammation in the peripheral airways. Inhaled noxious particles and gases from tobacco smoking but also occupational exposure or pollution are responsible for this inflammation [3]. Host factors put some subjects at risk for developing the disease as demonstrated by the fact that some smokers never develop COPD while others develop early disease due to a rare mutation in the gene coding for α1-antitrypsin, a major serine protease inhibitor [1, 4]. Indeed, it has been demonstrated that smokers with a severe deficiency in α1-antitrypsin have an increased risk for developing more severe COPD at a younger age [5].

COPD includes subjects with both chronic bronchitis and emphysema although some subjects with chronic bronchitis or emphysema do not have airflow obstruction and therefore do not meet the definition criteria for COPD.

Nowadays no treatment exists to cure COPD but some drugs can relieve symptoms caused by the disease and slow down its progression. However, as demonstrated by Anthonisen *et al.* (1994) [6] the best and up to now only way to slow down the lung function decline is to stop smoking. Indeed, as represented on Figure 1, reproduced from Anthonisen, the decrease of forced expiratory volume in one second ($FEV_1$) is more important in subjects who continued to smoke than in those who had stopped.

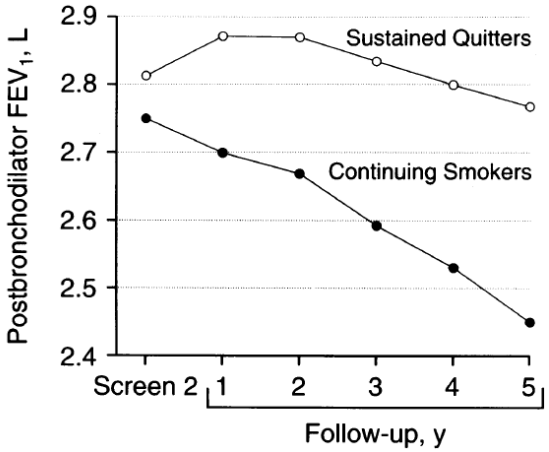


*Figure 1: Evolution of FEV1 in subjects who stopped smoking (empty circles) and in subjects who do not stopped (full circles). The FEV1 decline is faster in continuing smokers than in sustained quitters.*[1]

[1] From: Anthonisen, N.R., et al., Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. Jama, 1994. **272**(19): p. 1497-1505.

### 1.1.1. Chronic bronchitis

Chronic bronchitis has a clinical definition. It is defined by the presence of a productive cough for at least three months per year during two years. It is associated with an excess of phlegm in the airways caused by submucosal bronchial glands hypertrophy (Figure 2) and by an increase of the number of goblet cells in the airway epithelium. Together with increased connective tissue and smooth muscle in the airway wall, these factors concur to reduce airway diameter.

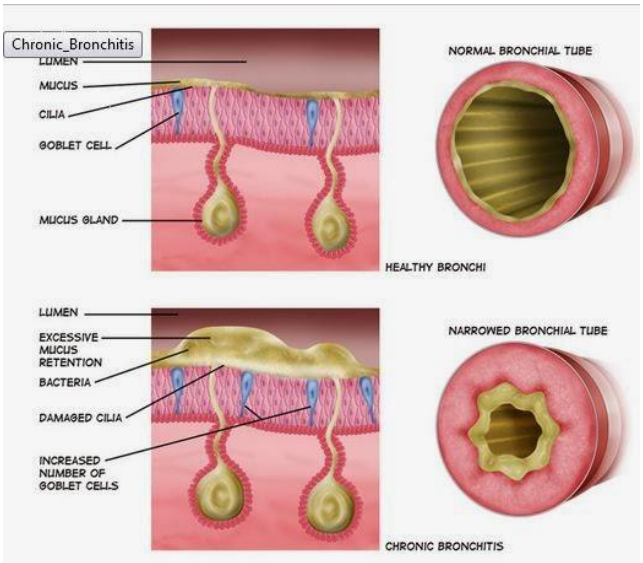


*Figure 2: Airway changes in COPD.*[2]

### 1.1.2. Emphysema

On the other side, emphysema has a histological definition: it is characterised by the presence of permanent alveolar space enlargement associated with alveolar wall destruction. Since lung biopsies are not performed easily, the best way to detect emphysema in the clinical setting is to perform a chest computerised tomography [7].

From a physiological point of view, emphysema is associated with a loss of lung elastic properties. Emphysema reduces the elastic recoil of the alveolar walls, which translates in increased lung compliance. Since alveoli cannot deflate normally, a larger volume of air will stay in the alveoli at end-expiratory lung volume (EELV) or functional residual capacity (FRC; Figure 3A) [8]. This increased lung volume is called lung hyperinflation. As discussed below, lung hyperinflation is a major determinant of dyspnea in COPD and other airway diseases. Referring to Figure 3B, emphysema subject have an increased FRC as compared to healthy people.

Since lung elastic recoil plays a critical role in the tethering of the small airways, emphysema also reduces the diameter of these small airways.

## 1.2. Dyspnea

Dyspnea is the most disabling symptom for subjects with COPD. Dyspnea is the sensation to be out of breath [9], to experience laboured breathing [10]. However, because it is a subjective sensation, the American Thoracic Society decided to define dyspnea as "*a term used to*

[2] From: http://2.bp.blogspot.com/-W2njYAtMXfE/UtOma0VHOuI/AAAAAAAAAWM/0vSpTK0rfT8/s1600/Chronic+Bronchitis-+Causes,+Symptoms,Types,+Diagnosis+And+Treatment.jpg@.

*characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity*" [11].

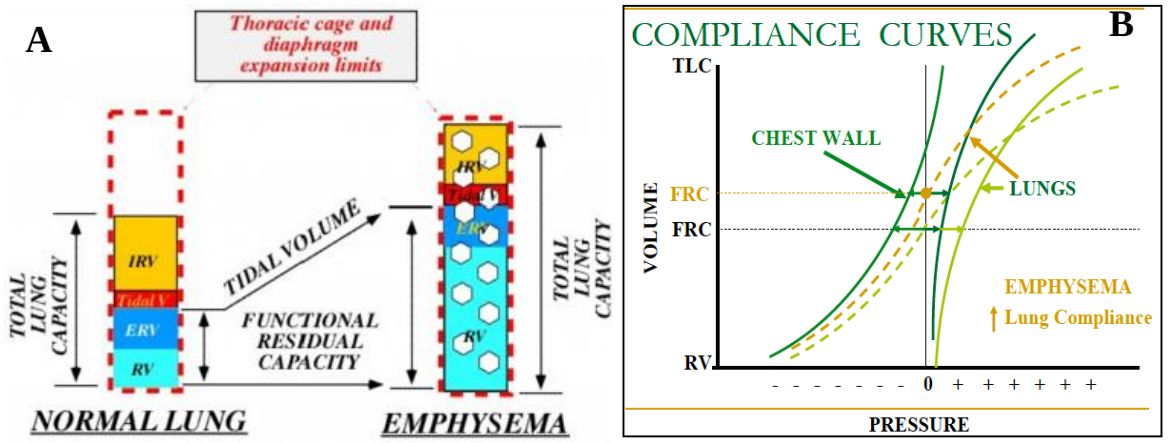


*Figure 3: A) Variation in lung volume compartments with and without emphysema. Emphysema is associated with an increased residual volume due to the enlargement of alveolar spaces secondary to emphysema, also leading to an increase in total lung capacity. IRV: inspiratory residual volume; Tidal V: tidal volume; ERV: expiratory residual volume; RV: residual volume.*[3]

*B) Pressure-volume curve representing the elastic properties of the respiratory system (dotted lines) and its components: lungs and chest wall. The lung P-V curve is shifted upwards and leftwards in emphysema (dark green) as compared to a healthy subject (light green) due to increased lung compliance. Chest wall compliance is the same for both subjects. The yellow dotted curve represents the sum of the chest wall and lung elastic properties in a subject with emphysema. Compared to the green dotted curve, it is easy to understand that FRC (corresponding to the equilibrium volume of the respiratory system, where recoil pressure is 0) is larger in emphysema due to the increase in lung compliance. RV: residual volume; FRC: functional residual capacity; TLC: total lung capacity.*[4]

However, dyspnea is not seen in all the subjects and its intensity depends on COPD severity and other factors. As dyspnea is subjective [12, 13], its severity depends on behavioural and psychological aspects [14].

Some subjects are complaining of a worsening of dyspnea when they adopt the supine position. This is called orthopnea. Orthopnea is commonly observed in left heart failure but is also common in COPD where, unlike heart failure where orthopnea occurs after more or less two hours, orthopnea can appear after less than 10 minutes [15]. Unfortunately, although it is a common clinical finding, there is a paucity of data regarding orthopnea in COPD subject. Moreover, its pathogenesis is still not well understood [16].

Dyspnea is related to the load imposed on the inspiratory muscles and to the capacity of inspiratory muscles. More precisely, dyspnea is positively related to the inspiratory muscles workload and inversely related to their capacity. As discussed below, COPD has detrimental influences on these two dimensions.

The inspiratory muscle workload has a resistive and an elastic component.

The resistive component is directly proportional to airway resistance ($R_{aw}$) and inspiratory flow. The elastic component is directly proportional to dynamic elastance and inspiratory volume. In COPD subjects, both $R_{aw}$ and dynamic elastance are usually increased.

[3] From: http://ispub.com/IJTCVS/5/2/7216#.
[4] From: https://www.studyblue.com/notes/note/n/final/deck/13097681.

According to the Poiseuille equation[5], $R_{aw}$ is inversely proportional to the fourth power of airways radius [17, 18]. The latter is reduced by multiple factors in COPD, such as airway muscle and connective tissue hypertrophy, increased airway smooth muscle tone, increased mucus in the airway lumen, and reduced small airway tethering due to emphysema. Accordingly, COPD is associated with increased $R_{aw}$.

The elastic properties of the respiratory system can be described by a pressure-volume (PV) curve (Figure 3B). The greater the elastance (which is the inverse of compliance), the greater the pressure drive needed to inflate the respiratory system (which translates in a flattened or horizontal PV curve). Due to the decreased elastance of the emphysematous lung, it might be difficult to understand why COPD is associated with an increased elastic load imposed on the inspiratory muscles. This apparent discrepancy can be resolved when considering that severe COPD subjects breathe at higher lung volumes when compared to healthy subjects. Accordingly, they breathe on a flatter portion of their respiratory system PV curve where elastance is increased. In fact, while healthy subjects have an EELV corresponding to the resting volume of their respiratory system (also known as the equilibrium volume); this EELV is higher than the resting volume in some COPD subjects. This phenomenon is called lung dynamic hyperinflation (DH).

The cause of DH is the reduction of airway lumen calibre and the resultant decrease in maximal expiratory flows (Figure 4) and the associated expiratory flow limitation (EFL). When severe, airway obstruction can be associated with EFL during tidal breathing. Accordingly, expiratory flows during tidal breathing are the maximal expiratory flow that can be generated in the airways. Indeed, as maximal expiratory flows progressively decrease, the resultant increase in expiratory time does not allow for adequate minute ventilation (VE) anymore. In this situation, the only way to increase expiratory flows to maintain adequate alveolar ventilation is to breathe at higher lung volumes, which corresponds to DH [19]. Initially, DH is only seen during physical exercise because of the higher VE (as can be seen from Figure 4) but as COPD worsens and maximal expiratory airflows decrease, it can even be present at rest.

DH plays a major role in the occurrence of dyspnea in COPD. Indeed, its detrimental role is not limited to an increased dynamic elastance. As EELV is higher than the resting volume of the respiratory system in case of DH, the air surplus that stays in the lungs after expiration creates a positive end expiratory alveolar pressure (PEEP) which needs to be neutralised by the inspiratory muscles before they are able to generate a negative alveolar pressure which is the drive for the inspiratory flow. PEEP adds to the workload faced by the inspiratory muscles. DH explains why dyspnea is influenced by reduced expiratory flows although it is a sensation mainly driven by afferences generated at the level of respiratory muscles during the inspiratory phase of the breathing cycle.

As can be seen from Figure 3B, the increased static lung compliance also plays a role to increase lung hyperinflation. Indeed, it increases the resting respiratory system volume. Accordingly, in case of emphysema associated with EFL, lung hyperinflation has both a dynamic and a static component. As already discussed, the inspiratory muscle workload is increased in the setting of COPD but lung hyperinflation also reduces the inspiratory muscle capacity. Indeed, it is associated with a flattening of the diaphragm and a reduced height of its vertical and muscular portion called the zone of apposition. The shortening of the zone of apposition of the diaphragm is the basis for the inspiratory effect of the main inspiratory muscle. As the diaphragm is put at mechanical disadvantage with lung hyperinflation, the inspiratory effort

[5] $R = 8\eta L/\pi r^4$ where R = resistance; $\eta$ = gas viscosity; L = length of the tube; r = radius of the tube.

must increase to inflate the lungs as compared to the normal situation. The reduced mechanical efficiency of the diaphragm is associated with a neuromechanical uncoupling between the efferences from the brain stem respiratory centre and the resultant mechanical effect of the inspiratory muscles. This is thought to be a major factor in the genesis of dyspnea in COPD[20].

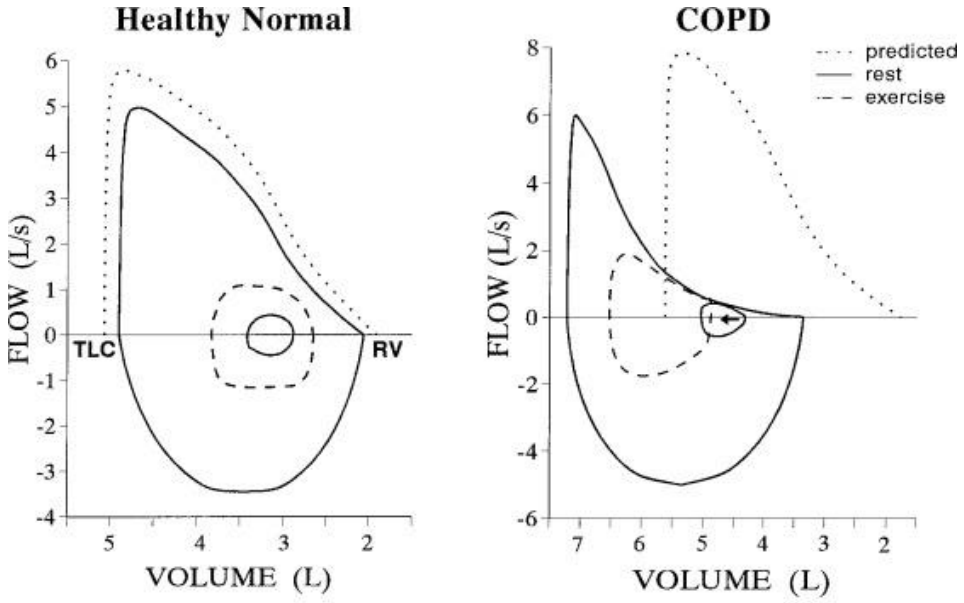


*Figure 4: Flow volume curves from a healthy (left) and a COPD subject (right). The largest envelopes represent the flow-volume obtained during a forced expiratory maneuver from TLC to RV followed by a forced inspiratory maneuver from RV to TLC. The small envelopes represent the tidal breathing flow-volume loops recorded at rest (continuous line) and during exercise (dotted lines). Abbreviations: TLC, total lung capacity; RV, Residual Volume.*[6]

## 1.3. Diagnostic tools

### 1.3.1. Spirometry

There are different tests to evaluate respiratory function. The most commonly used in the clinical setting is spirometry (or forced vital capacity maneuver). It is usually assessed with a pneumotachograph, an instrument allowing for the measurement of inhaled and exhaled airflows. From the measurements of flow in function of time, changes of the respiratory system volumes during inspiratory or expiratory maneuvers can be measured [21].

The most important parameters measured at spirometry are recorded during a forced expiratory maneuver from total lung capacity (the volume of the respiratory system after maximal inhalation). These parameters are (Figure 5):

- The $FEV_1$ and
- The forced vital capacity (FVC).

From these parameters, a third important parameter is calculated:

- The Tiffeneau index ($FEV_1$/FVC).

[6] From: http://bronchiectasis.com.au/wp-content/uploads/2015/09/Spirometry.png.

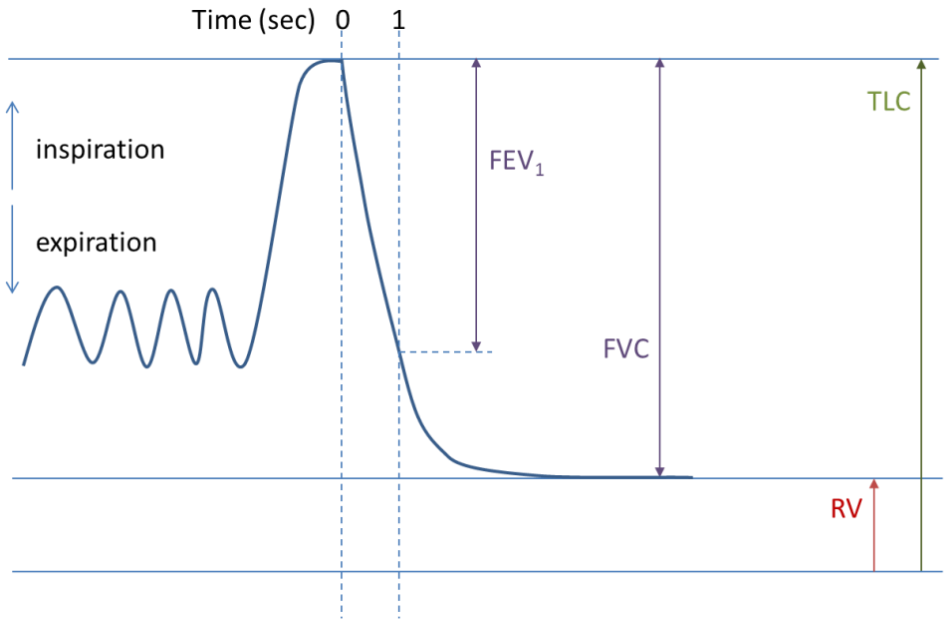


*Figure 5: Parameters measured by spirometry during a forced expiratory maneuver. As RV is a non mobilizable volume, RV and TLC cannot be measured with a pneumotachograph. $FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity.*[7]

A reduced Tiffeneau index is the criteria used to define the presence of airflow obstruction. According to GOLD, a diagnosis of COPD requires the presence of a reduced Tiffeneau index (defined in this case as lower than 70%) after bronchodilation [22]. Moreover, the level of $FEV_1$ allows the assessment of airflow obstruction severity according to GOLD (Table 1).

For a healthy subject, the graph representing airflow against lung volume during a forced expiration followed by a forced inspiration will be similar as the one seen on the left panel of Figure 4. In COPD, the graph will be different: expiratory flows are reduced for a given lung volume which can lead to EFL during tidal volume ($V_T$) breathing as already discussed. The reduced expiratory flows are responsible for the characteristic upper concavity of the maximal forced expiratory flow-volume curve seen on the right panel of Figure 4.

The major weakness of spirometry in the assessment of dyspnea is its poor association with the respiratory mechanics parameters that are associated with dyspnea such as airway resistance, lung compliance, tidal EFL or lung hyperinflation.

*Table 1: Classification of airflow obstruction severity in subjects with COPD according to GOLD*

| **COPD severity** | **Post-bronchodilator $FEV_1$ (% predicted)** |
|---|---|
| GOLD 1: Mild | ≥80 |
| GOLD 2: Moderate | 50-79 |
| GOLD 3: Severe | 30-49 |
| GOLD 4: Very Severe | <30 |

*A $FEV_1/FVC<70\%$ post-bronchodilator is required to make a diagnosis of COPD according to GOLD.*

[7] From: http://bronchiectasis.com.au/wp-content/uploads/2015/09/Spirometry.png.

### 1.3.2. Body plethysmography

Another test used in the clinic is the body plethysmography. Plethysmography is useful to assess some aspects of COPD since it can measure different parameters reflecting the functional and structural aspect of the lungs [23]. Unlike spirometry, body plethysmography can measure the static lung volumes: residual volume (RV), functional residual capacity (FRC), or total lung capacity (TLC) and above all, $R_{aw}$. Accordingly, it gives additional informations regarding the consequences of COPD, i.e. data regarding lung hyperinflation and $R_{aw}$, which are of interest when assessing the cause and the severity of dyspnea.

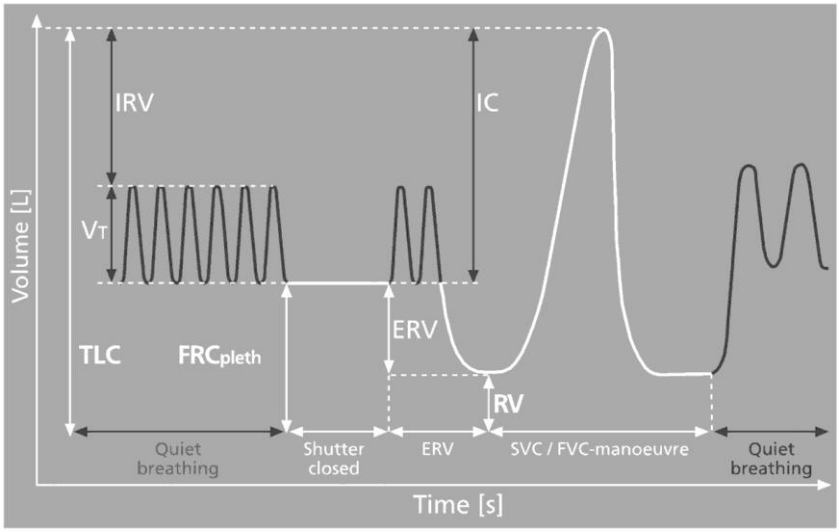


*Figure 6: Sequence of static lung volume measurement by body plethysmography. $V_T$: tidal volume; TLC: total lung capacity; IRV: inspiratory reserve volume; FRCpleth: functional residual capacity measured by whole body plethysmography; ERV: expiratory reserve volume; IC: inspiratory capacity; RV: residual volume; SVC/FVC: slow vital capacity/ forced vital capacity.*[8]

The measurement of FRC by body plethysmography relies on the Boyle-Mariotte's law (which states that the product of the pressure and the volume of a gas are constant in isothermic conditions). The body plethysmograph is a closed box where the subjects can sit. While the subjects perform in- and expiratory efforts against a closed shutter valve (occluded breathing), changes in box pressure and at the mouth (reflecting alveolar pressure) are recorded[23]. Pressure measured at the mouth during occluded breathing is a reflection of the alveolar gas pressure while pressure changes in the box reflect changes of thoracic and gas volume.

The measurement of $R_{aw}$ by body plethysmography is an estimation made from calculation of the specific airway resistance ($_sR_{aw}$) and $FRC_{pleth}$ [24, 25]. $_sR_{aw}$ is defined as the work needed to be made at a given volume to generate a flow rate [23].

Despite its advantages, the common body plethysmograph is not suited for the assessment of respiratory function in the supine position.

Moreover, spirometry and body plethysmography both have other disadvantages. They require good collaboration from the tested subjects, which can limit their use in young children or older subjects. Finally, they do not assess EFL or impedance of the respiratory system beyond resistance.

[8] From: https://ars.els-cdn.com/content/image/1-s2.0-S0954611111000552-gr1_lrg.jpg.

### 1.3.3. Forced oscillation technique

The forced oscillation technique (FOT) is a technique of non-invasive assessment of the respiratory mechanics based on the work of Dubois [26]. It consists in a sequence of sinusoidal waves at various frequencies (from 5 to 37 Hz) produced by a loudspeaker-in-box sent through the mouth into the airways in order to assess the impedance of the respiratory system at different oscillation frequencies, while the subject breathes quietly (tidal breathing). Impedance is composed of resistance ($R_{rs}$; represented by the upper curve on Figure 7) and reactance ($X_{rs}$; which encompasses elastance and inertance; represented by the lower curve on Figure 7) of the respiratory system. They are measured by assessing the changes in volume and flows induced by the oscillating pressure signal superimposed on the tidal breath of the subject. Calculation of impedance is performed by a software using a fast Fourier transform analysis [27, 28] of the pressure, flow and volume signals.

The FOT allows an evaluation of the small airways compartment which can be useful for the detection of early changes in illnesses such as asthma or emphysema [29]. Indeed, some oscillation frequencies are specific to small (peripheral) or larger (upper) airways. Frequencies higher than 20 Hz are assessing the upper airways because they travel shorter distances.[30] On the other side, frequency of 5 Hz will measure the total impedance. Therefore, subtracting $R_{20}$ from $R_5$ gives an index of peripheral airways resistance. In healthy adult subjects, resistance is almost independent of the oscillation frequency meaning that at low frequency such as 5 Hz the resistance will be more or less equal to the resistance measured at 20 Hz (upper curve of the left panel of Figure 7) [30]. In COPD patients however, the resistance will be dependent of the frequency due to small airway obstruction. Given that 5 Hz frequency will assess the total $R_{rs}$ while 20 Hz will stop in upper airways then resistance measured at 5 Hz will be higher than that measured at 20 Hz (upper curve of the right panel of Figure 7).

Reactance is frequency dependent for both normal and COPD subjects. However, in normal subjects the reactance curve (lower curve on the left panel of Figure 7) will cross the X axis at a frequency between 10 and 15 Hz, which is the resonant frequency (Fres). In COPD subjects, the reactance curve will be displaced downwards as compared to normal subject and accordingly, the Fres will be increased (lower curve on the right panel of the Figure 7).

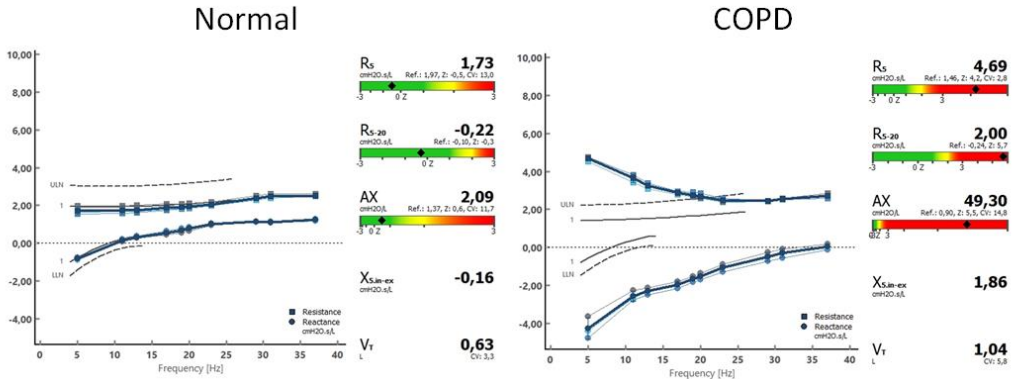


*Figure 7: Graphs obtained using the FOT. The left panel represents the results of a normal subject and the right panel those of a COPD subject. The upper curve represents resistance in function of oscillation frequency and the lower curve represents reactance. The frequency of resonance is the frequency at which the reactance curve crosses the Y axis (i.e. the frequency at which reactance is 0). It can be seen that there is a frequency dependency of the resistance and that the reactance curve is displaced towards lower value, which translates in a higher AX and Fres in the COPD.*

Reactance can be understood as a parameter assessing the elastic properties of the respira-

tory system. However, small airway disease might influence reactance parameters measured by the FOT. Indeed the phenomenon of choke point associated with airflow limitation as well as the small airway closure phenomenon potentially increases the $X_{rs}$ without influencing the static elastic properties of the lung.

A parameter of particular interest is the $\Delta X_5$ which is the difference between the expiratory and inspiratory reactance at 5 Hz. This index is useful for the detection of EFL [31-33]. Dellacà *et al.*(2004) [34] used the Mead and Whittenberger method [35] in order to detect EFL and assess if there were some associations with FOT measurements. In this study, the authors showed an association between the increase in $\Delta X_5$ above a threshold and the presence of EFL. The disproportionate increase in $X_5$ in the expiratory phase of the breathing cycle is explained by the appearance of a "choke point" when EFL occurs in an airway. When a choke point occurs, soundwaves produced by the FOT are stopped and cannot reach the alveoli which translates in an increased reactance. Flow limitation occurs only during expiration since the airway calibre is much lower in the small airways during the expiratory phase of the breathing cycle owing to a higher pleural pressure (which is less negative or even positive as compared to the inspiratory phase). According to Dellacà *et al.* (2007), a $\Delta X_5$ greater than 2,8 $cmH_2O.s.L^{-1}$ would be an ideal criterion (100% sensitive and 100% specific) for the detection of EFL [36].

Accordingly, FOT had numerous advantages over common measurements of respiratory mechanics used in the clinic:

- It brings more information on respiratory mechanics parameters of interest to explain dyspnea.
- It only requires minimal collaboration from the subject since measurements are performed during tidal breathing.
- The apparatus is light and small enabling its use in the supine posture.

### 1.4. Expectations

Based on the literature, some changes are expected concerning spirometric's parameters in the supine posture such as a decrease in $FEV_1$, FVC, VC and an increase in IC in the control group [37]. However, there is a lack of literature on these changes for COPD subjects.

One can also assume that there will be some changes in resistance and reactance parameters for both COPD and normal subjects since de gravity will have a different effect on the lungs and on pleural pressure. As the volume of lung in the dependent region increases in the supine posture, one can imagine that the pleural pressure will be less negative for a greater portion of the total lung volume in this position [38]. Therefore, a bigger part of the airways will have a reduced diameter what will tend to increase resistance. This decreased diameter will also increase the potential for the occurrence of EFL giving increased $\Delta X_5$ and $X_{5ex}$. In small airways, this reduction of the diameter might also lead to airway closure that can also influence reactance parameters as stated above [39].

## 2. Specific Aims

The study aims to assess the effect of the dorsal supine posture on respiratory mechanics in both COPD and healthy subjects. Although there is no thorough description in the literature, it is a common clinical finding that many subjects with COPD are complaining of orthopnea. In subjects with severe left heart failure, orthopnea is a typical symptom. It is explained by a shift of venous blood from the lower limbs and splanchnic organs to the thorax which increases the telediastolic ventricular pressure as well as the pulmonary venous and capillary pres-

sures. This leads to vascular distension and perivascular, peribronchiolar and interstitial oedema. There is however no evidence that these changes play a role in COPD [40] where the causes of orthopnea remain elusive. The present study will assess different aspects of the respiratory system mechanics using the FOT in order to get better insight in the cause of orthopnea in COPD.

To assess the changes of respiratory mechanics, different parameters were measured. Parameters measured by the FOT such as $R_5$, $R_{20}$, $R_{5\text{-}20}$, AX, $X_5$ and $\Delta X_5$ were chosen. They may give a better understanding on the mechanisms leading to orthopnea than spirometry.

In addition, $FEV_1$, FVC, the derived Tiffeneau index, inspiratory capacity (IC), vital capacity (VC) and forced expiratory flow at low lung volumes ($FEF_{50}$, $FEF_{75}$) were also measured by spirometry. $FEF_{50}$ and $FEF_{75}$ are 2 indices of small distal airway function. A reduced $FEF_{50}$ or $FEF_{75}$ without any reduction of the Tiffeneau index has been used as an index of early airway obstruction.

As EELV (or FRC) influences airway resistance –$R_{aw}$ being lower at higher lung volumes– and as FRC was not measured in the present study, we used the IC to assess the changes in EELV. Indeed, postulating an unchanged TLC [41] with the change in posture, a higher IC reflects a decreased EELV while a decrease in IC reflects an increased EELV. The latter was important since $R_{aw}$ is influenced by lung volumes.

## 3. COPD and normal subjects

Recruitment of COPD and healthy subjects started once the Ethical Committee of Mont-Godinne gave approval for the protocol. Prof. Marchand recruited COPD subjects at the ambulatory COPD clinic of the CHU-UCL Namur, site Godinne. Advertisements were displayed in University of Namur in order to recruit healthy volunteers. Some partners of recruited COPD subjects were also proposed to participate in the study as healthy volunteers. Inclusions/exclusions criteria for study participation are shown in Table 2.

Smokers and former smokers were accepted in the control group as it had already been demonstrated that smoking had no significant influence on FOT in healthy smokers [42, 43].

During recruitment two subjects refused to participate in the study, one did not show to the appointment, two were excluded due to an ongoing exacerbation; six had to be excluded for the analysis due to either insufficient collaboration for some measurements or problems in reproducibility.

Two subjects recruited as healthy smoker were diagnosed with COPD at the time of spirometry (reduced Tiffeneau index) and were included in the COPD group. Another healthy non-smoking volunteer was diagnosed with airway obstruction of unknown cause and was excluded of the analysis. This left 45 COPD subjects and 20 healthy subjects suitable for the data analysis.

*Table 2:Inclusion and exclusion criteria*

| | COPD subjects | Healthy subjects |
|---|---|---|
| Inclusion criteria | - COPD confirmed by pulmonary function tests;<br>- Smoker (old or current);<br>- Age ( >40 years old);<br>- Signed informed consent. | - Age ( >40 years old);<br>- Signed informed consent. |
| Exclusion criteria | - Severe obesity (BMI > 35 kg/m$^2$);<br>- Pregnant woman;<br>- Presence of other respiratory disease.<br>- Heart failure requiring diuretics;<br>- Use of oral corticosteroids or antibiotics within 14 days; | - Severe obesity (BMI > 35 kg/m$^2$);<br>- Pregnant woman;<br>- Heart failure requiring diuretics;<br>- Known respiratory or neuromuscular disease; |

## 4. Methods

### 4.1. Measurements

In order to assess the effects of position on respiratory mechanics and function, measures were made using the TREMOFLO$^{TM}$ (Thorasys Thoracic Medical System Inc, Montreal, Canada) for the FOT and Spirobank II (Medical International Research Inc, Rome, Italia) for spirometry.

Once the subject had completed a questionnaire (see annex 1), weight and height, hip and waist circumference were measured. The body mass index (BMI) and the waist to hip ratio were calculated. The latter parameter was recorded since it was hypothesized that abdominal obesity could influence respiratory mechanics in the supine position.

Respiratory function measurements started with the FOT. Three sets of runs were recorded:

1. In the sitting position on a chair.
2. In the supine position on a flat examination table.
3. Again in the sitting position on a chair.

The second set of measurements in the sitting posture was included in the protocol in order to ascertain that the differences observed between the sets of measurements were indeed due to the change in position rather than to other uncontrolled confounding factors.

For all the FOT measurements, the neck was placed in slight extension (~15°). Subjects breathed through a mouthpiece and wore a nose clip. Before starting the test, it was checked that the lips were sealed around the mouthpiece. During the FOT measurements, the subjects were asked to compress their cheeks with their hands in order to avoid any bias due to cheeks compliance (Figure 8) [27, 44]. For each run, subjects breathed spontaneously (tidal breath-

ing); once breathing was stable, oscillations waves were imposed within the airway through the mouth. Runs of 20 seconds were recorded. The duration of the run was increased in case of very low breathing frequency. Care was given to avoid coughing, glottis closure or swallowing artefacts.

In each of the three positions, three valid runs with less than 15% coefficient of variation had to be achieved [45]. Subjects were excluded if this requirement was not met after eight runs in any position. FOT parameters used for the analysis were the mean of the measurements achieved in the three valid runs.

After each set of runs of FOT measurements in a given posture, spirometry took place for the assessment of the IC in order to assess changes in EELV, postulating an unchanged TLC in the different postures as discussed before [41].

For IC measurement, the subject had to achieve a regular normal breathing (tidal breathing) before being asked to perform a maximal slow inspiratory maneuver up to TLC followed by a complete and slow expiration down to RV, allowing for the measurement of slow expiratory VC (EVC on Figure 9, reported as VC in the results section) [21]. A minimum of three acceptable IC maneuvers were recorded, with the difference between the two best values not being greater than 150 mL. The larger value of these two measurements was retained for the analysis.

As forced expiratory maneuvers are known to induce changes in $R_{aw}$ in some subjects, this maneuver was only performed after all FOT and IC measurements were achieved in the three different sets. For the forced expiratory maneuver, the subject had to breathe spontaneously two or three times, to make a maximal inspiration to TLC, to expire immediately as fast as possible down to RV.

*Figure 8: Description of the body posture during FOT measurements in the sitting position. Hands are supporting the cheeks; the head is in slight extension.*

A minimum of three acceptable maneuvers were recorded, with the difference between the two best values of $FEV_1$ and FVC not being greater than 150 mL or 5% whichever was greater. The larger value of these two measurements was retained for the analysis and for the Tiffeneau index calculation. The forced expiratory maneuver was only performed in two sets of postures, first in the sitting and then in the supine posture.

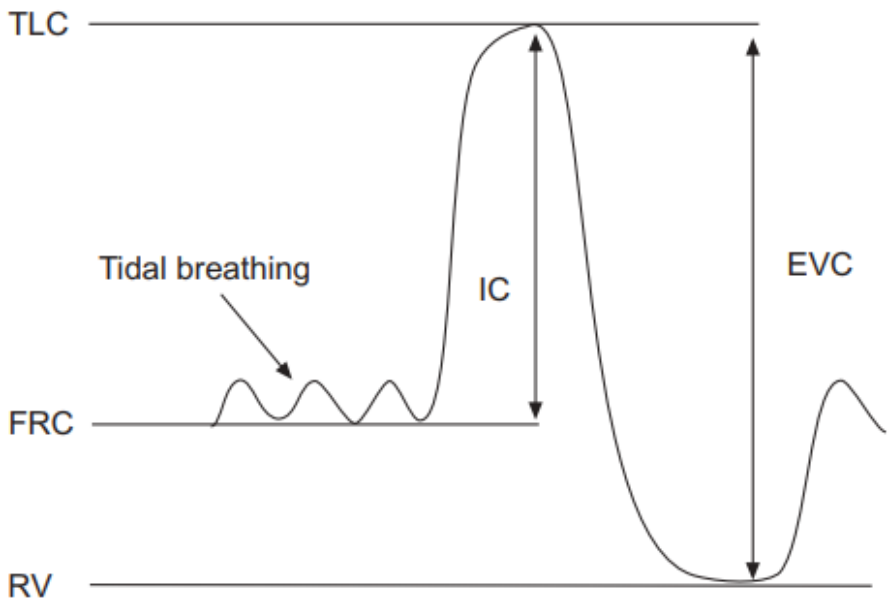


*Figure 9: Inspiratory capacity and vital capacity maneuver. The subject starts breathing normally before taking a deep inspiration up to TLC and then exhaling down RV. The IC is the difference between TLC and FRC. TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; IC: inspiratory capacity; EVC: expiratory vital capacity.*[9]

### 4.2. Statistical Analysis

Data are presented as mean +/- standard deviation. Comparisons between the three postures were performed using a repeated measure ANOVA.

As discussed below, we only found some small differences between the two sets of measurements performed in the siting posture. Accordingly, for further analysis, only the first set of runs performed in the sitting posture was retained for analysis.

Comparison between normal and COPD subjects or between orthopneic and non orthopneic subjects were performed with an unpaired t-test, Aspin-Welch test (in case of unequal variances between groups) or Wilcoxon-Mann-Whitney test (when data distribution was not Gaussian), as required.

Comparisons between proportions were performed using a Pearson's chi-square test.

The association between the change in dyspnea VAS between the sitting and the supine postures and other parameters was tested using a linear regression analysis.

Statistical significance was set at $p<0,05$.

## 5. Results

### 5.1. Characteristics of the study population in the sitting position

As can be seen from Table 3, both populations – controls and COPD – had similar anthropometric characteristics and gender representation but COPD subjects were significantly older than controls ($p<0,001$).

Fourteen (31%) and eight (17%) COPD patients described themselves as usually or sometimes orthopneic in the everyday life, respectively. Accordingly, nearly 50% of the included

[9] From: https://www.thoracic.org/statements/reFroms/pfet/PFT2.pdf

patients reported having experienced orthopnea.

*Table 3: Subjects characteristics, dyspnea and forced expiratory measurements in the sitting position and comparison between groups*

| | Controls (n=20) | COPD (n=45) | P value |
|---|---|---|---|
| **Orthopnea (Yes/Sometimes/No)** | 0/0/0 | 14/8/23 | <0,001 |
| **Dyspnea VAS** | 0,23±0,66 | 1,89±2,21 | <0,01 |
| **Gender (male/female)** | 9/11 | 24/21 | NS |
| **Smokers/Ex-Smokers/Non Smokers** | 2/3/15 | 7/38/0 | <0,001 |
| **Age (y)** | 54,46 ± 8,56 | 64,89 ± 8,56 | <0,001 |
| **Weight (kg)** | 69,06 ± 15,42 | 66,16 ± 16,63 | NS |
| **Height (cm)** | 169,2 ± 10,99 | 164,8 ± 10,52 | NS |
| **Waist/Hip** | 0,82±0,11 | 0,95±0,11 | <0,001 |
| **BMI (cm/kg²)** | 23,97 ± 3,66 | 24,33 ± 5,05 | NS |
| **GOLD I/II/III/IV** | NA | 2/13/15/15 | NA |
| **$FEV_1$ (L)** | 3,43 ± 1,01 | 1,14 ± 0,61 | <0,001 |
| **$FEV_1$ (% pred)** | 105,09 ± 12,66 | 42,5 ± 19,26 | <0,001 |
| **FVC (L)** | 4,32 ± 1,32 | 2,53 ± 0,97 | <0,001 |
| **FVC (% pred)** | 101,87 ± 11,28 | 73,13 ± 19,46 | <0,001 |
| **$FEV_1$/FVC (%)** | 79,65 ± 5,29 | 44,58 ± 12,78 | <0,001 |
| **$FEF_{50}$ (L/sec))** | 3,85±1,43 | 0,57±0,5 | <0,001 |
| **$FEF_{75}$ (L/sec)** | 1,2±0,47 | 0,22±0,14 | <0,001 |
| **$SpO_2$ (%)** | NM | 96,37±1,56 | NA |

Values are presented as mean ± SD. NS: not significant; NM: not measured; NA: not applicable; BMI: body mass index; $FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity; $FEF_{50}$: forced expiratory flow when 50% of the volume has been expired; $FEF_{75}$: forced expiratory flow when 75% of the volume has been expired; $SpO_2$: oxygen saturation.

GOLD stage 2, 3 and 4 were quite equally represented in the COPD group but stage 1 was underrepresented.

Per protocol, spirometric's parameters in the control group were within normal values, while $FEV_1$ and $FEV_1$/FVC were significantly lower in the COPD subjects. This was also the case for FVC, $FEF_{50}$ and $FEF_{75}$.

*Table 4: Comparison of FOT measurements between the control and COPD groups in the sitting position*

| | Controls (n=20) | COPD (n=45) | P value |
|---|---|---|---|
| **$R_5$ ($cmH_2O.s/L$)** | 2,79±0,77 | 5,38±1,51 | <0,001 |
| **$R_5$ (% pred)** | 106,08±31,55 | 187,44±57,82 | <0,001 |
| **$R_{20}$ ($cmH_2O.s/L$)** | 2,64±0,67 | 3,53±1,07 | <0,001 |
| **$R_{20}$ (% pred)** | 94,11±20,5 | 123,74±32,97 | <0,01 |
| **$R_{5-20}$ ($cmH_2O.s/L$)** | 0,16±0,32 | 1,85±0,95 | <0,001 |
| **$X_5$ ($cmH_2O.s/L$)** | -1,20±0,35 | -4,67±2,82 | <0,001 |
| **$X_5$ (% pred)** | 112,5±27,68 | 412,5±314,3 | <0,001 |
| **$\Delta X_5$ ($cmH_2O.s/L$)** | -0,50±0,32 | 2,90±3,36 | <0,001 |
| **$X_{5in}$ ($cmH_2O.s/L$)** | -1,48±0,49 | -2,92±1,11 | <0,001 |
| **$X_{5ex}$ ($cmH_2O.s/L$)** | -0,98±0,30 | -5,83±4,13 | <0,001 |
| **AX ($cmH_2O/L$)** | 4,60±2,94 | 48,52±31,65 | <0,001 |
| **AX (% pred)** | 186,4±1021 | 1914±1824 | <0,001 |

Values are presented as mean ± SD. VAS: visual analogue scale; $R_5$: resistance at 5 Hz; $R_{20}$: resistance at 20 Hz; $R_{5-20}$: difference between the resistance at 5 Hz and the resistance at 20 Hz; $X_5$: reactance at 5 Hz; $\Delta X_5$: difference in reactance measured at 5 Hz between inspiration and expiration; $X_{5in}$: inspiratory reactance at 5 Hz; $X_{5ex}$: expiratory reactance at 5 Hz; AX: area under the reactance-frequency curve.

All FOT parameters were significantly higher ($p<0,001$) in COPD compared to control subjects, except for $X_5$ which was significantly lower in the COPD group, reflecting a greater derangement in the reactance of the respiratory system.

Fres was not included in the analysis since 12 COPD subjects had a Fres in excess of the highest oscillating frequency used in the present protocol (35 Hz) in both the sitting and the supine postures.

Taking into account the 2,8 $cmH_2O.s/L$ $\Delta X_5$ threshold as a surrogate for EFL [36], none of the subjects in the control group presented EFL while 18 COPD patients experienced EFL in the sitting position.

5.2. Influence of posture in controls and COPD subjects

The dyspnea VAS was increased in 25 of the COPD subjects in the supine as compared to the sitting position but only in two of the control subjects. VAS only increased significantly ($p<0,001$) in the supine position in the COPD group.

As can be seen from Table 5 and Figure 10, adopting the supine position was associated with important changes in both resistance and reactance parameters in the COPD population. These changes were less striking in control subjects. Indeed, the most important changes were seen for $R_5$ and $R_{20}$ in the control group but parameters related to small airway resistance ($R_{5-20}$) or reactance were less ($X_5$ and $X_{5in}$) or not significantly influenced by the supine position in normal subjects.

The breathing pattern was not affected by the posture in controls. Minute ventilation, tidal volume and breathing frequency were reduced in COPD patients when adopting the supine position. These changes were significant.

As expected, the IC was significantly increased in the supine position in the control subjects. COPD subjects however had a significantly decreased IC in the supine position. The VC was slightly but significantly decreased in the supine position in both groups.

As expected, we observed a significant reduction in the various spirometric's parameters in the supine position, both in the control and in COPD populations except for the FVC that was only significantly decreased in the supine position in the control group. However, $FEF_{50}$ and $FEF_{75}$ were not significantly decreased in control and COPD groups.

The second run in the sitting position was used in order to ascertain that changes observed from the first sitting run to the supine position were due to the change of position rather to other uncontrolled potential confounding factors. Quite unexpectedly, there were significant differences between the first and second sets of measures acquired in the sitting position. None of the parameters measured by FOT were significantly changed in COPD subjects but we observed a significant increase in the breathing frequency (Table 5) in the second run. There was also a significant decrease in the second measurement in the sitting position for both IC and VC. These small differences might be due to the fatigue of some patients at the end of the recordings, after multiple runs of measurements. In the control group, we did not find any significant difference between the two sets of measures in the sitting position neither for FOT nor spirometry. As the changes observed between the two sets of measurements in the sitting posture in COPD subjects were small and probably related to fatigue, we always used the results obtained in the first set of runs obtained in the sitting position for further analysis and figures.

*Table 5: Changes between positions according the condition*

| | Controls (n=20) | | | | COPD (n=45) | | | |
|---|---|---|---|---|---|---|---|---|
| | Sit 1 | Supine | Sit 2 | P value | Sit 1 | Supine | Sit 2 | P value |
| **Dyspnea VAS** | 0,23±0,66 | 0,16±0,39 | 0,12±0,4 | NS | 1,89±2,21 | 2,87±2,85$^{*}$ | 2,15±2,09 | <0,001 |
| **$R_5$ ($cmH_2O.s/L$)** | 2,79±0,77 | 4,03±1,09$^{*}$ | 2,97±0,92 | <0,001 | 5,38±1,51 | 6,90±1,93$^{*}$ | 5,67±1,55 | <0,001 |
| **$R_{20}$ ($cmH_2O.s/L$)** | 2,64±0,67 | 3,65±0,84$^{*}$ | 2,77±0,72 | <0,001 | 3,53±1,07 | 4,33±1,52$^{*}$ | 3,6±1,13 | <0,001 |
| **$R_{5-20}$ ($cmH_2O.s/L$)** | 0,16±0,32 | 0,38±0,54$^{*}$ | 0,20±0,390 | <0,01 | 1,85±0,95 | 2,56±0,91$^{*}$ | 2,06±0,91 | <0,001 |
| **$X_5$ ($cmH_2O.s/L$)** | -1,20±0,35 | -1,47±0,91$^{‡}$ | -1,13±0,44 | <0,05 | -4,67±2,82 | -6,93±3,45$^{*}$ | -5,03±2,70 | <0,001 |
| **$\Delta X_5$ ($cmH_2O.s/L$)** | -0,50±0,32 | -0,30±0,92 | -0,40±0,29 | NS | 2,90±3,36 | 5,73±4,50$^{*}$ | 3,26±3,08 | <0,001 |
| **$X_{5in}$ ($cmH_2O.s/L$)** | -1,48±0,49 | -1,63±0,71$^{‡}$ | -1,36±0,52 | <0,01 | -2,92±1,11 | -3,54±1,05$^{*}$ | -3,05±1,16 | <0,001 |
| **$X_{5ex}$ ($cmH_2O.s/L$)** | -0,98±0,30 | -1,34±1,24 | -0,96±0,43 | NS | -5,83±4,13 | -9,25±5,17$^{*}$ | -6,30±3,82 | <0,001 |
| **AX ($cmH_2O/L$)** | 4,60±2,94 | 6,36±7,29 | 4,50±3,45 | NS | 48,52±31,65 | 70,06±38,60$^{*}$ | 52,53±29,8 | <0,001 |
| **$V_T$ (L)** | 0,75±0,32 | 0,81±0,36 | 0,73±0,35 | NS | 0,88±0,43 | 0,81±0,34$^{†}$ | 0,81±0,35 | <0,05 |
| **BF (cycle/min)** | 16,66±5,59 | 14,61±4,21 | 17,08±4,71 | <0,01 | 16,16±5,30$^{‡}$ | 15,09±4,81$^{*}$ | 17,33±5,96$^{†}$ | <0,001 |
| **VE (L/min)** | 11,65±3,87 | 11,01±3,52 | 11,53±3,54 | NS | 13,20±5,02 | 11,37±3,68$^{*}$ | 13,03±4,66 | <0,001 |
| **IC (L)** | 2,96±0,78 | 3,45±1$^{*}$ | 2,86±0,77 | <0,001 | 2,33±0,79 | 2,23±0,77$^{†}$ | 2,19±0,74$^{†}$ | <0,01 |
| **VC (L)** | 4,06±1,05 | 3,93±1,03$^{†}$ | 4,02±1,07 | <0,01 | 2,90±0,97 | 2,74±0,93$^{†}$ | 2,80±0,93 | <0,001 |
| **$FEV_1$ (L)** | 3,24±0,84 | 2,95±0,80$^{†}$ | NA | <0,001 | 1,14±0,62 | 1,09±0,60$^{†}$ | NA | <0,001 |
| **$FEV_1$ (% pred)** | 103±11,55 | 94,2± 11,74$^{†}$ | NA | <0,001 | 42,73±19,41 | 40,91±18,77$^{†}$ | NA | <0,001 |
| **FVC (L)** | 4,08±1,10 | 3,80±1,04$^{†}$ | NA | <0,001 | 2,55±0,97 | 2,49±0,95 | NA | NS |
| **FVC (% pred)** | 101,87± | 91,16±11,13$^{†}$ | NA | <0,001 | 73,17±19,42 | 71,66±19,22 | NA | NS |
| **$FEV_1$/FVC (%)** | 79,67±5,35 | 77,76±5,64$^{†}$ | NA | <0,001 | 44,44±12,38 | 43,20±12,39$^{†}$ | NA | <0,05 |
| **$FEF_{50}$ (L/sec)** | 3,85±1,43 | 3,46±1,21 | NA | NS | 0,57±0,5 | 0,52±0,48 | NA | NS |
| **$FEF_{75}$ (L/sec)** | 1,2±0,47 | 0,98±0,43 | NA | NS | 0,22±0,14 | 0,2±0,14 | NA | NS |
| **$SpO_2$ (%)** | NM | NM | NM | NA | 96,37±1,56 | 95,2±2,52$^{*}$ | 96,2±1,25 | <0,001 |

Values are presented as mean ± SD. NM: not measured; NS: not significant; VAS: visual analogue scale; $R_5$: resistance at 5 Hz; $R_{20}$: resistance at 20 Hz; $R_{5-20}$: difference between the resistance at 5 Hz and the resistance at 20 Hz; X5: reactance at 5 Hz; ΔX5: difference in reactance measured at 5 Hz between inspiration and expiration; $X_{5in}$: inspiratory reactance at 5 Hz; $X_{5ex}$: expiratory reactance at 5 Hz; AX: area under the reactance-frequency curve; $V_T$: tidal volume; BF: breath frequency; VE: minute ventilation; IC: inspiratory capacity; VC: vital capacity; $FEV_1$: forced expired volume in one second; FVC: forced vital capacity; $FEF_{50}$: forced expiratory flow when 50% of the volume has been expired; $FEF_{75}$: forced expiratory flow when 75% of the volume has been expired; $SpO_2$: oxygen saturation. Statistical analysis: $^{*}$: significant difference between supine and the two sitting position; $^{†}$: significant difference with sitting 1; $^{‡}$: significant difference with sitting 2.

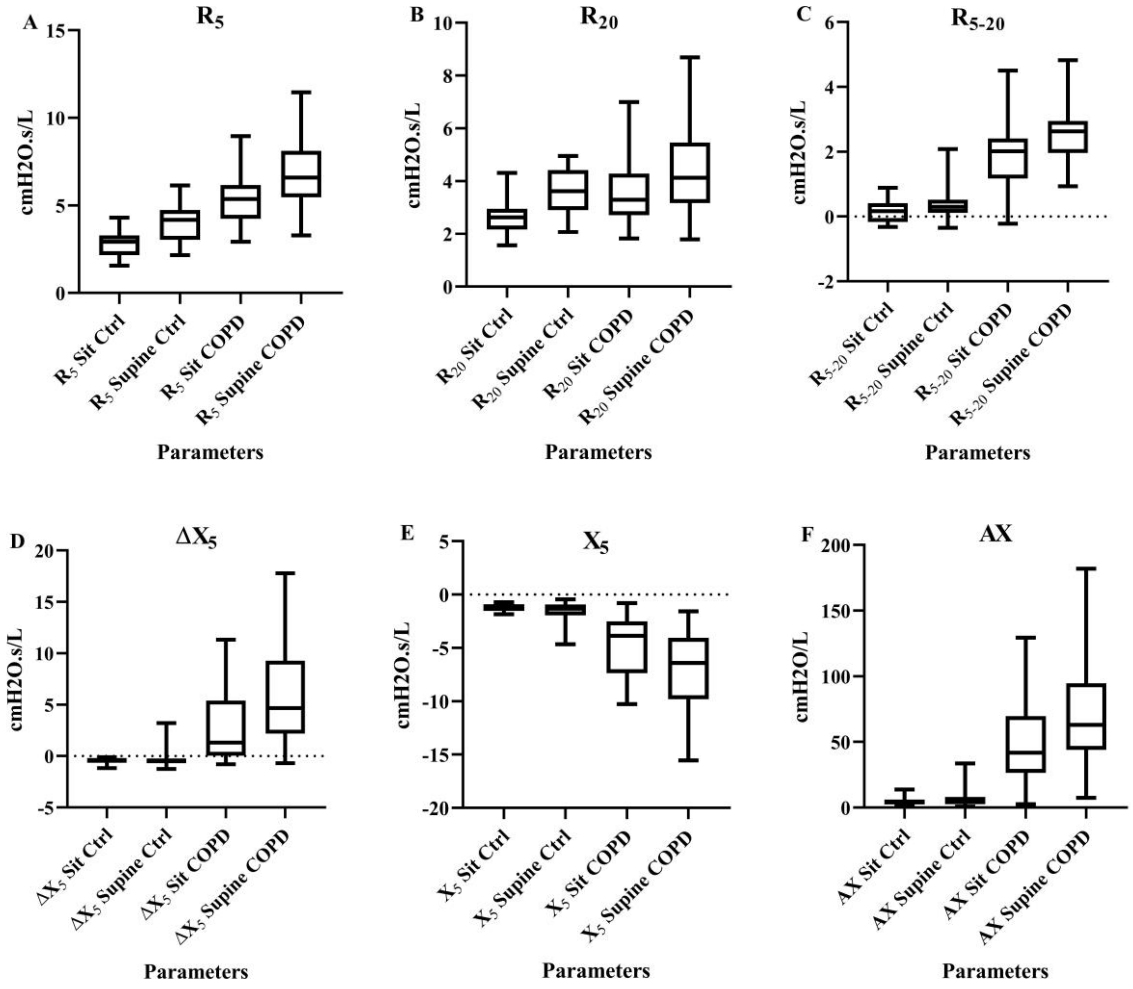


*Figure 10: Comparison of sitting and supine position for $R_5$ (panel A), $R_{20}$ (panel B), $R_{5-20}$ (panel C), $\Delta X_5$ (panel D), $X_5$ (panel E) and AX (panel F) in the control (Ctrl) and COPD groups. Results are represented as median, interquartile (boxes upper and lower limits), and minimal and maximal values (whiskers).*

### 5.3. Comparison of changes observed from the sitting to the supine posture between COPD and control subjects

When comparing the changes in dyspnea assessed by the VAS with position between controls and COPD, we observed a significant. Increase in dyspnea in the COPD group while in the control group the trend was a decrease in the supine position.

There were no significant differences between COPD and control group for the change in $R_5$ and $R_{20}$ with position while the change was significantly greater for $R_{5-20}$ in the COPD group. For all the parameters related to the reactance of the respiratory system, the changes observed when adopting the supine position were significantly greater in COPD than in controls. The differences in reactance changes between control and COPD subjects were more obvious in the expiratory phase of the breathing cycle, as demonstrated by the changes in $X_{5ex}$ and $\Delta X_5$.

*Table 6: Comparison of the changes from the sitting to the supine posture in dyspnea, FOT and slow vital capacity parameters in the control and COPD subjects*

| | Controls (n=20) | COPD (n=45) | P value |
|---|---|---|---|
| **Dyspnea VAS** | -0,07±0,45 | 0,94±1,46 | <0,01 |
| **$R_5$ ($cmH_2O.s/L$)** | 1,23±0,61 | 1,51±1,14 | NS |
| **$R_{20}$ ($cmH_2O.s/L$)** | 1,01±0,56 | 0,8±0,86 | NS |
| **$R_{5-20}$ ($cmH_2O.s/L$)** | 0,22±0,39 | 0,71±0,79 | <0,01 |
| **$X_5$ ($cmH_2O.s/L$)** | -0,28±0,65 | -2,25±2,46 | <0,001 |
| **$\Delta X_5$ ($cmH_2O.s/L$)** | 0,20±084 | 2,82±3,44 | <0,001 |
| **$X_{5in}$ ($cmH_2O.s/L$)** | -0,16±0,38 | -0,62±0,81 | <0,01 |
| **$X_{5ex}$ ($cmH_2O.s/L$)** | -0,36±1 | -3,42±3,82 | <0,001 |
| **AX ($cmH_2O/L$)** | 1,76±4,65 | 21,54±27,54 | <0,001 |
| **$V_T$ (L)** | 0,06±0,22 | -0,07±0,21 | <0,05 |
| **BF (cycle/min)** | -2,05±2,56 | -1,06±2,61 | NS |
| **VE (L/min)** | -0,64±2,96 | -1,83±2,69 | NS |
| **IC (L)** | 0,49±0,36 | -0,1±0,28 | <0,001 |
| **VC (L)** | -0,13±0,21 | -0,16±0,30 | NS |

Values were presented as mean ± SD. NS: not significant; VAS: visual analogue scale; $R_5$: resistance at 5 Hz; $R_{20}$: resistance at 20 Hz; $R_{5-20}$: difference between the resistance at 5 Hz and the resistance at 20 Hz; $X_5$: reactance at 5 Hz; $\Delta X_5$: difference in reactance measured at 5 Hz between inspiration and expiration; $X_{5in}$: inspiratory reactance at 5 Hz; $X_{5ex}$: expiratory reactance at 5 Hz; AX: area under the reactance-frequency curve; $V_T$: tidal volume; BF: breath frequency; VE: minute ventilation; IC: inspiratory capacity; VC: vital capacity.

Interestingly, the change in IC in the supine position was strikingly different between the two groups: IC increased in the control group as expected, while in the COPD group, there was a significant decrease in IC when adopting the supine position.

Taking into account the 2,8 $cmH_2O.s/L$ $\Delta X_5$ threshold as a surrogate for EFL, [36] 1 normal subject presented with EFL in the supine posture. This subject was a 72 years old woman also demonstrating an increase in both $R_{5-20}$ and AX in the supine posture. However, she did not present any signs of significant airway obstruction when lung function was measured by spirometry. In the COPD group, 31 had signs of EFL in the supine posture; 17 out of the 18 patients with EFL in the sitting posture also had EFL in the supine position.

### 5.4. Comparisons between orthopneic and non orthopneic COPD subjects in the everyday life

For these comparisons, the 22 patients (49% of the COPD group) describing themselves as orthopneic (n = 14) or sometimes orthopneic (n=8) were grouped (orthopneic patients in further analysis) and compared to the patients not complaining of orthopnea in the daily life (n=23).

#### 5.4.a. Comparison of anthropometric and other general parameters

No significant differences between orthopneic and non-orthopneic patients were observed regarding gender, age, weight, height, BMI or GOLD stage (Table 7). However, even if the BMI was not significantly different between the two groups the waist to hip ratio was significantly lower in the orthopneic group compared to the non-orthopneic group.

### 5.4.b. Comparison of parameters recorded in the sitting position

*Table 7: Comparison of the parameters recorded in the sitting position in strict orthopneic and non-orthopneic subjects*

| | Non-orthopneic(n=23) | Orthopneic (n=22) | P value |
|---|---|---|---|
| **Dyspnea VAS** | 1,15±1,70 | 2,66±2,45 | <0,05 |
| **GOLD stage (I/II/III/IV)** | 2/6/8/7 | 0/7/7/8 | NS |
| **Gender (F/M)** | 9/14 | 12/10 | NS |
| **Age (y)** | 64,3±8,98 | 65,5±8,28 | NS |
| **Weight (kg)** | 68,06±17,62 | 64,14±15,77 | NS |
| **Height (cm)** | 167,45±10,92 | 161,95±9,48 | NS |
| **BMI (cm/kg²)** | 24,16±5,21 | 24,5±4,99 | NS |
| **Waist/Hip** | 0,98±0,11 | 0,91±0,1 | <0,05 |
| **$R_5$ ($cmH_2O.s/L$)** | 5,05±1,40 | 5,73±1,57 | =0,13* |
| **$R_{20}$ ($cmH_2O.s/L$)** | 3,4±1,18 | 3,67±0,96 | NS |
| **$R_{5-20}$ ($cmH_2O.s/L$)** | 1,49±1,22 | 2,07±1,16 | NS |
| **$X_5$ ($cmH_2O.s/L$)** | -3,95±2,38 | -5,44±3,09 | NS |
| **$\Delta X_5$ ($cmH_2O.s/L$)** | 2,25±3,10 | 3,59±2,54 | NS |
| **$X_{5in}$ ($cmH_2O.s/L$)** | -2,6±0,71 | -3,26±1,35 | =0,06* |
| **$X_{5ex}$ ($cmH_2O.s/L$)** | -4,85±3,62 | -6,85±4,45 | NS |
| **AX ($cmH_2O/L$)** | 40,26±25,74 | 54,15±35,39 | NS |
| **$V_T$ (L)** | 0,99±0,47 | 0,77±0,36 | NS |
| **BF (cycle/min)** | 14,81±5,29 | 17,56±5,05 | NS |
| **VE (L/min)** | 13,61±5,49 | 12,77±4,57 | NS |
| **IC (L)** | 2,54±0,87 | 2,12±0,65 | <0,05 |
| **VC (L)** | 3,14±1,04 | 2,66±0,85 | NS |
| **$FEV_1$ (L)** | 1,30±0,70 | 0,97±0,47 | NS |
| **$FEV_1$ (%)** | 46,61±22,17 | 38,69±15,52 | NS |
| **FVC (L)** | 2,85±1,01 | 2,23±0,85 | <0,05 |
| **FVC (%)** | 77,8±18,94 | 66,75±20,48 | NS |
| **$FEV_1$/FVC (%)** | 45±14,18 | 43,86±10,48 | NS |
| **$FEF_{50}$ (L/sec)** | 0,7±0,62 | 0,44±0,29 | NS |
| **$FEF_{75}$ (L/sec)** | 0,25±0,18 | 0,19±0,08 | NS |
| **$SpO_2$ (%)** | 96,43±1,69 | 96,3±1,45 | NS |

Values were presented as mean ± SD. NS: not significant; BMI: body mass index; VAS: visual analogue scale; $R_5$: resistance at 5 Hz; $R_{20}$: resistance at 20 Hz; $R_{5-20}$: difference between the resistance at 5 Hz and the resistance at 20 Hz; $X_5$: reactance at 5 Hz; $\Delta X_5$: difference in reactance measured at 5 Hz between inspiration and expiration; $X_{5in}$: inspiratory reactance at 5 Hz; $X_{5ex}$: expiratory reactance at 5 Hz; AX: area under the reactance-frequency curve; $V_T$: tidal volume; BF: breath frequency; VE: minute ventilation; IC: inspiratory capacity; VC: vital capacity; $FEV_1$: forced expired volume in one second; FVC: forced vital capacity; $FEF_{50}$: forced expiratory flow when 50% of the volume has been expired; $FEF_{75}$: forced expiratory flow when 75% of the volume has been expired; $SpO_2$: oxygen saturation. * These parameters were significant (p value <0,05) when excluding a large outlier from the non-orthopneic group.

As can be seen in Table 7, subjects with or without orthopnea in everyday life did not significantly differ for parameters measured in the sitting position except for:

- dyspnea VAS which was higher in orthopneic patients;
- IC and FVC expressed in absolute values which were significantly lower in orthopneic patients.

When excluding one large outlier from the non-orthopneic group some parameters were significantly higher in the orthopneic group:

- $R_5$
- $X_{5in}$.

Taking into account the 2,8 $cmH_2O.s/L$ $\Delta X_5$ threshold as a surrogate for EFL [36], 11 out

of the 22 subjects describing themselves as orthopneic (50%) present an EFL in sitting position against 7 out of the 23 non orthopneic subjects(30%). The difference between the two groups was not significant.

5.4.c. Comparison of parameters recorded in the supine position

In the supine position, there were more clear-cut differences between orthopneic and non-orthopneic COPD subjects, as shown in Table 8.

Regarding resistance parameters, both $R_5$ and $R_{20}$ measured in the supine position were significantly higher in the orthopneic group while there was no significant difference for $R_{5-20}$ ($p = 0,08$).

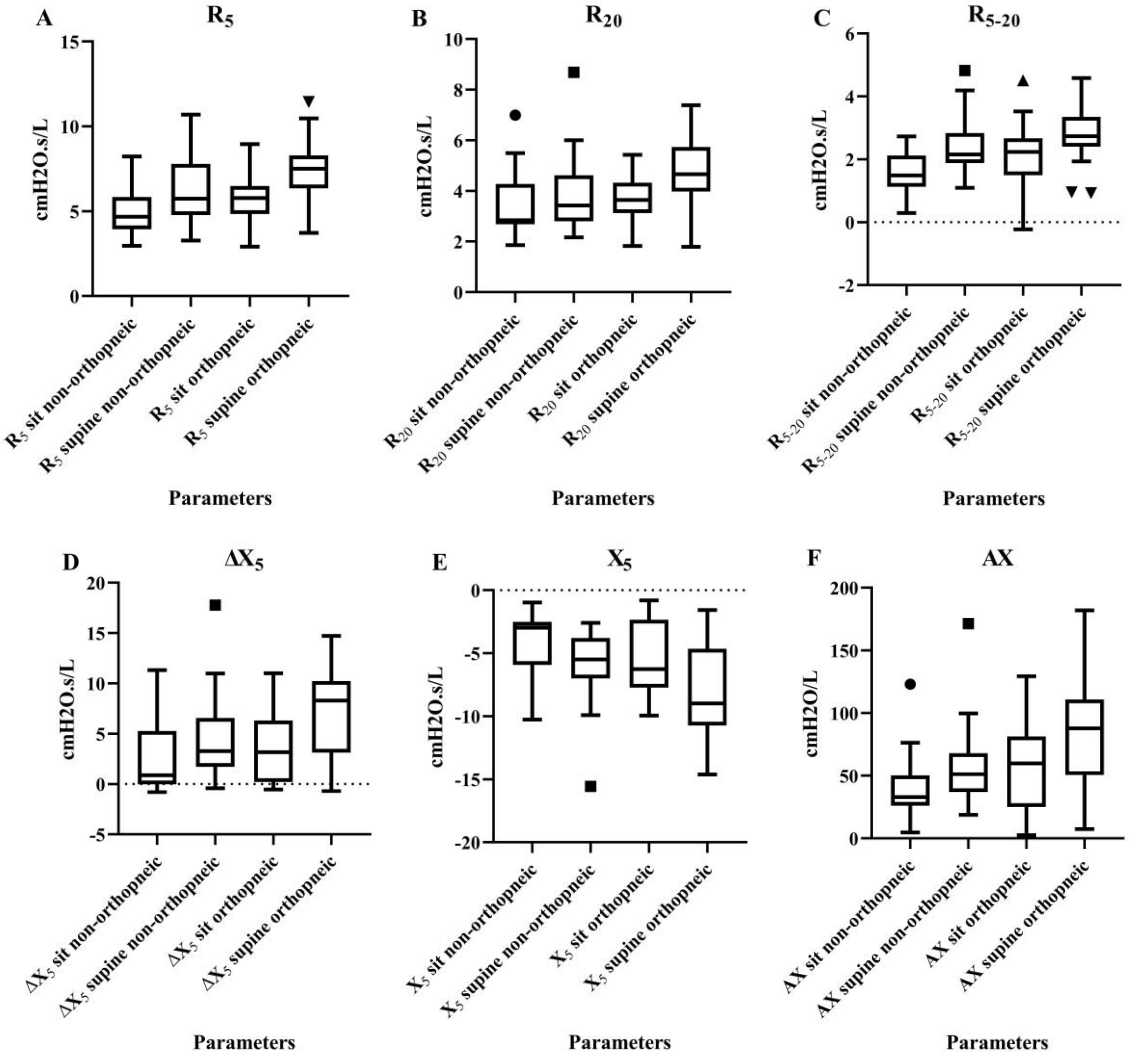


*Figure 11: Comparison of sitting and supine position for $R_5$ (panel A), $R_{20}$ (panel B), $R_{5-20}$ (panel C), $\Delta X_5$ (panel D), $X_5$ (panel E) and AX (panel F) in the non-orthopneic and orthopneic groups. Results are represented as median, interquartile (boxes upper and lower limits), and ± 1,5 interquartile ranges (whiskers). Individual points on some panels represent outliers.*

AX was significantly increased in the orthopneic group and there was a strong tendency for larger impairment in the other reactance parameters as well. These all became significant after exclusion of the large outlier in the non orthopneic group. These appeared to be more important in the expiratory phase of the breathing cycle, as reflected by the important differences in $\Delta X_5$ and $X_{5ex}$, as compared to $X_{5in}$.

Taking into account the 2,8 $cmH_2O.s/L$ $\Delta X_5$ threshold as a surrogate for EFL[36], respectively 18/22 (82%) orthopneic subjects and 13/23 (56%) non-orthopneic subjects presented with EFL in the supine posture. The difference was not significant between the two groups (p=0,07).

Orthopneic subjects had a significantly lower IC, $FEV_1$ and FVC when expressed in absolute values, without any differences in breathing pattern.

*Table 8: Comparison of the parameters recorded in the supine position in orthopneic and non-orthopneic subjects*

| | Non-orthopneic(n=23) | Orthopneic (n=22) | P value |
|---|---|---|---|
| **Dyspnea VAS** | 1,5±2,02 | 4,3±2,91 | <0,001 |
| **$R_5$ ($cmH_2O.s/L$)** | 6,28±1,92 | 7,55±1,77 | <0,05 |
| **$R_{20}$ ($cmH_2O.s/L$)** | 3,91±1,5 | 4,78±1,45 | <0,05 |
| **$R_{5-20}$ ($cmH_2O.s/L$)** | 2,37±0,92 | 2,77±0,88 | NS |
| **$X_5$ ($cmH_2O.s/L$)** | -5,94±2,91 | -7,595±3,72 | =0,06* |
| **$\Delta X_5$ ($cmH_2O.s/L$)** | 4,71±4,18 | 6,79±4,67 | =0,1* |
| **$X_{5in}$ ($cmH_2O.s/L$)** | -3,27±0,88 | -3,82±1,15 | =0,08* |
| **$X_{5ex}$ ($cmH_2O.s/L$)** | -7,94±4,58 | -10,61±5,49 | =0.08* |
| **AX ($cmH_2O/L$)** | 58,25±32,78 | 82,41±41,02 | <0,05 |
| **$V_T$ (L)** | 0,88±0,34 | 0,73±0,32 | NS |
| **BF (cycle/min)** | 14,27±4,8 | 15,95±4,77 | NS |
| **VE (L/min)** | 11,8±3,9 | 10,92±3,48 | NS |
| **IC (L)** | 2,42±0,77 | 2,04±0,74 | <0,05 |
| **VC (L)** | 3±0,92 | 2,47±0,87 | =0.06* |
| **$FEV_1$ (L)** | 1,25±0,67 | 0,92±0,48 | <0,05 |
| **$FEV_1$ (% pred)** | 44,74±20,58 | 36,9±16,19 | NS |
| **FVC (L)** | 2,81±0,99 | 2,15±0,79 | <0,05 |
| **FVC (% pred)** | 76,53±18,27 | 66,56±19,25 | NS |
| **$FEV_1$/FVC (%)** | 44,04±13,52 | 42,32±11,34 | NS |
| **$FEF_{50}$ (L/sec)** | 0,53±0,58 | 0,41±0,3 | NS |
| **$FEF_{75}$ (L/sec)** | 0,23±0,17 | 0,18±0,09 | NS |
| **$SpO_2$ (%)** | 95,19±2,77 | 95,2±2,31 | NS |

Values were presented as mean ± SD. NS: not significant; BMI: body mass index; VAS: visual analogue scale; $R_5$: resistance at 5 Hz; $R_{20}$: resistance at 20 Hz; $R_{5-20}$: difference between the resistance at 5 Hz and the resistance at 20 Hz; $X_5$: reactance at 5 Hz; $\Delta X_5$: difference in reactance measured at 5 Hz between inspiration and expiration; $X_{5in}$: inspiratory reactance at 5 Hz; $X_{5ex}$: expiratory reactance at 5 Hz; AX: area under the reactance-frequency curve; $V_T$: tidal volume; BF: breath frequency; VE: minute ventilation; IC: inspiratory capacity; VC: vital capacity; $FEV_1$: forced expired volume in one second; FVC: forced vital capacity; $FEF_{50}$: forced expiratory flow when 50% of the volume has been expired; $FEF_{75}$: forced expiratory flow when 75% of the volume has been expired; $SpO_2$: oxygen saturation. * These parameters were significant (p value <0,05) when excluding a large outlier from the non-orthopneic group.

### 5.5. Correlation between the changes in dyspnea VAS from the sitting to the supine position and various parameters in the COPD subjects

As expressing orthopnea according to dyspnea VAS as a binary parameter might induce a loss of information, we also assessed dyspnea during the experimental procedures in a quantitative manner by using a dyspnea VAS. We looked at the correlation between the absolute change in dyspnea VAS when adopting the supine position and anthropometric characteristics and the various parameters recorded in the sitting and the supine position as well as their changes with position. The change in dyspnea VAS with position was only significantly correlated with changes observed between the sitting and supine positions for the following parameters: $\Delta X_5$, $X_5$, $X_{5ex}$ and AX (p<0,01 for all correlations) (Figure 12).

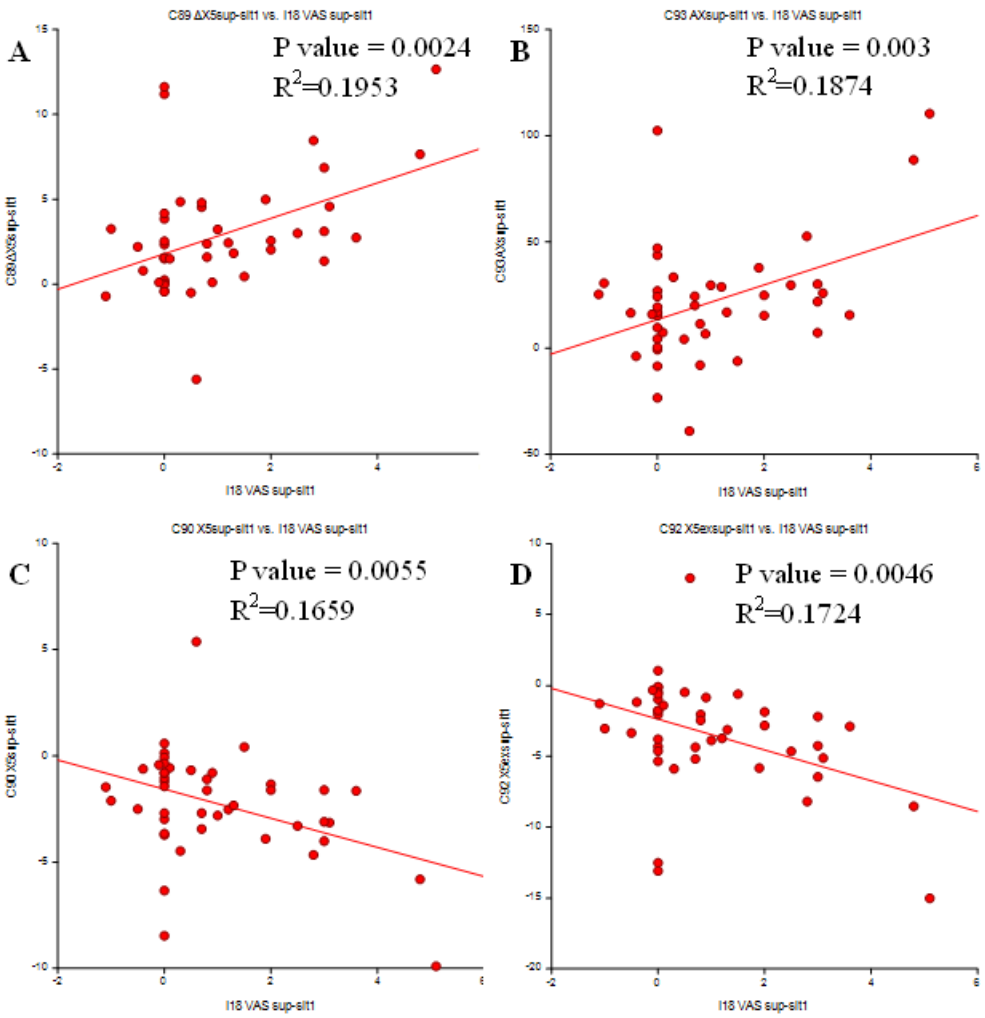


*Figure 12: Graphs representing the regression line and the relationship between the changes in dyspnea VAS from the sitting to the supine position (X axis) and the change from sitting to supine position in $\Delta X_5$ (panel A), AX (panel B), $X_5$ (panel C) and $X_5$ex (panel D).*

An increase in VAS was thus associated with an increased derangement of these reactance measurements when adopting the supine posture. We also observed a poor but significant correlation with the breathing frequency recorded in the sitting posture (p=0,03) (Figure 13). All correlation coefficients were however below 0,2.

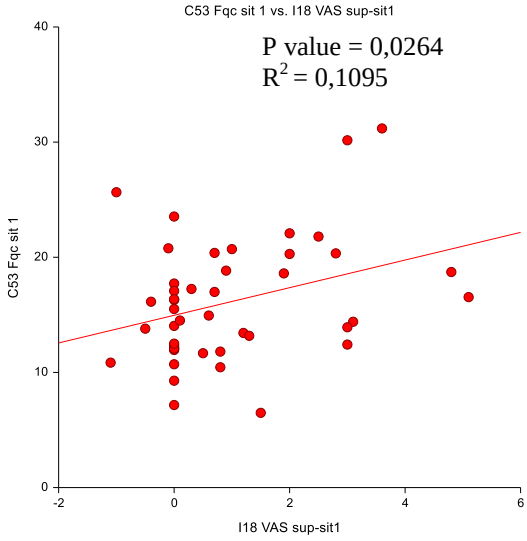


*Figure 13: Graph representing the regression line and the relationship between the changes in dyspnea VAS from the sitting to the supine position (X axis) and the BF in sitting position.*

## 6. Analysis and Discussion

Orthopnea is a frequent clinical finding in COPD. This is confirmed by statements of the COPD subjects included in the present study which were non selected stable patients without hypoxemic respiratory insufficiency from a tertiary care ambulatory COPD clinic. Indeed, 14 (31%) and eight (17%) of them described themselves as usually or sometimes orthopneic in the everyday life respectively. Among these orthopneic patients, 13 out of the 14 subjects who reported orthopnea in everyday life had the sensation of increased breathlessness when adopting the supine posture in the experimental protocol, five who previously said that they sometimes had the orthopnea experienced it during the test and seven out of the 23 who said that they never had orthopnea had actually an increased dyspnea VAS in the supine posture.

In the following discussion, we will discuss in more details the main findings of the present study. First, we will briefly discuss the already well described differences that can be found in COPD subjects compared to normal subjects in the sitting position. Second, we will discuss the changes observed in both the control and COPD subjects when going from the sitting to the supine position since these changes can potentially help us understand the pathogenesis of orthopnea. Interestingly, some of these changes were more pronounced in the COPD group and the changes in IC with position were opposite in the two groups which also has important consequences for the interpretation of the data. Third, within the COPD group, we will discuss differences found between orthopneic and non-orthopneic subjects firstly according their answer to the presence of orthopnea in everyday life and second according to the change in dyspnea observed with position during the experimental procedures. As will be discussed, these results point towards an increased small airway obstruction in the supine position which probably plays an important role in the genesis of orthopnea in COPD.

### 6.1. Difference between COPD and control subjects in the sitting position

Although gender and other anthropometric were well balanced between the COPD and control group, the latter was significantly younger and had a significantly lower waist to hip ratio. The higher waist to hip ratio observed in the COPD group might be related to age as this ratio increases with age in both genders [46].

#### *6.1.1. Spirometry*

As expected and by definition, forced parameters obtained by spirometry were always higher in normal subjects for each of the five parameters. IC was also lower in COPD subjects due to their lung dynamic and static hyperinflation. VC was also significantly decreased in COPD subjects; this was explained by the increased RV due to the loss of elastance of the alveoli and small airway closure. The increase in RV is greater than the increase in TLC which explains the decreased IC in COPD subjects.

#### *6.1.2. Resistance*

The present study was concordant with the results reported in other studies such as the ECLIPSE study [47]. Indeed, the resistance of the respiratory system is increased in COPD due to the different physiopathological changes observed with the disease. In accordance with the literature, $R_5$ was much higher than $R_{20}$, suggesting an obstruction predominantly at the level of the small airways in COPD subjects. Accordingly and as seen on Figure 7, there was a frequency dependency of resistance in COPD but not in control subjects. This translates in a higher $R_{5-20}$ in COPD subjects. As discussed before, this parameter is considered as a good index of small airway function [48, 49].

### *6.1.3. Reactance*

Parameters derived from reactance are related to the elastance of the respiratory system. As discussed before, in dynamic conditions such as during tidal breathing, reactance is however also influenced by other factors related to airway function [50, 51] such as:

- The choke point phenomenon occurring in airways in case of EFL;
- The phenomenon of small airway closure.

As can be seen from Table 5, the greatest proportion of the increase in $X_5$ observed in COPD subjects was found in the expiratory phase of the breathing cycle. As the diameter of the small airways is reduced in expiration as compared to inspiration, this suggests that the increase in reactance observed in COPD subjects was mostly related to dynamic factors rather than to an increased elastance of the respiratory system.

We did not report the results of Fres because it was not possible to measure in the oscillation frequencies applied during the recordings in the present study in some COPD patients. This problem also impacts somewhat the AX measurement as the latter is underestimated in patients where no Fres could be determined. This problem occurs when the Fres was upper than 35 Hz, the upper frequency sent by the Tremoflo™.

6.2. Effect of the supine position in controls and COPD subjects

Before discussing other results, it is important to recognize an important difference between COPD and control subjects regarding lung volumes and breathing pattern. Indeed, as opposed to control subjects, patients with COPD had no increase in IC in the supine position.

As already discussed, we did not measure the FRC (which is equal to EELV) in the present study as body plethysmography is not feasible with usual equipment in the supine position. FRC can be measured in both the sitting and the supine postures with the helium dilution method. However, the latter has important limitations in COPD. Indeed it under evaluates FRC in patients with poorly ventilated lung areas which are present in COPD [52]. As the supine position influences small airway function as discussed below, the undervaluation of FRC with the helium dilution method might increase in the supine position. This probably explains the paucity of data in the literature regarding changes in FRC with postures in COPD. Available data suggest that neither TLC nor FRC (measured by the helium dilution method) change appreciably when adopting the supine position in severely hyperinflated patients [53]. Accordingly, we used the IC as a surrogate for FRC. Indeed, the sum of IC and FRC represents TLC. Postulating a constant TLC during the measurements of the present study, an increased IC reflects a decreased FRC and vice versa. Data from the literature suggest that a constant TLC in the short term is a reasonable assumption, including when changing position from the sitting to the supine posture [41].

The changes in IC observed in the two groups thus suggest that FRC was significantly decreased in the supine position in the control subjects, as expected [37] whereas it did not change in the COPD group, so as observed by Tucker and Sieker [53]. This has important consequences for interpretation of the data since an increased airway resistance is expected with a decreased FRC such as when adopting the supine posture in controls, and the reverse when FRC increases, such as when adopting the supine position in COPD subjects [18].

A decrease in FRC in the supine position in normal subjects has been demonstrated in several studies. It is explained by an increase of the intra-thoracic blood volume. The latter is

explained by a shift from the venous blood from the lower limbs and splanchnic compartment due to gravity [41, 54]. This shift might be impaired in COPD subjects due to higher positive intrathoracic pressures in the expiratory part of the breathing cycle which is prolonged in case of airway obstruction but other factors discussed below may explain the lack of increase in IC in the supine position.

Moreover, we also observed significant differences regarding the breathing pattern according to position, which were restricted to the COPD group. Indeed, VE, breathing frequency and $V_T$ were significantly reduced in the supine position. This pattern of breathing is susceptible to decrease alveolar ventilation and increase $PaCO_2$. An increased $PaCO_2$ might increase the chemoreceptor afferences to the respiratory centers and induce dyspnea because of neuromechanical uncoupling [20]. We did not measure blood gases in the present study. Although we cannot exclude that some patients developed or had increased hypercapnia in the present study, it is unlikely that it played a significant role since we excluded patients with hypoxemic respiratory insufficiency.

Hypoventilation might induce an increase in resistance but this has only been demonstrated for the upper airway resistance [55, 56].

### *6.2.1. Spirometry*

As expected, $FEV_1$ and FVC significantly decreased in the control group when adopting the supine posture. There was also a small but significant reduction of the Tiffeneau index. However, all these parameters stayed within the normal range of the American Thoracic Society guidelines as it was the case in other studies [37, 57].

$FEV_1$ and $FEV_1$/FVC were also significantly decreased in the supine posture in COPD subjects. This is concordant with data reported for example by Melam (2014) [58]. Since FVC was not reduced in the supine position in the COPD subjects, this suggests increased airflow obstruction in the supine position, as discussed below [55]. However, the decrease in $FEV_1$, even if significant, was really small in absolute terms. In fact, there was only a 50 mL mean difference between both postures in COPD compared to a 290 mL mean difference in normal subjects. A 100 mL decrease is usually used as a clinically meaningful change [59]. As discussed below, the changes in FOT parameters were far more striking in the COPD group and this points to the fact that the FOT technique adds significantly to spirometry for the assessment of the derangements of respiratory mechanics.

As discussed above, the second run in the sitting position was used in order to ascertain that changes observed from the first sitting run to the supine position were indeed due to position rather than other uncontrolled potential confounding factors. Unexpectedly, we found some minor differences between the two sets of runs performed in the sitting position. These changes observed between the two sitting positions were observed in the COPD groups for the slow vital capacity maneuver including the IC and the VC that were significantly lower in the second than the first set. These small differences might be due to the fatigue of the patient at the end of repeated recordings.

### *6.2.2. Resistance*

In the control group, $R_5$, $R_{20}$ and $R_{5-20}$ were significantly increased in the supine position as compared to the sitting position. This is consistent with the results of Navajas *et al.*(1988) who showed that the supine posture was associated with a significantly increased resistance in young healthy subjects [42]. The increase in $R_{20}$ which reflects upper airway resistance could

be explained by the reduced cross sectional area of the oropharynx lumen while the increase in $R_5$ and $R_{5-20}$ reflects higher small airway resistance in the supine position which is probably accounted by a reduced FRC in the supine position. The latter is suggested by an increased IC. Another potential explanation for the increased $R_{5-20}$ is the changes due to gravity in the supine posture. The latter is associated with a larger portion of the lung volume in the dependent zone (dorsal part of the thoracic cage) where the pleural pressure is higher, meaning that a bigger portion of the small airways will have a reduced airway diameter. These explanations for the changes in airway resistance apply for both groups with the notable exception of the decreased FRC, as suggested by the decreased IC in the COPD group.

In the COPD group $R_5$, $R_{20}$ and $R_{5-20}$ were also increased in the supine posture and this increase was similar to the control group for $R_5$ and $R_{20}$. $R_{5-20}$ however increased more importantly in the COPD group than in the control group despite the decrease in IC. This enhances the fact that the position itself influenced the small airway diameter. Part of the increase in $R_{20}$ in the COPD group might be explained by the change in breathing pattern observed in the supine position [55, 56].

### *6.2.3. Reactance*

In normal subjects, the small but significant increase in $X_5$ and $X_{5in}$ may be related to small airway closure. The closing capacity, which is the highest lung volume at which small airway closure appears, decreases with age. Moreover, the closing capacity is closer to FRC in the supine position. Accordingly, the closing capacity is usually close to FRC in healthy subjects older than 65 in the sitting position but already around 45 years onwards in the supine posture[60].

The changes observed for reactance parameters in COPD subjects with position were much more pronounced than in control subjects. The most important changes were observed for $\Delta X_5$ and $X_{5ex}$. This suggests that dynamic changes in the expiratory part of the breathing cycle explain these changes, most probably due to the appearance of EFL secondary to increased small airway obstruction. The changes in $\Delta X_5$ and $X_{5ex}$ which suggest EFL might also explain the reduced IC due to DH observed in the supine posture in COPD subjects. The reduced IC also can contribute to orthopnea [20, 60].

According to the 2,8 $cmH_2O.s/L$ $\Delta X_5$ threshold for defining EFL, only one control subject presented an EFL in the supine posture [36]. This subject was a 72 years old woman. She also experienced an $R_{5-20}$ and AX in the supine position. In the COPD group, the number of subjects having a $\Delta X_5$ above 2,8 $cmH_2O.s/L$ went from 18 subjects in the sitting position to 31 subjects in the supine posture.

## 6.3. Difference between orthopneic and non orthopneic

Subjects defining themselves as orthopneic in the daily life did not differ much from non orthopneic subjects regarding anthropometric parameters or lung function parameters measured in the sitting position.

Interestingly, we found a significantly lower waist to hip ratio in orthopneic patients. We could imagine that because the waist to hip ratio is bigger in the non-orthopneic group normally these subjects should have a greater impairment. However, O'Donnell *et al.* (2012) have already showed the presence of a relationship between overweight (OW)/obesity (OB) and lung function in COPD subjects [61]. In OW/OB subjects, there was an increase in IC/TLC ratio meaning that these subjects had less lung hyperinflation than those having a

normal weight[62].

Orthopneic subjects already had a higher dyspnea-VAS in the sitting position, suggesting that the severity of dyspnea in the erect posture is a predisposing factor for experiencing orthopnea.

There were no significant differences regarding GOLD stages proportion or $FEV_1$ suggesting that orthopnea prevalence was not significantly influenced by disease severity as assessed by FEV. However, IC was smaller in orthopneic subjects than non-orthopneic. IC reduction has already been associated with increased dyspnea, which underlies the role of hyperinflation in the genesis of dyspnea both in the erect as in the supine posture as discussed below [63].

Quite unexpectedly however, there were no significant differences in the sitting posture between orthopneic and non-orthopneic patients in FOT parameters, although there was a tendency for a greater impairment for both the resistance and reactance parameters. The results were however influenced by a severe outlier in the non orthopneic group. When the statistical analysis was controlled after exclusion of this outlier, significant differences were found for $R_5$ and $X_{5in}$.

In the supine posture, orthopneic subjects also had a decreased IC associated with an increased dyspnea VAS compared to non-orthopneic (with and without the outlier). Nevertheless, they also had higher $R_5$ and $R_{20}$, and $X_5$. Here again the results were influenced by the same outlier. When excluded, we found significant differences in all FOT parameters related to reactance, and particularly $\Delta X_5$, suggesting an association between EFL and orthopnea. This is also suggested by a strong tendency for a higher proportion of orthopneic patients defined as EFL according to the 2,8 $cmH_2O.s/L$ threshold for $\Delta X_5$.

### 6.4. Difference between subjects having or not an increased VAS in supine

As assessing orthopnea in the daily life in a binary fashion is subject to limitations due to the multiple dimensions of dyspnea sensation as well as its complex pathophysiology, we were interested to measure dyspnea and its changes with posture in a more quantitative way during the experimental procedures with the aid a VAS. More precisely, we assessed the associations between changes in VAS and

- Various parameters (anthropometric, spirometric's and FOT parameters) and
- Changes in various parameters related to respiratory function from the sitting to the supine position.

We could not demonstrate any significant correlations between the dyspnea VAS changes with posture and anthropometric, spirometric's or FOT measurements either in the sitting or the supine position. However, there were significant correlations between changes in the dyspnea VAS from the sitting to the supine posture and changes with posture in $\Delta X_5$, $X_5$, $X_{5ex}$ and AX. As discussed above, these parameters are influenced by the presence of EFL and potentially airway closure. These results again suggest that an increase in dyspnea in the supine position is related to an increase in EFL in that position. This is in accordance with the findings of Eltayara *et al.* (2001) who showed that orthopnea was related to EFL in the supine position, as assessed by the negative expiratory pressure technique [16].

Moreover, the change in breathing frequency was also correlated with the change in dyspnea.

## 7. Study limitations

This study had some limitation. Firstly, the control group was younger than the COPD group and it is know that resistance, reactance and spirometric's measurements are influenced by age [44]. However, age cannot explain by itself the differences observed between the COPD group and control group. Indeed, the comparison of the results expressed in predicted value (according height, weight and age) when available also showed significant differences between the two groups.

Another limitation of the study is the absence of direct measurement of FRC in the present study. It was postulated that TLC was unchanged in the supine posture and so we used IC to infer changes in FRC. Even if applying this to our control group showed results similar to those seen in the literature for normal subjects we cannot exclude that TLC significantly changed with posture in the COPD patients. As discussed above, would FRC be measured by the helium dilution method, it will be underestimated [52]. On the contrary, body plethysmography would overestimate the FRC because the body plethysmography method assumes that the change in alveolar pressure is equal to the change in mouth pressure. This assumption is not true as the alveolar pressure is underestimated by mouth pressure measurements if a small flow is produced during the maneuver against the closed shutter. This results in an overestimation of the FRC with while body plethysmography. The higher the airway resistance the higher will be the overestimation so that the changes in posture might also result in different overestimations of FRC by the body plethysmography method [64].

## 8. Conclusion and perspectives

This study highlighted the high prevalence of orthopnea in COPD since more than 50% of the patients included in the present study reported or experienced orthopnea during the experimental procedures.

We also confirmed that FOT parameters are significantly different between normal and COPD subjects. This is true for both resistance and reactance parameters.

To the best of our knowledge, this study is the first to report the changes in FOT parameters induced when adopting the supine posture in COPD subjects. As expected, we observed significant increases in resistance parameters in controls which are largely influenced by the decrease in EELV reflected by an increased IC.

On the contrary, the IC decreased in the supine posture in COPD, suggesting an increase in FRC. This points to the fact that other factors are at play to explain the increase in resistance parameters observed in the supine position in COPD subjects. As there were also marked increase in the reactance parameters in the supine posture and as those were particularly prominent in the expiratory part of the breathing cycle, this suggests that the small airway obstruction increases when COPD are going supine, leading to EFL and DH.

We also were able to show significant differences between orthopneic and non-orthopneic COPD subjects. These comparisons also point to the role of small airway changes induced by posture to explain orthopnea.

This study was able to show the relevance of FOT to assess orthopnea. An increase in the dyspnea-VAS in the supine posture was only correlated with changes in FOT parameters: an increase of AX and $\Delta X_5$ and a decrease of $X_5$ and $X_{5ex}$ from the sitting to the supine posture. Given that an increase in $\Delta X_5$ and a decrease in $X_{5ex}$ are related to the occurrence of EFL, our

results suggest that EFL is an important mechanism implicated in the genesis of orthopnea in COPD subjects, confirming results obtained by the NEP technique by Eltayara *et al*. (2001). EFL on its turn can explain the reduced IC observed in the supine position in COPD subjects. A reduced IC is known to induce dyspnea by increasing the workload imposed to inspiratory muscles.

In order to confirm on one hand the results of the study and on the other hand the role of EFL and the increased closing capacity in FOT parameters changes and orthopnea, we can image the addition of two different tests:

- the negative expiratory pressure technique to confirm the association between reactance parameters and EFL;
- the nitrogen washout technique to test the hypothesis that reactance parameters are influenced by the closure of small airways since this method had already been used to assess the closing capacity in anesthetized subjects [65, 66].

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**Annex 1**



# Questionnaire

Evaluation de l'effet de la position sur la mécanique respiratoire par la technique des oscillations forcées chez des sujets normaux et souffrant de BPCO.

***Nom, prénom du patient :***

_____

Professeur Eric Marchand
[Date]

**Annex 1**

QUESTIONNAIRE

## 1. ***Données personnelles :***

- ✓ Date de naissance : / /
- ✓ Age : _____
- ✓ Sexe : *Homme - Femme*
- ✓ Tabagisme : *Oui - Jamais - Ancien(ne) fumeur-se*

**Nombre de cigarettes par jour : _____**

**Nombre de paquet par année : _____**

## 2. ***Données anthropomorphiques :***

- ✓ *Poids : _____*
- ✓ *Taille : _____*
- ✓ *Tour de taille : _____*
- ✓ *Tour de hanche : _____*
- ✓ *IMC : _____*

## 3. ***Données médicales :***

a) Pour patients sains :
Souffrez-vous d'une maladie respiratoire chronique ?

La ou lesquelles ; depuis quand

Souffrez-vous d'une maladie cardiaque?

La ou lesquelles ; depuis quand

b) Pour patients BPCO :
Depuis quand êtes vous soigné pour votre bronchopneumopathie chronique obstructive (bronchite chronique-emphysème) ; depuis quand avez-vous des traitements en inhalation ?

- Avez-vous présenté une dégradation de votre état respiratoire ayant nécessité la prise d'antibiotiques ou de corticostéroïdes (Medrol) au cours des 12 derniers mois ? Quand (date), combien d'épisodes ? Avec hospitalisation ? Dernier épisode dans les 15 jours ?

_____

_____

## 4. ***Antécédents médicaux :***

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## 5. ***Antécédents chirurgicaux thoraciques :***

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## 6. ***Traitement :***

***a)*** Quels médicaments prenez-vous actuellement ?

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_____
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_____
_____

Médicaments inhalés ?

_____
_____
_____

b) A quelle heure avez-vous pris vos inhalés médicaments la dernière fois ?

1 Médicament : Date et heure

2 Médicament : Date et heure

3 Médicament : Date et heure

## *7. Examen :*

- ✓ Date de la dernière Epreuve Fonctionnelle Respiratoire : / / 20

QUESTIONNAIRE

**Vous sentez-vous plus essoufflé en position couchée, tout-à-fait à plat ?**

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| **Tout-à-fait d'accord** | | | | | **Pas du tout d'accord** |

**Annex 1**

QUESTIONNAIRE

Pouvez-vous mettre un **trait vertical** sur la ligne ci-dessous (sachant qu'une extrémité est représentée par l'absence d'essoufflement au repos et que l'autre est représentée par un essoufflement maximal) afin que nous puissions voir comment vous évaluez votre dyspnée ?

## ***Position assise :***

**Pas d'essoufflement** **Essoufflement maximal**

---

**Annex 1**

QUESTIONNAIRE

# ***Position couchée :***

**Pas d'essoufflement maximal** **Essoufflement**

**Annex 1**

QUESTIONNAIRE

# ***Position assise :***

**Pas d'essoufflement maximal** **Essoufflement**