Diurnal Variations in the Acute Response to Exercise in Chronic Obstructive Pulmonary Disease (COPD)

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Abstract

Diurnal Variations in the Acute Response to Exercise in COPD

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Purpose: Indices of lung function and symptoms have been shown to vary throughout the day. In COPD, these variations may have clinical repercussions. The general aim of this study was to investigate the impact of time of day on the acute response to exercise in individuals with COPD. **Methods:** Subjects followed a counterbalanced randomized design, performing three symptom-limited incremental cycling tests -each preceded by a pulmonary function test- at 08:00, 12:00, and 16:00. COPD medications were withdrawn 6-24 hours prior to each test. Physiological response was measured breath by breath at rest and during exercise. Changes in outcomes were assessed with repeated-measures ANOVAs using the General Linear Model. Friedman tests were performed for non-parametric data. **Results:** Fourteen subjects (9 men, 5 women) aged 71 ± 7 years with moderate airflow obstruction (FEV_1: 58 ± 13% predicted) completed all evaluations. No overall time effect was found for peak exercise capacity ($p= 0.22$) or pulmonary function. However, changes at or beyond the suggested minimal clinically important difference were observed in nine of the 14 subjects for both variables. Resting RER was higher in the morning than at other time points ($p = 0.001$). Trends for time effects were found for mean V_T ($p = 0.096$) and HR ($p = 0.08$). VT tended to decrease throughout the day, while HR tended to increase from morning to afternoon. **Conclusion:** These results suggest that diurnal variations in the acute response to exercise may be heterogeneous among COPD patients and may follow more than one pattern.

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Author Contributions for the Manuscript

Emilie Chan-Thim is the primary author of the manuscript of this thesis. She is responsible for generating the main idea for the thesis project, the literature review, recruitment and collection of the data, data analysis and assembly of the manuscript.

Véronique Pepin is the main supervisor to the primary author and oversaw the research project and manuscript. Dr. Pepin oversaw in the study design and data analysis, in addition to ensuring the accurateness and completeness of the manuscript. Dr. Pepin was the primary editor of the manuscript.

Marie Dumont is the co-supervisor to the primary author and contributed to the study design, oversaw recruitment procedures and assured the accurateness and completeness of the manuscript in relation to the field of chronobiology.

Gregory Moullec aided in the statistical analyses.

Barbara Trutschnigg was responsible for the laboratory and equipment setup, and ensured patient safety while aiding in data collection.

Amanda Rizk, Rima Wardini and Myriam de Lorimier assisted in the equipment setup and recruitment of patients.

Simon Parenteau was responsible for patient safety, medical clearance and supervision of data collection.

Chapter 1

1.0 Literature Review

1.1 Definition

The working definition of COPD, based on the widely recognized Global Initiative for Chronic Lung Disease (GOLD), is that it is *a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with abnormal inflammatory response of the lung to noxious particles or gases* [1].

The Canadian Thoracic Society broadly agrees with this definition; however, it has made a few adjustments. The Canadian Thoracic Society defines COPD as *a respiratory disorder largely caused by smoking, and is characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations* [2].

1.2 Burden of Chronic Obstructive Pulmonary Disease

COPD is a major cause of lung-related and all-cause mortality and disability [3-5] and is recognized as the fourth leading cause of death in Canada and worldwide [2, 3, 6]. The morbidity and mortality rates are projected to rise as the population ages and become the third leading cause of death worldwide by the year 2020 [2, 7]. The province of Quebec has the second highest COPD-related mortality rate in the country after the Northwest Territories [4]. The prevalence of COPD is markedly higher in current smokers and ex-smokers as compared to non-smokers, in those over the age of 40 years, and is greater in men than in women [6]. The presentation of symptoms becomes apparent around the age of 55 years or greater [6, 8, 9]. The main symptoms of COPD are shortness of breath, cough, and sputum production [1, 2, 8, 10, 11]. Currently, the presentation of a chronic cough and sputum production which lasts for at least 3 months in each of 2 consecutive years is necessary for COPD diagnosis [1, 10] . Nonetheless, significant airflow limitation may develop without chronic cough and sputum production being present [1]. Therefore diagnoses may be made at any stage of the disease, yet patients often do not receive diagnosis until the presentation of COPD is well advanced [2, 8, 10]. This may account for the under reported diagnosis of this disease. The disease progression typically follows a downward spiral with the initial

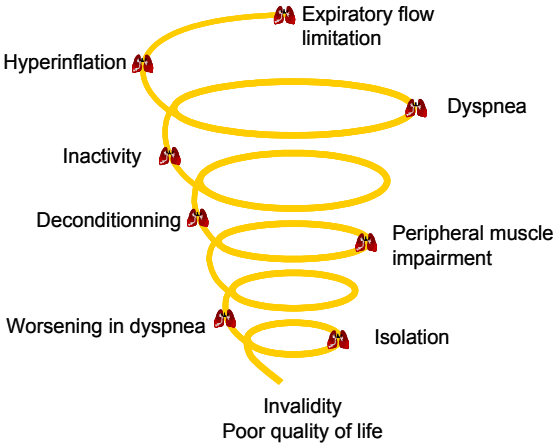

Figure 1. COPD disease downward spiral. Adapted from la Clinique du Souffle la Solane, Osséja, France.

presentation of chronic airflow limitation, to increasing inactivity, invalidity and poor quality of life (Figure 1).

The socioeconomic burden of COPD is not without costs. In 2004-05, hospitalizations in relation to respiratory diseases were ranked as third, behind circulatory diseases and digestive disorders [5]; among respiratory diseases, COPD was ranked first [5]. Overall, respiratory diseases account for about 7% of total health care costs – or about $8.63 billion – in Canada [5]. COPD is comprised of direct costs which include the diagnosis and medical management of the disease, in addition to indirect cost as a result of disability, absences from work, the expense for a caregiver and premature death [1]. As the disease progresses there exists a direct relationship with the financial burden on the health care system as patients require more direct care, in terms of hospitalizations and oxygen (O_2) therapy [1, 12].

1.3 Risk Factors for COPD

1.3.1 Tobacco smoking

The most commonly associated risk factor for COPD is smoking [1]. In 80 to 90% of cases, cigarette smoking is believed to be responsible for the development of COPD [4]. Exposure to tobacco smoke has a cumulative effect over time, progressively increasing the risk of developing COPD [1]. Smoking cessation is the most successful intervention to reduce the risk of developing COPD and in slowing down the disease progression in individuals with COPD [13, 14].

Important factors to consider in risk assessment are the age when the individual started smoking, total consumption of tobacco smoking which can be calculated in pack years (the number of packs smoked per day multiplied by the number of years smoked), and current smoking status [1, 10]. Risk has been demonstrated to be dose related in current smokers [15]. Yet there is no defining amount, in terms of tobacco consumption, where increased risk for COPD occurs [1]. Not all smokers develop COPD which suggest that other factors may play a contributing role.

1.3.2 Genetics

When comparing two individuals with the same smoking history, one may be diagnosed with COPD while the other may not [1]. This may be due to a genetic predisposition and what is known as the gene-environment interaction [1]. In certain cases, individuals who have never smoked may still end up with COPD [1]. Indeed, a rare hereditary deficiency in alpha-1-antitrypsin greatly increases the risk for an individual to develop COPD [2, 6, 8, 10]. Alpha-1-antitrypsin is a major inhibitor of serine proteinases; when unchecked,

proteolysis may occur and lead to lung tissue damage [16]. In the COPD population, alpha-1-antitrypsin deficiency is present in only about 1-2% of cases [7]. However, in individuals with COPD who are less than 40 years of age, 50% of cases are likely attributed to alpha-1-antitrypsin deficiency [7]. In addition, if these genetically susceptible individuals are smokers, it has been demonstrated that they may have an accelerated lung function decline [10].

1.3.3 Occupational exposure

According to the American Thoracic Society, occupational exposure accounts for approximately 15% of the burden of COPD [17]. Long-term exposure to occupational dusts, chemical fumes or agents increases the risk of developing COPD, independent of smoking habits [1, 10, 18]. When inhaled, these noxious particles have been shown to cause an inflammatory response in the lungs [8]. Repeated exposure to these particles increases the lung function decline and may increase the risk of respiratory exacerbations (a worsening of respiratory symptoms) in those who already suffer from COPD [10].

1.3.4 Air pollution

In developing countries, indoor air pollution carries a heavy burden. It is estimated that over two million women and children are killed each year from exposure to biomass fuel and from exposure to wood burning stoves [1]. Biomass fuels, coal, wood, and dung are used in open fireplaces and in stoves in developing countries as a means for cooking and heating [1]. Indoor air pollution represents an important risk factor in the development of COPD and the numbers, especially in women, continue to grow [1].

In urban areas, the impact of outdoor sources of air pollution in COPD remains unclear [1]. It is thought that the role of air pollution is small in COPD in comparison to the risk associated with cigarette smoking [10]. Part of the problem is that sources of outdoor air pollution are difficult to pinpoint to a single culprit and in trying to identify the long-term effects of exposure to individual pollutants [1]. However, research has demonstrated that fossil fuel combustion and motor emissions have been associated with decreased respiratory function [19]. Indeed, outdoor air pollution has been shown to be harmful in those individuals with existing heart and lung disease [1].

1.3.5 Lung growth and development

New concepts are emerging looking at the role of early lung development on future susceptibility to develop adult-onset chronic respiratory diseases, such as COPD [20]. It has been hypothesized that COPD may have origins stemming from as early as the fetal stage of life, since bronchial tree development is known to occur by the 16^{th} week of gestation [21]. Factors which may adversely impact lung development and subsequent lung function include early environmental factors such as exposure to intrauterine smoke, maternal health and nutrition, childhood exposure to pollutants, exposure to corticosteroids, prematurity, exposure to O_2, imbalance in growth factors, abnormal signaling or injury to capillary vascularization [20, 22]. Alveolar development may continue up until the age of seven years, and it is believed that maximal lung function is reached by early adulthood [20, 22]. Poor lung growth has been associated with a decreased forced expiratory volume in 1 second (FEV_1) in adulthood [22].

Another approach to investigating this late-onset disease is to determine the intrinsic effect of aging on COPD [22]. Yet, the challenge to this type of studies is how to determine the natural history of aging in addition to the amount of time required to make such observations[22]. Research has focused on determining the relationship with extrinsic factors and aging and what has been demonstrated is that a young lung does not react to a given stimulus in the same manner as an older lung [22]. For example, an older lung may demonstrate a greater effect from smoking than a younger lung [22]. In an older active smoker with more severe airway obstruction, the rate of decline in lung function may not normalize upon smoking cessation [22, 23]. A contributing factor may be associated with the immune response which has been shown to begin to decline by the age of 50 years [24]. Therefore, the aging process, under the influence of extrinsic factors, may increase the risk of an individual to develop COPD yet it does not mean an individual will result in COPD [22].

1.3.6. Infections

Infections, both viral and bacterial in origin, may increase the risk of developing COPD and the risk of having a COPD exacerbation [25, 26]. A healthy human airway is sterile, yet in COPD, the immune response becomes compromised and cannot respond to infections adequately [26]. In the case of a viral infection, the lung epithelial cells demonstrate an amplified inflammatory response [25]. With bacterial infections, the microbial pathogens have a propensity to invade the lower airways and result in the inflammatory response [26]. Overall, the inflammatory response in COPD is amplified [18].

Increased risk of infections has been suggested to be linked to low birth weight [18]. An infant with a low birth weight has an increased probability of being hospitalized for respiratory tract infections [18, 27]. Repeated childhood respiratory tract infections may be indicators of the future onset of respiratory complications, such as decreased lung function in adulthood and an increased presentation of respiratory symptoms [2, 8, 10, 18]. An important component in COPD is the lungs' ability to respond to an insult. Infection has been shown to accelerate the presentation of COPD [18].

1.3.7. Oxidative stress

The lungs are naturally exposed to oxidants through processes such as phagocytocis, however further exposure may result from external sources such as pollutants and cigarette smoke [28]. When the balance between oxidants and anti-oxidants shifts away from the protective effects of antioxidants, this is known as oxidative stress [28]. This may occur in the presence of excess oxidants or through the depletion of antioxidants [28].

As a result of smoking, an excessive oxidative burden is placed on the lungs [28]. For example, inflammatory leukocytes have been shown to migrate to the lungs and release O_2 radicals [28]. Meanwhile, smoking has also been shown to reduce the amount of plasma antioxidants, a response which is also observed under conditions of acute exacerbation in COPD [28]. This oxidative stress triggers a plethora of additional responses, critical in COPD, such as the inactivation of antiproteases, mucus hypersecretion, airspace injury, increased influx of neutrophils into the lungs, transcription factor activation and gene expression of pro-inflammatory mediators [28]. It

is hypothesized that oxidative stress may have a key role in the pathogenesis of COPD [28].

1.4 Pathology, Pathogenesis and Pathophysiology of COPD

1.4.1 Pathology

The two most common underlying disease processes that lead to COPD are emphysema and chronic bronchitis [4, 10]. Chronic bronchitis is described by small airway disease, where chronic inflammation causes structural changes resulting in narrowing of the small airways [6]. Emphysema is described by the destruction of the gas-exchanging surfaces of the lungs (i.e. the alveoli) [10]. In essence, COPD is a heterogeneous disorder by nature, characterized by the dysfunction of the small and large airways, as well as by the destruction of the lung parenchyma and its vasculature, which can be represented in highly variable combinations [11]. Developing insidiously over time, COPD is viewed as a preventable and treatable disease [2, 6].

1.4.2 Pathogenesis

1.4.2.1 Inflammatory response

In COPD, the inflammatory mechanisms underlying this disease are not fully understood, yet an amplification of the normal inflammatory response is thought to occur [1, 29]. The inflammatory response is initiated after chronic exposure to irritants such as cigarette smoke or inhaled toxic particles or gases [1, 29]. In certain individuals, genetic determinants may increase an individual's susceptibility to an amplified immune response [29, 30]. The amplified immune response may persist even after smoking cessation as tissue damaged through a history of smoking is not simply repaired upon smoking cessation [30].

Obstruction is thought to originate in the small airways and progresses to the gas-exchanging surfaces [31, 32]. The airway epithelium is the first line of defense against toxic inhalants [33]. Damage to the airways initiates the innate and adaptive inflammatory immune responses [31]. The innate immune response reacts quickly in an unspecified manner to inflammation however, it does not retain any memory of the event to assist with any future re-occurrences [31]. Meanwhile, the adaptive immune response transpires at a much slower pace, yet retains memory of prior insults and expresses greater specificity to those pathogens or nefarious agents [29, 34].

The role of the innate host defense is to enhance mucus production and clearance and maintain the epithelial barrier [31, 35]. Additionally, the innate host defense leads to the exudation of plasma proteins into all regions of the airways [29, 36]. The inflammatory immune response instigates a response where there is an influx of inflammatory cells into the airway lumen and in the airway walls, including neutrophils, macrophages and T lymphocytes (both CD+4 and CD+8) [37]. These cells then release inflammatory mediators such as chemotactic factors, proinflammatory cytokines and growth factors [18]. This response is meant to clear the lungs and resolve inflammation however, in COPD this reaction also contributes to the worsening of the disease as the repair process is altered and tissue dysfunction is the result [34, 36]. The extent to which the airway lumen is filled with inflammatory and mucus exudates, reflects the severity of the repair and remodeling process [31].

An accumulation of dendritic cells in the epithelium is important as it provides a link between the innate and adaptive immune response [29]. The dendritic cells may initiate

the adaptive immune response presenting antigen to T and B lymphocytes [29]. A signal is initiated where antibody-producing plasma cells or memory cells are formed, yet in COPD this process is not clearly understood and it has been proposed that antigens may be derived from inert or even infectious particles detrimentally affecting the immunes response [29].

In conjunction with infiltration in the alveolar wall by the innate and adaptive inflammatory immune response, an accumulation of fibrotic tissue can cause thickening of the alveolar wall [31, 36]. Transforming growth factor-beta (TGF-β), is an influential mediator in the immune response and can stimulate the fibroblast matrix and resultant fibrosis [36]. Under normal repair processes the lung architecture is preserved [36]. Yet in COPD, the lungs repair response and remodeling response initiate changes to the lung tissues such that the airway walls thicken and obstruct the lumen of the conducting airways [1, 33]. It has been hypothesized that airway inflammation may be responsible for changes in the structure and contractility of airway smooth muscles [38]. Moreover, increased smooth muscle in addition to thickened airway walls and mucus accumulation may contribute to airway narrowing and occlusion in COPD [39]. Yet the interaction between inflammatory cells and smooth muscles cells is not fully understood and requires further research [38].

1.4.2.2 Protease-antiprotease imbalance

Proteases may be derived from inflammatory and epithelial cells and may be found in excess amounts in COPD [1]. Proteases breakdown connective tissue components such as elastin in the lungs, meanwhile antiproteases protect against this effect [1, 8]. Yet in

COPD, an imbalance exists between proteases and antiproteases where an increase in proteases leads to the weakening of the parenchyma walls, which is characteristic of emphysema [1].

1.4.3. Pathophysiology

1.4.3.1 Expiratory flow limitation and hyperinflation

COPD is a respiratory disease, yet to gain a full scope of what is occurring during respiration, a brief overview of the lung volumes and capacities needs to be addressed. The lung can be broken down to four lung volumes and four capacities. When we inspire and expire under normal conditions, this is known as the tidal volume (V_T) [40]. Yet, we have the ability to take a larger breath in, tapping into our inspiratory reserve volume (IRV) should the need be required [40]. We can additionally tap into our expiratory reserve volume (ERV) and exhale beyond our usual V_T [40]. Yet even when trying to exhale maximally, air remains trapped in our lungs and this is called the residual volume (RV) [40]. The total lung capacity (TLC) is the measure of all four lung volumes [40]. The point where the lungs are at basal level of inflation is termed as the functional residual capacity (FRC) or end-expiratory lung volume (EELV) [40]. Other respiratory capacities may be measured using spirometry measurements [40]. At the end of a normal exhale, a maximal intake of breath is known as the inspiratory capacity (IC) [40]. A complete maximal inhale and maximal exhale is a measure of vital capacity (VC) [40]. Lung volume measurements are recapitulated in Figure 2 [40].

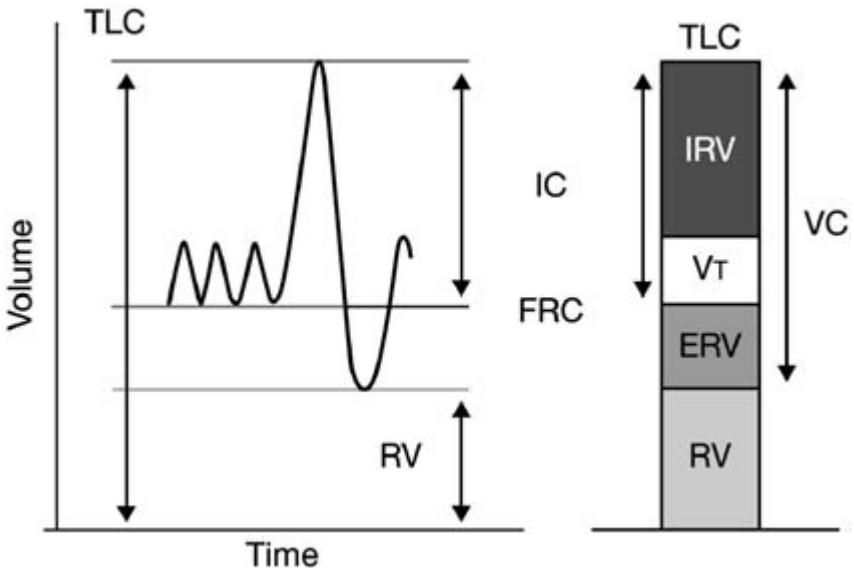

Figure 2 – Lung volume measurements.

TLC = total lung capacity (IRV+V_T+ERV+RV), VC = vital capacity (IRV+V_T+ERV), IC = inspiratory capacity (IRV+V_T), FRC = functional residual capacity (ERV+RV), IRV= inspiratory reserve volume, V_T = tidal volume, ERV = end respiratory reserve volume, RV = residual volume [40].

Spirometry is a physiological test which is used to detect the presence of airflow limitation by measuring the flow or volume of air inhaled and exhaled over a specified amount of time [41]. Forced vital capacity (FVC) and FEV_1 are the two most important measures to assess COPD airflow limitation [41]. Indeed, airflow limitation is the standard by which COPD classification and progression are determined [18]. The stages of COPD severity is based on the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), as shown in Table 1 [18].

FVC is measured from a full inspiration and corresponds to the volume expired forcefully and completely, while FEV_1 is the volume delivered within the first initial second of the FVC maneuver [41]. Airflow limitation is typically characterized by an accelerated decline in FEV_1 and/or a decreased ratio of FEV_1 over FVC [10, 40]. The decreased

FEV_1 and FEV_1/FVC ratio primarily result from the extent of inflammation, fibrosis and narrowing of the peripheral airway [18]. Peripheral airways, when obstructed, progressively trap air during expiration, resulting in hyperinflation [18]. With emphysema, the destruction of air sacs can be observed, enlarging the air space within the lungs causing additional air trapping. Air trapping can occur as the weakened structure collapses on expiration and traps air within the lungs, leading to hyperinflation of the lungs [40]. The hyperinflation may further decrease the FEV_1 and FEV_1 to FVC ratio [42].

Table 1 - Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV_1

Stage	Severity	Airflow limitation criteria
I	Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted
II	Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
III	Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted
IV	Very Severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mmHg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa(50 mmHg) while breathing air at sea level. Adapted from Global Initiative for Chronic Obstructive Pulmonary Disease, Updated 2009 [18].

Hyperinflation can be qualified as either static or dynamic or in a combination of both. Static hyperinflation is caused by a decrease in elasticity of the lung parenchyma [40]. Dynamic hyperinflation is more common and may occur independent of or in addition to static hyperinflation [40]. Dynamic hyperinflation stems from air being trapped within

the lungs after each breath when inhalation is instigated before full exhalation has been achieved, creating a disequilibrium between the volumes inhaled and exhaled [40]. Therefore, air trapping is perpetuated with each successive breath [40]. Dynamic hyperinflation may occur without prejudice at any stage of COPD [40]. The ability to exhale depends on the degree of airflow limitation and the time available for exhalation [40]. Therefore, dynamic hyperinflation often occurs in situations associated with increased ventilation, such as during physical activity, and during exacerbations of COPD [40].

Lung volumes are measures which best correspond with the presentation of symptoms and impairment of functional capabilities [40]. When the V_T during exercise encroaches on the TLC envelope, further volume expansion is impossible [11]. The IC is often used to indirectly measure hyperinflation during repeated exercise tests in COPD [41, 43]. The IC maneuver tracks the changes in EELV in hyperinflation [43].

1.4.3.2 Mucus hypersecretion

Mucus production occurs in the lining of the airway epithelium and is caused by bronchial glands and by goblet cell secretions [33]. Chronic stimulation by toxic particles induces a dysregulation in the mucus response where more mucus is produced through goblet cell metaplasia and, when mucus clearance is unable to keep up with this increased production, this can lead to a buildup of mucus in the airway lumen [29]. Additionally, secretions can detrimentally compromise the airway surface tension causing airway instability, increasing the risk of airway closure and mucus obstruction [44]. Further

disruption in the epithelial barrier can occur, allowing the infiltration of damaged tissue [29]. Infiltrates include macrophages, CD8+, CD4+, T lymphocytes and B cells [29].

1.4.3.3 Gas exchange limitations

Under everyday conditions, healthy individuals are rarely limited by their ventilatory capacity. Healthy individuals can adapt to increases in demand on the respiratory system to meet the increased O_2 demand and carbon dioxide (CO_2) production [45]. However, in chronic lung diseases, several factors impede gas exchanging properties. Gas exchange is initiated at the level of the alveoli within the lungs, where the distribution of O_2 through the vascular bed is known as gas perfusion [46]. Gas perfusion is not uniform across the lungs as the lungs are made up of many compartments and each compartment may have different ventilation to perfusion ratios (V/Q) [46]. In COPD, a broad range in V/Q distributions can be expected as both ventilation and the distribution to blood flow may be altered [46]. The different V/Q ratio's can range from 0, for example in the case of a shunt were venous blood returns to the heart bypassing the gas-exchanging surfaces, to infinite, when there is ventilation to an area of the lungs where there is no blood flow [46]. The more uniform the distribution, with a mean value approaching 1.0 signifies a better gas exchange capacity [47, 48]. However, a reduction in the V/Q can lead to an increase in CO_2 circulating in the blood and this is known as hypercapnea [18, 45]. Increased CO_2 in the circulating blood is known to decrease the blood pH [49]. Furthermore, evidence of increased lactic acid production in COPD patients has been demonstrated to increase ventilation as well as forecast greater muscle fatigue [3].

Ventilatory limitation can also occur under conditions of increased workload placed on the respiratory system, which can result from increased airway resistance, respiratory muscle dysfunction or increased risk of hyperinflation, tipping the balance between load and respiratory capacity [45]. This, in turn, can lead to hypoxemia, which is a decrease in the partial pressure of oxygen (PO_2) available in the circulation [18]. Hypoxemia is measured through arterial PO_2 (PO_2 below 55 mmHg) or by pulse oxymetry (SpO_2 <85%) [18, 45]. Yet, the most common cause of hypoxemia has been identified to be due to ventilation-perfusion mismatch [46].

Further limitations to gas-exchange and perfusion can occur in the emphysematous patient, as structural changes to the parenchymal wall results in damage to the alveoli and the alveolar-capillary interface [18, 45]. Therefore, a smaller surface area is available for gas-exchange [46].

In summary, gas exchange limitation occurs in COPD with the decrease in available O_2 and increase in the circulating CO_2. The exchange in gases deteriorates with the progression of the disease. The poor V/Q may be used as an indicator of increasing emphysema severity [18].

1.4.3.4 Respiratory muscle dysfunction

In normal lungs, EELV is the point at which the respiratory muscles are at rest and a balance is achieved between the counter pressures of the chest wall and of the lungs [40]. In COPD, destruction of elastic tissues alters the lung recoil pressure shifting the balance between counter pressures [40]. A greater FRC results, contributing to lung hyperinflation as air remains trapped within the lungs and places the respiratory muscles

in a mechanically disadvantageous position [40, 50, 51]. The diaphragm is the main generator of tidal breathing [52]. When the optimal diaphragm length-tension relationship has been compromised, this requires that a greater respiratory force be exerted during tidal breathing [53]. Initially the diaphragm can adapt to the overload and generate greater force [51]. The diaphragm demonstrates adaptations to resist fatigue by increase the proportion of slow, fatigue-resistant fiber types [52, 54]. Additionally, adaptations to myofibril sarcomere length have been demonstrated, adapting to work at a shortened length increasing muscle fatigue resistance [55]. Yet with time the respiratory muscle strength and endurance are compromised in COPD due to the increasing load placed on them [51]. As a consequence of reduce respiratory muscle strength, hypercapnea, dyspnea, nocturnal O_2 desaturation and poor exercise tolerance are evidenced [50].

1.4.3.5 Peripheral muscle dysfunction

It has been postulated that skeletal muscle dysfunction in chronic respiratory disease may be associated to a number of pathophysiological abnormalities, namely to sedentary lifestyle deconditioning, systemic inflammation, oxidative stress, blood gas disturbances, corticosteroid use, malnutrition, and reductions in muscle mass [50]. Lower limb ambulatory muscles have been most commonly studied [50]. The generalizability of these findings to other peripheral muscles is, as yet, unclear [50].

Unlike respiratory muscles which demonstrate adaptations similar to an endurance trained athlete, the skeletal muscles demonstrate atrophy and consequently there is a reduction in aerobic capacity [56]. Currently, these findings point to peripheral muscle adaptations instigated by deconditioning and a switch in fiber typing toward more

fatigable fibers [54, 56]. The proportion of slow twitch fibers is decreased and the proportion of fast-twitch fibers is increased [50, 54, 56]. The resultant reduction in aerobic capacity entrains an increase in lactic acidosis production for a given work rate in COPD and subsequent increases in minute ventilation (V_E) [57].

1.4.3.6 Exercise intolerance in COPD

Until recently, ventilatory limitation was thought to be the only limiting factor to exercise capacity in COPD patients [45]. However, it has been shown that with comparable ventilatory capacities, there exists a wide range in the exercise tolerances attained in a COPD patient population [58]. Therefore, the mechanisms involved in exercise intolerance in patients with COPD are actually much more complex and suggest the involvement of several systems [45, 53]. Moreover, poor exercise tolerance has been closely related to impairment and disability in COPD and is a better predictor of poor quality of life and subsequent survival than are spirometry measures alone or the need for O_2 therapy [42, 59].

Studies have been conducted to investigate the two most commonly reported symptoms related to exercise cessation, namely leg fatigue and dyspnea [3, 60, 61]. The onset of dyspnea may be related to ventilatory limitations, the increased work of breathing, hyperinflation and/or gas exchange limitations [3, 40]. To relieve the sensation of dyspnea, V_E and respiratory rate (RR) increase [62]. However, as RR increases, expiratory time is further decreased and a vicious cycle of gas trapping and progressive dynamic hyperinflation occurs [40]. As a result of gas trapping in the lungs, individuals with COPD respire at a much higher EELV and this is termed static lung hyperinflation

[63]. The TLC does not change, even under conditions of exercise, and an IC maneuver is an indirect measure of the changes to the EELV or the scope of hyperinflation [64]. Under exercise conditions, individuals with COPD become physiologically limited by the maximal TLC envelope and, during exertion, it forces premature exercise termination as they are unable to keep up with the body's demand for O_2 [58]. Drugs exist which can deflate the lungs, and permits a greater IRV such as bronchodilators which relax the airway smooth muscle and improve expiratory flow rates reducing dyspnea and improving exercise tolerance [2].

The effectiveness of respiratory medications are significant in terms of improving ventilation, yet the effects are limited in patients with a greater susceptibility to leg fatigue during exercise tolerance testing [61, 65, 66]. Despite similar improvements to expiratory flow it is the muscle fatigue which limits performance, hypotheses have been proposed to try and elucidate the mechanism behind muscle fatigue in COPD [66, 67]. Muscle fatigue in COPD has been linked to peripheral muscle impairments, such as poor oxidative capacity, muscle atrophy and muscle weakness [66]. An increased susceptibility to contractile fatigue and increased lactate accumulation as well as early muscle acidosis may also have contributing roles [66, 67]. Additionally, the type of exercise modality (eg. walking versus cycling) has been shown to influence symptom perception (eg. dyspnea and leg fatigue, respectively) [61, 65, 66]. In these patients, treatment of the peripheral muscles in combination with pharmacological interventions should be incorporated into the management plan [58].

1.4.3.7 Pulmonary complications

Pulmonary hypertension frequently develops further on in the progression of COPD [18, 68]. Pulmonary hypertension is the result of small pulmonary arteries constricting in response to reduced levels of O_2 in the circulation [18]. The arterial constriction increases the resistance to blood flow and increases the work required for the heart to pump through the pulmonary circulation [68]. The pulmonary arterial constriction has been shown to induce structural changes in the intimal thickness (hyperplasia) and smooth muscle hypertrophy [18, 68]. The presence of pulmonary hypertension has been associated with shorter survival and worst clinical outcomes [68]. Pulmonary hypertension may lead to right ventricle hypertrophy and cardiac failure or cor pulmonale [18].

Further pulmonary complications result from transitory changes such as during a respiratory exacerbation. An exacerbation is perceived as the amplification of subjective respiratory symptoms; dyspnea, cough and sputum production [8, 69]. Exacerbations are associated with physiological deterioration resulting in poor expiratory flow, increased dyspnea, and increased inflammatory markers [69, 70]. It is believed that as many as 50% of episodes of exacerbations go unreported, the median reported exacerbations ranging between 2.5 and 3 episodes per year [71]. Exacerbations may be triggered by bacterial or viral infections or environmental pollutants [18, 70]. Relief from exacerbation symptoms takes a median of seven days, whereas recovery of peak flow may range from 6 to 35 days and, in a significant number of patients, approximately 7% do not return to prior baseline lung function values [72]. It has been hypothesized that the incomplete return to

initial baseline lung function after an exacerbation may contribute to the disease progression and decline in lung function [70]. Treatments with oral corticosteroids have been documented to improve the rate of recovery from an exacerbation [73-75]. Antibiotics are the preferred pharmacotherapy treatment when changes in sputum are present [70].

1.4.3.8 Comorbid conditions

COPD has been linked to multiple comorbid conditions including ischemic heart disease, osteopenia or osteoporosis, glaucoma, cataracts, cachexia, sleep-related disorders, anxiety and depression [2, 18]. As COPD presents itself in an older population, comorbidities are quite common and may be as a result of the aging process or of COPD [18]. Currently, specific guidelines for the management of such comorbidities do not exist and therefore are managed on an individual basis [18].

1.5. Management of COPD

There is no known cure for COPD [6, 8]. However, modern management of the disease does allow for a deceleration in the progression of the disease. The goal of COPD management, as stated by the Canadian Thoracic Society, includes prevention of disease progression; reduction of the frequency and severity of exacerbations; alleviation of dyspnea and other respiratory symptoms; improvement of exercise tolerance; prompt treatment of exacerbations and complications of the disease; improvement of health status; and reduction of mortality [2]. This can be achieved through a stepwise approach (Figure 3) [2].

The management and assessment of COPD are done on an individual basis and should include a thorough medical evaluation, patient history as well as a physical examination [2]. The single most effective intervention to reduce the risk of developing COPD, or to

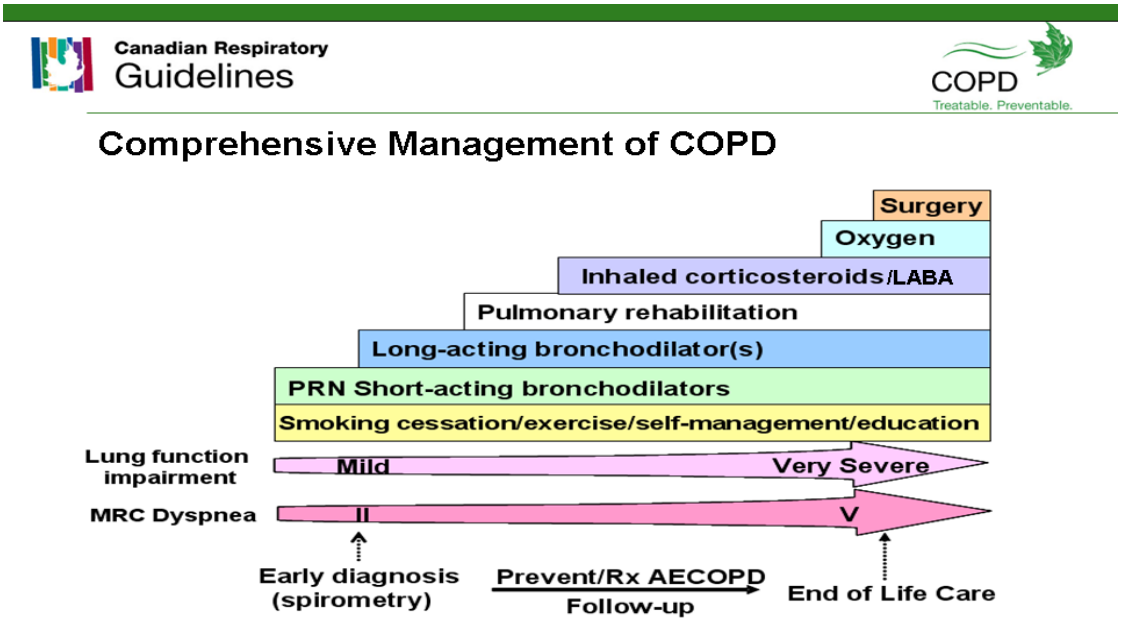

Figure 3. A comprehensive approach to the management of chronic obstructive pulmonary disease (COPD). AECOPD Acute exacerbation of COPD; LABA Long-acting beta2-agonist; MRC Medical Research Council; PRN As needed; Rx Treatment. Can Resp J 2008; 15 (Suppl A): 1A-8A

slow down the progression of the disease, is through smoking cessation [2].

In the management of COPD, pharmacotherapy comprises an integral role. Due to the progressive nature of COPD, the pharmacological treatments tend to be cumulative over time [1]. Furthermore, the number and frequency of exacerbations, comorbidities and other complications may influence the course of pharmacological treatment [1, 2]. However, pharmacotherapy has its limitations such that it has been unable to demonstrate an improvement in the progressive decline in pulmonary function [76].

Changes achieved through pharmacological intervention may be reflected in changes in FEV_1 and improvements in lung volumes which help alleviate symptoms of dyspnea [8]. Bronchodilators are prescribed first of which there are three types, namely beta agonists, anticholinergics and methylxanthines [8]. β_2-agonist, such as salbutamol, salmeterol, formoterol and terbutaline, relax airway smooth muscle by stimulating the β_2-adrenergic receptors, increasing cyclic adenosine monophosphate(cAMP) and producing antagonist bronchoconstriction [1]. Anticholinergics such as ipatropium bromide, oxibromide and tiotropium bromide block the acetycholine effect and increases the bronchodilating duration [18]. Methylxanthines' role in COPD pharmacotherapy remains controversial. Methylxanthines, such as theophyllines and aminophyllines, have a bronchodilating effect, display anti-inflammatory properties, control blood plasma levels and have been reported to reduce exacerbations in COPD [8, 77]. However, this medication has a risk of toxicity [1]. Methylxanthines are a nonselective phosphodiesterase inhibitor, which can be cumulative in the system as with age a decreased clearance of the drug has been seen [1]. Therefore, there is an increase in adverse events in using this medication, from a risk

of overdose, to cardiovascular or neurological dysfunction to less severe effects including headaches or nausea etc. [1, 2]. Overall changes seen in methylxanthines only demonstrate modest improvements in pulmonary function, exercise capacity and dyspnea [2].

Bronchodilators can be further dichotomized into short and long-acting categories. Short-acting bronchodilators, which include anticholinergics and β_2-agonists, are used to improve pulmonary function, dyspnea and exercise capacity [2, 78]. The benefits however are inconsistent [2]. Long-acting bronchodilators, such as long-acting β_2-agonist (LABA), provide more sustained benefits in pulmonary function, dyspnea and health status in moderate to severe disease [2]. However, side effects include risk of palpitations, tachychardia, irritation, insomnia, muscle cramps and tremors [2]. Long-acting anticholinergics (LAACs) used in moderate and severe disease have greater sustained effects on pulmonary function, dyspnea and health status [2]. Few side effects, such as dry mouth and on rare occasion's arrthymias, have been associated with LAACs, but in general they are well tolerated [2]. Furthermore, there are combination drugs of long-acting bronchodilators, LAACs and LABAs, such as salbutamol/ipatropium, providing complimentary benefits in moderate and severe disease and exhibit greater consistency in health status and fewer exacerbations [1, 2, 8].

Glucocorticoids affect the inflammatory cascade [8]. Inhaled corticosteroids (ICS), such as fluticasone, budesonide and beclometasone dipropionate, act as stand-alone drugs and are a controversial method of treatment in COPD as they demonstrate inconsistent results [1, 2]. ICS aim to improve airway inflammation, pulmonary function, symptoms

presentation, decrease the number of exacerbations and improve health status [2, 18]. Chronic use of ICS may result in reduced bone density, repeated bouts of pneumonia, cataracts and glaucoma [2]. Side effects may include dysphonia (impairment of the voice), oral candiasis (thrush or fungal infection) and ecchymosis (bruise) of the skin [2]. Therefore, combination therapy has been used where pharmacological agents from two different classes have been combined, such as long-acting bronchodilators and inhaled corticosteroids (ICS/LABA), like with fluticasone/salmeterol and budesonide/fomoterol [1, 2, 8]. ICS/LABA have demonstrated greater consistency above what is found individually in moderate and severe disease on pulmonary function and exercise capacity and improves the occurrence of exacerbations, pulmonary function and health status [2, 8].

Oral corticosteroids, like prednisone or prednisolone, carry higher risks of adverse side effects such as adrenal suppression, osteoporosis, cataracts, diabetes, skin thinning, muscle weakness, hypertension and psychosis [1, 2]. However, this mode of treatment has been shown to increase FEV_1 in a subset of the COPD patient population [2]. Overall, sustained use of this medication is not recommended [2].

Selection of pharmacotherapy may also be in part due to cost and convenience [18]. It is easier to take one medication versus two, ergo combinations of medications. As the disease severity increases, it becomes more effective to take a long-acting medication as compared to short-acting interventions, which would need to be taken at increasing frequencies [18]. As well, the chronic treatment of glucocorticosteroids is to be discouraged as they may have a toxic effect [18].

Other interventions include vaccines, alpha-antitrypsin augmentation therapy, antibiotics used in the treatment of infections and during exacerbations, mucolytics agents as an alternative to glucocorticosteroids, yet research has shown little benefit and do not widely recommended mucolytics, antioxidants agents, immunoregulators, vasodilators and others [2, 18].

Education is crucial for self-management, in the instruction of proper use of inhalers and O_2 if necessary, in aiding in early recognition of signs of exacerbation, and in end-of-life issues [2]. Other non-pharmacological interventions exist, namely pulmonary rehabilitation and, if needed, O_2 therapy and/or surgical intervention [2].

Pulmonary rehabilitation is a multidisciplinary intervention combining exercise training, education, nutritional intervention and psychosocial support and has gained widespread support in the management of systemic consequences of COPD [2, 18, 50, 79]. Pulmonary rehabilitation promotes lifelong management and has been shown to significantly reduce symptoms of dyspnea and to increase exercise tolerance and health related quality of life as compared to standard of care alone in COPD patients [50, 80]. Exercise training is considered the key component as it is responsible for many of the benefits associated in pulmonary rehabilitation [2, 50, 79]. Exercise training can improve muscle function, improve cardiovascular function, decrease symptoms, reduce mood disturbances, and improve cognition [50, 80-83]. Physiological adaptations which occur with exercise training include increased peak oxygen consumption (VO_{2peak}), greater peak work rate or endurance time to constant-load exercise, reduced V_E for a given workload, and improvements in the oxidative capacity [57, 81, 84]. However, the optimal exercise

training dose (intensity, duration and frequency) has yet to be determined to elicit the most benefits [50, 80].

As COPD progresses, O_2 therapy may initially be needed to assist during exercise training, so as to delay ventilatory limitation and/or exercise-induced O_2 desaturation. It may also be needed at night only, to prevent nocturnal hypoxemia. Eventually, in cases of severe resting daytime hypoxemia, continuous O_2 supplementation may be used, potentially increasing survival in these patients [2, 50].

In individuals afflicted with severe COPD surgery may be required either through lung-volume reduction or lung transplantation [85]. Lung transplantation is a more limited option as it is accompanied by increased risks of complications which may impair survival [86]. Pulmonary rehabilitation is recommended before and after surgery to help bolster prospective outcomes [87]. Transplantation is usually only considered when FEV_1 is < 25% of predicted values [86]. Lung-volume reduction surgery improves static lung-recoil, respiratory muscle function, increases lung function and decreases hyperinflation [40, 85]. The improvements from the reduction surgery are preserved over the long-term unlike exercise training or pharmacological interventions which are only effective so long as they are being practiced [86]. However, future research is aimed at determining if the pharmacological use of tiotropium could be used with sufficient magnitude so as to mimic the effects of lung-volume reduction. Pharmacotherapy could then potentially eliminate the need for surgery, which is a much more invasive procedure [40].

In summary, optimal management is desired to prevent or reduce the disease progression, decrease the number, frequency and severity of exacerbations, alleviate symptoms, and

increase activity levels and quality of life [2]. Current management is achieving this, yet further research is needed. Suggestions have been made to investigate the link between airflow limitation and smooth muscle constriction in COPD [38] Emerging research is suggesting that pulmonary rehabilitation may be an aid in smoking cessation [88]. As well, further research is needed to determine the optimization of pulmonary rehabilitation programs (dose, duration and frequency) [50, 80].

1.6. Clinical Assessment

1.6.1. Diagnosis

Pulmonary function tests, such as spirometry and measurement of lung volumes and diffusion capacities are key to confirm diagnosis and determine disease severity [18]. A spirometry test should be undertaken by current or former smokers over the age of 40 years if they are demonstrating any of the following symptoms; regular cough either with or without phlegm, feelings of shortness of breath while performing simple chores, wheezing at night or under exertion, or susceptibility to frequent colds lasting longer than usual [2]. For diagnosis of COPD, a post-bronchodilation spirometry needs to be performed, where FEV_1 and FVC are measured. A ratio of FEV_1 over FVC less than or equal to 0.7 is indicative of airflow limitation [1, 8]. Further pulmonary function tests can be conducted to track the progression of the disease, to help clarify diagnostic uncertainties and determine patient eligibility for surgical intervention [1]. Additional tests such as a chest x-ray may be helpful in identifying other comorbidities and in discarding alternative diagnoses [1].

1.6.2. Other investigations

A complete medical assessment should be conducted evaluating risk factors, family history of COPD, past medical history (ie. frequent childhood respiratory infections, allergies, asthma or other respiratory conditions), and the presence of concurrent comorbidities, in addition to the evaluation of the patient's current management, family support, history of exacerbations and hospitalizations, modifications of risk factors (ie. through smoking cessation) and pharmacotherapy treatment and response [18]. A

physical assessment should be conducted, yet physical signs of airflow limitation may not become apparent until significant impairment has occurred and are therefore not used for diagnosis [89, 90]. Physical examination may be useful in detecting changes in the chest wall; in cases of hyperinflation, a more rapid shallow RR may be noticeable, while lower leg and ankle edema may be detectable in the presence of right heart failure [1].

Arterial blood gas measurements should be done under stable conditions and are especially important in the more advanced stages of the disease, when FEV_1 is less than 50% of the predicted value or when clinical signs of respiratory failure (PaO_2 <60mmHg) or right heart failure are present (ie. cyanosis, ankle swelling) [1].

Finally, evaluations of exercise intolerance are also important to help indicate a patient's current health status as well as predict their future prognosis [1]. Exercise tests have become routinely used for the clinical evaluation of COPD patients [91].

1.6.3. Exercise testing

Cardiopulmonary exercise testing (CPET) provides a comprehensive measure of the global response of the major systems including the cardiac, pulmonary and muscular systems [42]. CPET objectively measures functional capacities and impairment, limiting factors to exercise, pathophysiological respiratory mechanisms and exertional symptoms [42, 92-95]. Overall health status has been shown to be more strongly correlated with exercise tolerance than with measures of resting pulmonary and cardiac function [42]. Greater awareness of the benefits of reliably predicting exercise performance and functional capacity has lead to the increased use exercise tolerance testing [42, 53]. In

addition, technological advancements have made the CPET equipment much more user-friendly [53].

The most common indications to perform exercise testing are to diagnose the presence of cardiovascular and/or respiratory diseases, to evaluate disease severity, prognosis and response to treatment in individuals with known disease, and to determine exercise/functional capacity for preoperative purposes, disability assessment, return to work evaluation and/or exercise prescription [42]. Exercise testing is thus useful in all phases of clinical decision making, from diagnosis to assessment of severity, disease progression, prognosis, and response to treatment [42].

Exercise testing may be conducted either in the field or in a laboratory-based setting [53]. Field tests may be more reflective of daily activities (e.g. six-minute walk, shuttle walk, stair-climbing test, etc.) [92]. In a laboratory setting, the treadmill and stationary cycle ergometer are the preferred modes of testing [42]. Each mode of exercise has its own advantages and disadvantages. Research has revealed that it is most efficient to utilize larger muscle groups during testing, whereby greater physical stress is then exerted [42]. With treadmill testing, a larger muscle mass is utilized as compared to cycle ergometry; this is reflected through the physiological measure of maximal oxygen consumption (VO_2), which typically reaches higher values when testing is performed on a treadmill than on a cycle ergometer [42]. However, the cycle ergometer is less expensive and requires less space than a treadmill [42]. Moreover, the cycle ergometer is less prone to introduce movement and noise artifact into measurements (e.g. electrocardiogram (ECG) and blood pressure (BP) monitoring). In general, if exercise testing is being used to

provide a prescription for subsequent exercise training, then it may be advantageous to use the same exercise modality in testing as in training [42].

Several protocols exist to evaluate exercise response in patients with COPD. The protocols can be classified by whether they are *(i)* maximal or sub-maximal in nature, *(ii)* incremental or constant load, and *(iii)* externally paced or self-paced [53]. A test is termed maximal if volitional fatigue is attained, whereas it is termed sub-maximal if it is stopped when a pre-determined endpoint has been reached (e.g. 80% of maximum predicted heart rate (HR)) [53]. Incremental exercise tests submit patients to a consistently increasing workload, whereas constant-load exercise tests subject patients to a fixed work rate, often determined as a percentage of their peak capacity [53]. An externally-paced protocol is one where the workload (e.g. cycling resistance, walking speed) is imposed on the patient, whereas self-paced protocols allow the patients to dictate their own work rate (e.g. six-minute walk test) [53].

Within a COPD patient population, there currently exists no consensus as to which protocol is best suited to evaluate exercise tolerance [53]. The different modalities for exercise testing do not demonstrate the same responsiveness to each test when dealing with patients with COPD [58, 61, 96-99]. Exercise intolerance in COPD manifests itself in a complex array of interactions in symptomology, ventilatory and respiratory mechanics impairment, gas-exchange limitations and peripheral muscle fatigue [58]. Furthermore, in patients with COPD, exercise termination may occur prior to the occurrence of predictors of maximal exercise attainment, such as the attainment of maximal VO_2 [58]. Therefore, it is important to comprehensively evaluate these

measures. According to the American Thoracic Society and the American College of Chest Physicians, the most commonly used test with COPD patients in clinical practice is the maximal incremental cycle ergometer test [42].

Once the appropriate protocol has been selected for clinical exercise testing, it is essential to take into consideration the nature of the measured variables as well as their validity and reproducibility [42]. The main measurements involved in CPET typically include respiratory gas exchange (VO_2, carbon dioxide output (VCO_2), and V_E, ECG, HR, BP, and SpO_2 [100]. Values of HR, VO_2, SpO_2, V_E, ventilatory threshold (VT), and RR reached during maximal progressive exercise are all highly reproducible [101, 102]. The response obtained from the first exercise procedure is considered representative [102, 103]. Factors that may contribute to variability in these measurements include changes in clinical status, symptoms, and medication(s), patient motivation, patient instructions, test procedures, equipment calibration errors, and the time of day [42]. These factors must be meticulously controlled to minimize discrepancies in measured exercise responses [42]. Changes in clinical status may occur as COPD is a progressive disease. As a susceptible patient population, symptoms may be subject to the effects of respiratory exacerbations. Additions or changes to medications are also common in this patient population. Patient instructions and test procedures are linked and should both optimally be standardized [104]. Offering encouragement to the patient has been demonstrated to have a significant effect on exercise performance, probably via patient motivation; encouragements should therefore be avoided or, perhaps preferably, standardized [104]. Equipment calibration is recommended prior to each test [42] since changes in environmental conditions can play a crucial role and invite variability into the experiment's results. Finally, the American

Thoracic Society guidelines have recommended testing to be undertaken at the same time of day [42] since significant diurnal variation in physiological measures have previously been reported [102, 103]. This potential confounding factor is discussed in details in the next section.

1.7. The Basis of Diurnal Variations in Various Physiological Parameters

Chronobiology is the study of time-dependent changes in physiological variables [105]. Circadian rhythms are characterized as recurring 24-hour patterns of physiological functions and are the result of the endogenous oscillator [105-108]. Endogenous rhythms are self-sustaining rhythms and are thought to originate from the suprachiasmatic nuclei (SCN) in the anterior hypothalamus [105, 108-110]. The endogenous rhythms are the body's internal biological clock or pacemaker [105, 108-110]. Therefore, the circadian rhythm is thought to be the causal factor in biological rhythms [108]. However, further research is required in this area as the SCN has not conclusively been identified as the sole regulator of rhythmicity [105].

Biological rhythms can further be described as diurnal, where an observed 24 hour pattern can be identified [108]. A diurnal rhythm may originate either from internal cues, which are known as endogenous rhythms, or through external influences, which are known as exogenous rhythms [108]. Exogenous influences can be affected by outside influences such as behavioral or environmental conditions [109]. Factors which influence exogenous rhythms include activity, meals, posture as well as light, temperature and allergens [105, 108, 109].

Laboratory constant routine protocols may be used to control for the effect of masking [108]. The objective behind a constant routine protocol is to eliminate as many external cues as possible and to unmask the underlying endogenous circadian rhythm [108]. Performing studies with constant routines are inherently more challenging and are

therefore less reported, diurnal studies are incidentally more commonly used in clinical studies as they are more closely related to real life situations [108].

Circadian variations in many physiological variables have been clearly established in the literature [111, 112]. Variations have been demonstrated in pulmonary function, metabolic (VO_2 and VCO_2, V_E) and cardiorespiratory responses (HR, and BP), [105, 112]. When considering rhythms of physiological function related to exercise response, resting cyclical rhythms must be first considered [106]. Physiological rhythms detected at rest may be cancelled or weakened, maintained or intensified under active conditions [106]. Below is a description of the circadian variations documented to date for the main pulmonary, metabolic and cardiorespiratory variables related to resting and exercise performance.

1.7.1 Pulmonary function

Chronobiology is particularly significant when applying it to pulmonary function [107, 113]. Indices of lung function have been shown to differ throughout the day as a consequence of changes in airway resistance [106]. Changes in airway resistance may be signaled in patients by an increase in their symptoms, namely an increase in shortness of breath. Patients with airway obstruction often report a worsening of their symptoms at specific times of the day [113, 114]. However, it remains unclear when COPD patients are affected the most. Based on patient reports, varying patterns have been noted: a morning reduction, an evening reduction, a double dip pattern where both a morning and evening reduction is observed, or no change in pattern [115-117]. Knowledge of the patient's regular patterns of reduced airflow is more likely to be useful in planning preventative therapeutic strategies and optimizing treatments [107, 115]. Even small

increases in airway obstruction may be enough to burden those with pulmonary disease and result in severe disability [107, 114].

Pulmonary function may also be objectively represented by the amount of airway resistance, measured by forced expiratory flow (FEV_1) and peak expiratory flow (PEF), which vary with time of day and are at their lowest between 0300 hours and 0800 hours [117-119]. Arguably, airway caliber is the foremost determinant of diurnal variation in ventilation [117]. This has been extensively researched in an asthmatic population where there is a clear increase in airway resistance in the morning [120]. In healthy individuals, there is a peak in airway resistance in the morning followed by the lowest airway resistance at noon and by an increase in resistance in the afternoon [107].

In COPD, other variables may play a detrimental role, where hyperinflation of the lungs appears to be greater in the morning [40] while bronchiole secretions and mucous production are greater in the morning and evening [121]. Carbon monoxide diffusion capacity (DLCO) measures were found to peak in the morning between 0800 and 0900 hours and progressively decrease into the evening [107, 122]. The decrease in DLCO has been postulated to cause or be linked to the corresponding fall in hemoglobin and hematocrit [122]. Similarly higher alveolar volumes (V_A) have been identified in the morning and decreases into the evening [123]. Potentially V_A may contribute to the decrease observed in DLCO [123]. The mechanism of change for V_A is not completely understood, however it has been proposed that the lung surface area may decrease and a smaller area for gas exchange would be the reasoning behind the changes observed in DLCO [123]. Additionally, the change in DLCO may be related to changes in lung recoil

pressure [124]. A greater decline in DLCO values may depend on the posture maintained throughout the day (e.g. standing erect, bank teller or if an individual is seated, secretary) [123]. An erect posture imposes a downwards gradient, shifting blood and tissue fluid, to the lower body intensifying the decrease in DLCO [122].

1.7.2 Metabolic response

Evident during resting conditions are rhythms in VO_2, V_E, and VCO_2 [125, 126]. A positive correlation exists between VO_2 and VCO_2 [125]. At rest, VO_2 and V_E coincide in phase, where their values are greatest at 1800 hours and are at their lowest at approximately 0400 to 0600 hours [125, 127]. Meanwhile, in healthy subjects no change in respiratory exchange ratio (RER), the ratio of VCO_2/VO_2, has been seen at rest, suggesting that substrate utilization does not vary throughout the day [112, 126].

Under increasing exercise intensities, these rhythms seem to persist with light, moderate and peak exercise intensities [105, 106, 126]. Most notably, the rhythm observed in V_E is amplified at light to moderate intensities as airway resistance increases the resistance to breathing [106]. However, at maximum capacity, rhythms for VO_2, VCO_2 and V_E have been shown to be less identifiable [126]. Interestingly, the V_T, which determines the point where VCO_2 or V_E begins to increase disproportionately from VO_2, has not been shown to vary irrespective of time of day [125, 126, 128].

A distinction between peak and maximal capacities needs to be made. During exercise, maximum is defined as the point where volitional fatigue is achieved [53]. In a COPD patient population, there is no universally accepted marker for the attainment of maximal capacity, as leg dyspnea and shortness of breath are important limiting factors [42]. The

gold standard for determining VO_2max has typically been if a plateau in VO_2 had been achieved [42]. In a COPD patient population, a clear plateau may not be achieved before symptoms limit exercise capacity [42]. Therefore, a maximal test may be difficult to attain. Yet literature seems to suggest that VO_2max remains stable and is independent of time of day [106, 125]. Debate exists as to whether VO_2max varies with time of day and whether a true VO_2max is attained through exercise testing; if not, it can lead to erroneous conclusions [129-131].

1.7.3 Cardiorespiratory response

Within the cardiorespiratory response, the research on HR rhythms variability is unclear [105]. Some studies have suggested that heart rate did not vary depending on time of day [132, 133]. In contrast, several others have shown that HR demonstrates a time of day rhythm, which is evident under constant routine, at rest, and during exercise (at light to moderate and maximal exercise intensities) [106, 108]. These later investigations have documented a peak in HR between 1400 and 1500 hours [105, 126]. Within a cardiac population, a significant increase in HR has been perceived in the afternoon, when individuals are on medications such as beta-blockers [134].

With BP, external influences can muddy the possible circadian rhythms [105]. BP may be influenced by behavioral and environmental factors, however under a constant routine protocol in healthy individuals, no significant circadian variations were detected [108]. In individuals with coronary artery disease, BP was shown to peak both in the early morning and in the evening [135]. Therefore, further research is required in chronic disease states.

1.7.4 Confounding factors

1.7.4.1 Sleep and alertness

Circadian rhythm controls sleep timing and wakefulness, consequently sleep disorders have been linked to perturbations in the circadian rhythm [136]. The sleep-wake cycle affects circadian rhythmicity in that sleep lost affects cognitive function more so than gross motor actions [106]. Gross motor tasks and lung function have been shown to be more resistant to the effects of sleep deprivations in healthy individuals [106]. A single night of recovery is typically enough to reverse the effects of sleep deprivation [106, 109]. However, patients with pulmonary disease are more vulnerable to sleep loss for a number of reasons, including symptom presentation throughout the night, insomnia and esophageal reflux; side effects of certain respiratory medications [137, 138]. A measure of the quantity and quality of sleep should preferentially be conducted, as decreased alertness may affect performance under clinical exercise testing conditions [139]. However, short bouts of exercise (e.g. a warm up) may help increase arousal level, counteracting detrimental effects, for an unspecified period of time [105, 106].

1.7.4.2 Clock time and circadian time

Humans are entrained by a 24 hour clock, where they habitually sleep during the night and are active during the day [106]. A normal physiological range is between 24 and 24.3 hours [140]. It should be noted that clock time is not always the same as circadian (biological) time [105, 141]. Biological rhythms are adaptive to change [142]. Changes to routine, such as when conducting shift work (e.g. night shift) or when there is a shift in phase (e.g. after travelling through different time zones), can affect performance [106]. Additionally, chronotype – i.e. whether an individual is characterized as a morning or evening type – can shift circadian phases. Morning types have been shown to demonstrate an advanced phase of about two hours on average, going to sleep earlier and

waking up earlier [128]. This can have implications on performance, where morning types may be more alert than their evening-type counterparts for morning evaluations and vice versa for late afternoon evaluations. Diurnal variations in VO_2max in healthy individuals were found to be greater in the afternoon in evening types as compared to morning types, despite similar exercise duration seen in both groups [128].

1.7.4.3 Environmental conditions

Environmental conditions may affect diurnal rhythm in that morning types are exposed to greater amounts of light than an evening type of individual [106, 143]. Greater light exposure may consequently entrain an earlier phase type [106]. Older individuals have been observed to demonstrate an earlier phase shift and a positive correlation has been found between age and morningness [144]. Older individuals have been shown to yield weaker cues in COPD; where the disease follows a progressive path and the patient population is often comprised of older individuals [145]. However, in a more physically active population, greater rhythm amplitudes were demonstrated [146]. The amplitude of a rhythm may be an indicator of the strength and stability of the rhythm [146, 147].

Chapter 2

Rationale

COPD is associated with frequent changes in clinical status, as a result of the progressive nature of the disease. In addition, circadian/diurnal variations in many physiological variables have been established in this patient population. Indeed, indices of lung function as well as symptom perception have been shown to vary throughout the day, generally as a consequence of changes in airway resistance. The functional implications of such circadian variations have seldom been investigated. Given that even small increases in airway obstruction can significantly burden those with pulmonary disease, circadian variations in physiological parameters are likely to have important clinical repercussions in COPD patients.

CPET is a commonly used tool which allows the evaluation of the global and integrative response of the major systems. It provides exclusive information above what is found from resting measures. Current exercise testing guidelines recommend that repeated exercise testing be undertaken at the same time of day to avoid the potential confounding effect of circadian variations in exercise measures. Yet, in COPD patients, the impact of time of day on exercise performance remains to be examined. The general aim of the present study was to investigate the impact of time of day on the acute response to exercise in individuals with COPD, to assess the implications of daily biological variations in this patient population and to clarify current exercise testing guidelines.

Chapter 3

Research Objectives and Hypothesis

Primary Research Objective:

1) To evaluate, in individuals with COPD, the effect of time of day on peak exercise capacity.

Secondary Research Objectives:

1) To evaluate the effect of time of day on resting pulmonary function (FEV_1, FVC).

2) To evaluate the effect of time of day on resting and exercising physiological response (VO_2, VCO_2, V_E, HR, etc.).

3) To evaluate the effect of time of day on resting and exercising symptoms (dyspnea and leg fatigue).

Research Hypotheses

It was hypothesized that significant diurnal variations would be observed in a COPD population both at rest and during exercise. More specifically, our hypotheses were:

1) Peak exercise capacity will be lowest in the morning and highest in the afternoon.

2) Pulmonary function will be lowest in the morning and highest at noon.

3) Metabolic responses (VO_2, VCO_2, V_E) will be highest in the afternoon. HR will be greatest in the afternoon, while BP will be greatest in the morning.

4) The perception of symptoms will be greatest in the morning.

Chapter 4

Diurnal Variations in the Acute Response to Exercise in Chronic Obstructive Pulmonary Disease

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Abstract

Purpose: Indices of lung function and symptoms have been shown to vary throughout the day. In COPD, these variations may have clinical repercussions. The general aim of this study was to investigate the impact of time of day on the acute response to exercise in individuals with COPD. **Methods:** Subjects followed a counterbalanced randomized design, performing three symptom-limited incremental cycling tests -each preceded by a pulmonary function test- at 08:00, 12:00, and 16:00. COPD medications were withdrawn 6-24 hours prior to each test. Physiological response was measured breath by breath at rest and during exercise. Changes in outcomes were assessed with repeated-measures ANOVAs using the General Linear Model. Friedman tests were performed for non-parametric data. **Results:** Fourteen subjects (9 men, 5 women) aged 71 ± 7 years with moderate airflow obstruction (FEV_1: 58 ± 13% predicted) completed all evaluations. No overall time effect was found for peak exercise capacity ($p= 0.22$) or pulmonary function. However, changes at or beyond the suggested minimal clinically important difference were observed in nine of the 14 subjects for both variables. Resting RER was higher in the morning than at other time points ($p = 0.001$). Trends for time effects were found for mean VT ($p = 0.096$) and HR ($p = 0.08$). VT tended to decrease throughout the day, while HR tended to increase from morning to afternoon. **Conclusion:** These results suggest that diurnal variations in the acute response to exercise may be heterogeneous among COPD patients and may follow more than one pattern.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive and partially irreversible disease characterized by chronic airflow limitation [1]. It is the fourth leading cause of death in the world and in Canada [1]. As a result of the progressive nature of the disease, COPD is associated with frequent changes in clinical status over a period of time. Yet indices of lung function and symptom perception have also been shown to vary over the period of a single day.

Chronobiology is the study of time-dependent changes in physiological variables [105]. Variations occurring over a 24-hour period can be classified as either circadian or diurnal [105, 106, 107]. Circadian rhythms are the result of the endogenous oscillator, which is described as being the causal factor in biological rhythms [108]. The endogenous rhythms are the body's internal biological clock, which is a self-sustaining rhythm thought to originate from the suprachiasmatic nuclei (SCN) in the anterior hypothalamus [105, 108-110]. Biological rhythms can be additionally influenced by external cues, creating 24-hour patterns which are known as diurnal variations [108]. The external cues are exogenous influences such as behavioral or environmental conditions [108, 109]. Factors which influence exogenous rhythms include activity, meals, posture as well as light, temperature and allergens [105, 108, 109].

In a more susceptible population such as COPD patients, given that even small increases in airway obstruction can pose a significant burden, the variations in physiological parameters are likely to have important clinical repercussions [107, 114]. Spirometry can be used to objectively measure changes in pulmonary function, yet overall health status

has been shown to be more strongly correlated with exercise tolerance [42]. A greater awareness of the benefits of reliably predicting exercise performance and functional capacity, has lead to the routine use of CPET [42]. CPET measures the global and integrative response of the major systems and provides exclusive information above what is found from resting measures [53]. In healthy populations, physiological rhythms detected at rest have been shown to be either obliterated, attenuated, maintained or amplified under exercise conditions [106]. In COPD patients, the potential impact of time of day on exercise tolerance has yet to be examined.

The general aim of the proposed study was to determine the impact of time of day on the acute response to exercise in individuals with COPD. More specifically, the primary objective was to evaluate, in individuals with COPD, the effect of time of day on peak exercise capacity. Secondary objectives were to evaluate the effect of time of day on i) resting pulmonary function, ii) resting and exercising physiological response (VO_2, VCO_2, V_E, HR, BP), and iii) resting and exercising symptoms (dyspnea and leg fatigue).

Methods

Study Design and Procedure

The study followed a counterbalanced research design, where each participant acted as his/her own control. Candidates who met the eligibility criteria agreed to take part in the study, and obtained medical clearance for the exercise testing protocol were asked to come to the research facility for a total of four visits (Figure 4).

The first visit consisted of baseline measurements, explanation of the patient folder, and familiarization to the testing procedure. Baseline measurements included demographics and clinical information (age, sex, height, weight and body mass index (weight/height^2)), chronotype assessment and pulmonary function testing. Participants were then instructed on how to complete the patient folder, which included questions about sleep quality and quantity, dietary and pharmacological intake, and physical activity, to be filled several times daily throughout the study period (Appendix A). Familiarization to the testing procedure consisted of allowing subjects to practice the symptom limited cycle ergometer test. More specifically, after receiving the same instructions as prior to a real test and after having been introduced to the testing equipment (facemask, electrodes, BP monitor, oxymeter, Borg scale, etc.), participants embarked on the cycle ergometer and pedaled at the prescribed rate until they felt comfortable with the procedure.

Subjects then entered the counterbalanced design (visits 2-4) where they each completed three symptom-limited incremental cycling exercise tests, each conducted on a different day, at a different time of day (08:00, 12:00, and 16:00, ± 15 minutes), and each preceded by a pulmonary function test. The selected testing times were chosen to cover the range of hours when exercise tests are typically conducted in clinical practice. In order to limit the potential confounding effect of learning on test performance, the sequence of testing times was determined through block randomization; however, participant availability and accessibility to medical supervision were also considered. Study visits were separated by at least 36 hours, but no more than 1 week.

In order to limit the potential confounding effect of COPD medication on diurnal variations in exercise performance, subjects were asked to withhold the following medications before visits 2-4: short acting β2-agonists (6 hours), short-acting anticholinergic agents (6 hours), combination products of short-acting agents (6 hours), long acting β2-agonists (24 hours), inhaled corticosteroids (24 hours), and combination products of long-acting β2-agonists and inhaled corticosteroids (24 hours). Subjects taking a long-acting anticholinergic agent (tiotropium) were switched to a short-acting anticholinergic agent (ipratropium bromide) 40 μg QID by a collaborating respirologist 2 weeks prior to the beginning of the trial and for the duration of the trial (approximately 1 week). These subjects were asked to withhold their short-acting agent 6 hours prior to visits 2-4, as others. They were returned to their original medication regimen upon completion of their last study visit.

The research protocol was approved by the institutional ethics committee and a signed informed consent was obtained from each subject.

Subjects

Subjects were recruited from the outpatient COPD clinic at Hôpital du Sacré-Coeur de Montréal as well as from a pool of patients who had completed previous studies in our laboratory and who had consented to be contacted for future investigations. Eligibility was ascertained according to the following inclusion criteria: 1) clinically stable COPD; 2) age 40 years or older; 3) smoking history of at least 10 American pack-years (20 cigarettes per pack); 4) post-bronchodilation FEV_1 less than 80% of the predicted normal value; 5) FEV_1 to FVC ratio less than 0.7; and 6) previous experience of exercise testing.

Participants were deemed ineligible for the study if the following exclusion criteria were present: 1) exacerbation of respiratory symptoms in the past 4 weeks (change in dyspnea or volume/colour of sputum, need for antibiotic treatment, or need for hospitalization); 2) any contraindication to exercise testing based on guidelines from the American Thoracic Society [42]; 3) any active condition other than COPD that can influence exercise tolerance (unstable coronary heart disease, left congestive heart failure, neoplasia, severe claudication, severe arthritis, etc.); 4) need for O_2 therapy; and 5) prescribed Theophylline. These eligibility criteria were mostly meant to differentiate COPD from other respiratory diseases and to ensure clinical stability and patient safety.

Assessments

Chronotype Questionnaire

At the initial visit, subjects completed the morning-evening questionnaire (MEQ) [148]. MEQ is a 19-item scale which has been established as a valid measure and classifies subjects as either morning, intermediate or evening types [148, 149]. Scores on the MEQ vary from 16 to 86; high scores (59-86) identify morning-type individuals, low scores (16-41) correspond to evening-types and scores from 42-58 are intermediate or neither types. Morning types, as compared to evening types, loosely follow an advanced timing of the endogenous circadian clock.

Sleep Measures

The Pittsburgh Sleep Diary is used to evaluate the subjects' sleep quantity and quality [150]. Two questionnaires were given: a morning questionnaire that assess the subjects' sleep the night prior to the day of the evaluation as well as their morning routine, and an

evening questionnaire based on the current events during the day leading up to sleep. This instrument has demonstrated to be both a valid and sensitive measure [150].
In addition, during the period of testing, patients were asked to respect the targeted 8 hours of sleep per night; an interval of 30 minutes was accepted for both bedtime and wake time; therefore predicted sleep duration could vary between 7 and 9 hours.

Dietary Intake

Subjects completed a food journal during the week of their evaluations. An explanation on how to complete the dietary journal was given at the initial visit. The subjects were asked to log the date and time that meals were ingested.

Physical Activity Levels

Subjects completed a physical activity journal during the week of their evaluations. An explanation on how to complete the journal was given at the initial visit. The subjects were asked if they performed any physical activity during the course of the day and, if so, to indicate the time and type of activity which was performed.

Pulmonary Function Testing

Spirometry was performed at baseline and before each evaluation according to recommended techniques [41]. Values were compared to predicted normal values from the European Community for Coal and Steel/European Respiratory Society [151].

Exercise Testing

Exercise testing consisted of symptom-limited incremental cycling exercise tests. This protocol was selected as it is frequently used in respirology [152]. Subjects were seated

on an electromagnetically braked cycle ergometer (Ergoselect 200P, Ergoline, Germany) and connected to a cardio-respiratory circuit through a mouthpiece. The cardio-respiratory circuit consisted of a digital volume sensor (TripleV), O_2 and CO_2 analyzers, and 12 –lead ECG (Jaeger Oxycon Pro, CareFusion, Germany). After five minutes of rest and three minutes of unloaded pedalling, the workload was increased in a stepwise manner every minute, up to the individual's maximal capacity. The workload was increased by 5-10 watt increments (5-watt increments for subjects with a predicted work rate < 50 watts; 10-watt increments for those with a predicted peak work rate > 50 watts). Gas exchange parameters (V_E, O_2 uptake, CO_2 excretion), pulse oximetry (SpO_2), and HR were measured at rest and during exercise on a breath-by-breath basis. Inspiratory capacities were conducted at rest and every other minute during the exercise test, in accordance to the American Thoracic Society/European Respiratory Society guidelines, to evaluate the degree of lung hyperinflation [41, 43]. Standardized instructions were given prior to each test and any encouragement given during the test was standardised, every 30 seconds. Peak exercise capacity was defined as the highest work rate maintained at a pedalling speed of at least 50 revolutions per minute for a minimum of 30 seconds. These tests were completed under medical supervision.

Symptoms

The common factors that limit exercise in COPD patients are dyspnea and leg fatigue [60]. These factors were measured at rest and every other minute during the exercise tests using the modified 10- point Borg scale [153].

Statistical Analyses

To determine the overall effect of time of day (independent variable with three levels: 8:00, 12:00, and 16:00) on peak exercise capacity and resting pulmonary function (dependent variables), one way repeated-measures analyses of variance (ANOVAs) were conducted using the General Linear Model. If a significant main effect was obtained, pairwise comparisons with Bonferroni corrections were conducted to identify between which time points the differences occurred. Friedman non-parametric tests were performed to analyze the overall effect of time of day on any non-parametric data.

To further investigate the primary outcome of peak exercise capacity and potentially generate new hypotheses, a series of interaction analyses were conducted using the General Linear Model. These exploratory analyses examined the interactive effect of time of day (independent variable 1) with a number of descriptive measures and potential confounders (independent variable 2) on peak exercise capacity (dependent variable). The descriptive measures examined, which were believed to be potential covariates in the relationship between time of day and exercise performance, were chronotype (morning vs. intermediate), age (under 70 vs. 70 and over), sex (male vs. female), and BMI (normal weight vs. overweight to obese). The potential confounders examined where last dietary intake (below the median split; at or above the median split), and sleep quantity (less than 8 hours vs. 8 hours or more). Post hoc Student Newman-Keuls (SNK) were performed for any significant findings.

Finally, changes in physiological measures and symptoms were examined between the two states (resting and peak) and at the three levels of testing times (08:00, 12:00 and

16:00) with a 2x3 repeated-measures ANOVA. If a significant interaction between state and testing time was detected, simple main effect tests were conducted to identify the state (resting or peak) for which differences between testing times were significant. If a significant simple main effect was obtained, pairwise comparisons with Bonferroni corrections were conducted to identify between which testing times the differences occurred. For these analyses, any non-parametric data was transformed using the square root function to parametric data and was analyzed. Analyses were conducted at the 5% level of significance and performed with SPSS version 18.0 (Chicago, IL).

Results

Subjects

A total of 81 patients were contacted, 76 of which were eligible to take part in the study, and 5 of which were ineligible due to reasons such as being prescribed theophylline (n =2), being prescribed O_2 (n = 1), working the night shift (n =1) and not meeting the pulmonary function criteria (n = 1). Of the 76 eligible patients, 41 patients refused, the most predominant reasons being lack of interest (n = 8), health reasons (n = 8), transportation limitations (n = 6), schedule conflict (n = 6), not wanting to change their medications (n= 3) or various other reasons (n = 10). In total, 14 patients accepted to participate and completed all measurements. The baseline characteristics of the study group are presented in Table 2. The sample was composed of a majority of older, slightly overweight, morning-type, males, with moderate to severe airflow obstruction based on the GOLD classification [1].

Effect of Time of Day on Peak Exercise Capacity

Individual results and group means for peak exercise capacity are shown in Figure 5. No significant overall time effect for peak exercise capacity was found ($p = 0.22$, $eta^2 = 0.11$). Exploratory analyses looking at potential interactive effects of time of day and a number of descriptive measures on peak exercise capacity detected no significant interactions between testing time and chronotype ($p = 0.851$), age ($p = 0.923$), sex ($p = 0.784$), and BMI ($p = 0.61$) (Figure 6).

Time spent in bed was found to be significantly less the night prior to the morning visit (8:00) as compared to the other two visits ($p = 0.01$, $eta^2 = 0.41$), but the interaction between time of day and sleep quantity on peak exercise capacity was not statistically significant ($p = 0.368$). Likewise, the time since last dietary intake was found to be shorter for the morning visit than for the noon and afternoon visits ($p = 0.036$). However, no significant interaction effect was found between testing time and time since last dietary intake on peak exercise capacity ($p = 0.937$).

Effect of Time of Day on Pulmonary Function

The individual data and group means for FEV_1, FVC, and FEV_1/FVC values obtained at rest prior to each exercise tests are shown in Figure 7. No significant overall time effect was detected for FEV_1 ($p = 0.56$, $eta^2 = 0.04$), FVC ($p = 0.79$, $eta^2 = 0.18$), or FEV_1 /FVC ($p = 0.87$, $eta^2 = 0.01$). Likewise, no significant overall effect of time was found for IC measures obtained at rest ($p = 0.32$, $eta^2 = 0.08$) and during exercise ($p = 0.91$, $eta^2 = 0.007$), as shown in Figure 8.

Effect of Time of Day on Resting and Exercising Physiological Response

Group means for resting and peak VO_2, VCO_2, V_E, RR, V_T, SpO_2, HR, and BP, are shown in Table 3. A significant effect of testing state (rest vs. peak) was detected for all variables but diastolic BP. More specifically, significant increases from rest to peak were seen in VO_2, VCO_2, RER, V_E, V_T, RR, HR, and systolic BP ($p < 0.001$ for all). In return, a significant decrease from rest to peak was found for SpO_2 ($p < 0.001$).

A significant interaction between testing state and time of day was detected for RER ($p = 0.002$). Simple main effect tests further revealed that the effect of time of day on RER was significant at rest only ($p = 0.001$). Results from pairwise comparisons suggested that resting RER was significantly higher in the morning than at the other two time points ($p < 0.05$ after Bonferroni correction).

Furthermore, a trend was seen for the overall effect of testing time on V_T ($p = 0.096$). More specifically, V_T tended to decrease throughout the day. Post-hoc comparisons did not reveal any significant differences between pairs of testing times, but a trend was found between the earliest and latest tests. Finally, a trend was found for the effect of testing time on HR ($p = 0.082$). Pairwise comparisons did not reveal any significant difference between the three times of day, but HR tended to increase throughout the day. No other significant effect was found.

Effect of Time of Day on Resting and Exercising Symptom Perception

A significant effect of testing state was detected for symptoms, as subjects' ratings of dyspnea and leg fatigue significantly increased from rest to peak ($p < 0.001$ for both). No

time effect or state by time interaction were found for either dyspnea or leg fatigue. The group means are shown in Table 4.

Discussion

Effect of Time of Day on Peak Exercise Capacity

The primary objective of the present study was to evaluate the effect of time of day on peak exercise capacity in individuals with COPD. It was hypothesized that significant diurnal variations in exercise capacity would occur and, more precisely, that a greater peak workrate would be achieved in the afternoon than in the morning. However, our findings do not support this hypothesis, as no time effect was found for peak exercise capacity in a group of individuals with moderate to severe airflow obstruction.

Previous research has suggested that aerobic capacity follows the circadian rhythm of body temperature, peaking in the afternoon [105, 110, 132, 133]. However, physiological rhythms detected during exercise have also been shown to vary depending on the intensity of the exercise, being either amplified or maintained, abolished or weakened under different intensities [106, 132, 133]. Various exercise testing protocols may therefore have different capabilities to detect circadian rhythms in exercise tolerance depending on their intensity level. In the present study, the symptom-limited incremental cycle ergometer protocol was chosen because it is the most commonly used protocol in clinical practice in respirology [42]. Yet, there is no current consensus as to which protocol is optimal to assess exercise tolerance in COPD patients. Maximal or peak tests have been shown to lack sensitivity to changes in exercise tolerance after various interventions, such as pulmonary rehabilitation or bronchodilation [98, 154, 155]. These

protocols may thus also lack sensitivity to circadian variations in exercise tolerance. Constant-load protocols, which submit patients to a fixed workrate, have gained popularity in latest years because of their high responsiveness to treatment and because they are believed to more closely represent the intensity of daily activities [42, 43, 97, 155, 156]. These protocols could therefore also be more prone to detect circadian variations in exercise tolerance than maximal tests. However, constant-load or endurance exercise tests are typically conducted at a certain percentage of the highest workrate achieved on a maximal incremental test [42]. As such, circadian variations in the response to peak exercise had to be investigated first before studies examining variations in the response to constant-load testing could be conducted.

In this study, changes in peak exercise capacity across the different testing times were heterogeneous within the study sample. Indeed, although no overall time effect was detected for exercise capacity, a number of patterns occurred, as shown by the individual data across the three testing times (Figure 5). It was hypothesized that the different patterns observed were perhaps influenced by other factors [106]. Therefore, analyses were performed to examine whether chronotype, age, sex, BMI, sleep quantity the night before or time since last dietary intake interacted with time of day to affect exercise capacity. Sleep quantity the night before and time since last dietary intake where the only measures which a significant time effect was detected. Both were found to be significantly less for the morning visit than for the other two time points. However, neither variable significantly interacted with time of day to affect peak exercise capacity.

A study by Bougard et al. [157] specifically investigated the effects of waking time and prior dietary intake on the acute response to an exercise test conducted in the early morning. A later waking time was associated with a significantly increased exercise capacity, VO_2, and VCO_2 [157]. However, the subjects in Bougard's study only got 5-6 hours of sleep the night prior to testing. Having extra time to sleep in the morning may have a greater influence on subsequent exercise response in such individuals than in those who get a good night sleep [157]. In addition, their subjects were young healthy males of either intermediate or evening chronotype. In contrast, subjects from the present study reported an average of 7-8 hours of sleep the night prior to testing and were older, afflicted with COPD, and of morning or intermediate chronotype. This may explain why sleep quantity the night before testing did not play a significant role on exercise performance in the current investigation. Bougard and colleagues [157] also reported a significant effect of dietary intake on mean VCO_2 and RER values, which were both increased after food intake. However, dietary intake did not affect peak exercise capacity, which is in line with the results from the present study [157].

Finally, peak exercise capacity may not have demonstrated statistically significant changes across the three testing times in the current study, but consideration of the clinical significance of our findings could prove interesting. The minimal clinically important difference (MCID) refers to the smallest clinical difference in a measure that can either be perceived by the patient or that is believed to be clinically pertinent by expert opinion [158]. A study by Sutherland and Make [159] has suggested the MCID for maximum exercise capacity in COPD to be within a range of 0.9 to 10.5 watts in patients

with severe COPD. This estimate was obtained using both expert opinion and distribution-based methods with data from the National Emphysema Treatment Trial [159]. In the current study, nine out of the 14 subjects showed a ≥ 10 watts change in peak exercise capacity between the different testing times. These numbers indicate that although no overall time effect was detected for peak exercise capacity, a clinically significant change may have occurred in a majority of our subjects. Given this observation and the fact that changes in exercise capacity across the different testing times were heterogeneous within the study sample, it is possible that more complex analyses will need to be conducted to determine whether different patterns of response exist in this patient population.

Effect of Time of Day on Pulmonary Function

The secondary objective of this study was to investigate the effect of time of day on pulmonary function in COPD. We hypothesized that pulmonary function would be lowest in the morning and highest at noon. This hypothesis was not supported by our results, as no overall time effect was found for FEV_1, FVC, FEV_1/FVC, or IC.

Pulmonary function is widely acknowledged to have a circadian rhythm in both healthy and COPD populations, yet the precise pattern of change remains to be clarified [107, 113, 116, 160]. In COPD specifically, four different patterns of circadian variations in FEV_1 have been observed: a morning reduction, an evening reduction, a double dip pattern where both a morning and evening reduction is observed, or no change in pattern [107, 119, 160]. Certain COPD medications, such as tiotropium –a long-acting anticholinergic bronchodilator- have also been shown to shift the timing of FEV_1

variation [160]. This finding may explain, at least partly, the different patterns reported in the literature and highlights the importance of controlling for respiratory medications. In the present study, although no overall time effect was found for measures of pulmonary function, individual data suggest that different patterns of change may have occurred within our study sample, especially for FVC and FEV_1/FVC (Figure 7b and 7c). Given that subjects were weaned off their COPD medications prior to each exercise test, these patterns would likely not be the result of a confounding medication effect. Pattern analyses could potentially provide more information regarding the nature of the relationship between time of day and pulmonary function.

Additionally, timing of the tests may play an important role as the mean daily circadian variation in FEV_1 has been shown to change by as much as 286 ml when comparing maximum and minimum values over a 24-hour period [160]. In order to optimally detect circadian changes, six equidistant times must be measured [161]. Therefore, the testing times chosen may influence the magnitude of change. In the present study, the three testing times were selected to cover the range of when exercise tests are typically conducted in clinical practice and not specifically for optimal detection of circadian changes. This can be considered as a study limitation; however, the present investigation was designed to answer a practical clinical question.

Using the same approach as for peak exercise capacity, the clinical significance of changes seen in pulmonary function was also considered. Although MCIDs for measurements of spirometry have yet to be confirmed, some experts have suggested the value at 100ml for FEV_1 [162]. The reproducibility criteria recommended by current

guidelines for repeated FEV_1 measures taken within a single session is 150 ml [41]. Although there is no consensus as to the acceptable range for FEV_1 measurements obtained on different occasions, Herpel et al. [163] have estimated the reproducibility between sessions to range from 150 ml to 225 ml [163]. Interestingly, ATS guidelines state that successful bronchodilation typically translates into a 200 ml improvement in FEV_1 [164]. In the present study, nine out 14 patients showed a variability ≥ 100 ml in FEV_1 between visits, while three subjects showed changes ≥ 150 ml. Furthermore, the variability for FVC values was shown to be greater than what was demonstrated for FEV_1. The reproducibility criteria recommended by current guidelines for repeated FVC measures taken within a single session is 150 ml [41]. Herpel et al. [163] suggests that a value greater than 325 ml would be reasonable to detect change in FVC. In the present study, twelve out 14 subjects showed a variability ≥ 150 ml in FVC between visits, while ten out of 14 subjects showed changes ≥ 325 ml.

Forced expiratory volumes are essential for COPD diagnosis, for disease classification and prognosis [162]. However, clinical trials have highlighted the fact that FEV_1 and FVC may not be the best measures to assess changes in patients' condition, showing weak associations with exertional dyspnea, quality of life or endurance [155, 165]. IC, which is a measure of hyperinflation, has been proposed as the link between lung function, exercise capacity and symptoms of dyspnea [155, 166]. Circadian rhythms have been documented for IC in COPD; more specifically, IC is reportedly lowest in the morning [40, 167]. Measures of IC were taken during the course of this study both at rest and at peak, yet no overall time effect was found. However, individual data seem to

reveal different patterns of change (Figure 8). Further analyses will be needed to support this observation.

Effect of Time of Day on Physiological Measures during Rest and Exercise

Circadian rhythms have been detected in certain metabolic variables, but how these rhythms are influenced under exercise and disease conditions has yet to be determined [168]. For the present study, it was hypothesized that metabolic response would be highest in the afternoon in COPD patients. This hypothesis was based on findings on healthy individuals, in whom resting VO_2, VCO_2 and V_E have been shown to peak in the afternoon following peak core body temperature [126]. Our results, however, did not support this hypothesis, as no significant variations in resting or peak VO_2, VCO_2, and V_E were found across the three testing times. Other researchers have come to similar conclusions: discrepancies in methodology, time of day, and study population could potentially account for these differences [112, 169].

Despite the fact that no changes were observed in resting VO_2 and VCO_2, resting RER - which corresponds to the ratio of VCO_2 to VO_2 – was found to be significantly higher in the morning than at the other two time points. This may be due to the influence of last dietary intake, which was found to be significantly closer to testing time for the morning than for the afternoon visits. The effect of food intake versus a fasted state on RER has been studied, and the fasting state was shown to yield a significantly lower RER [170]. Therefore, to limit variability and control for this potential confounding factor, a standardized intake time could have been set apriori; however, for the morning test, this would likely have meant earlier wake times, which could have introduced another bias. It

should also be noted that as the subjects in this study had a mean age of 71 years, they may have been prescribed other non-respiratory medications requiring food intake.

The variation seen in resting RER was not duplicated at peak. It is currently unknown whether or not variations in resting RER resulting from substrate utilization would persist under exercise conditions [171]. Results from the present study suggest that they may not persist.

In other measures, a trend was seen for the effect of testing time on V_T. Prior evidence has shown that, in expiratory flow-limited individuals, as the absolute value for V_T increases, EELV tends to increase as well, leading to hyperinflation of the lungs, as IRV and IC decreases [42, 172]. These changes would thus take place in a cascade effect, where hyperinflation would occur in response to an increase in V_T. In the present study, V_T tended to be higher in the morning than in the afternoon. According to the "cascade effect" described above, this should have led to more hyperinflation (i.e. smaller IC) in the morning than in the afternoon. The mean IC value was smaller for the morning visit than for the afternoon visit, but this time effect was not significant. Furthermore, there was no time by state interaction for V_T, suggesting that the response to exercise was similar across testing times.

Finally, a trend was observed for the effect of testing time on HR, which tended to increase throughout the day. In previous studies, diurnal variations in HR have been calculated to fluctuate between 2 and 6 beats per minute [126, 173]. In the current study, HR was 3.3 beats per minute greater in the afternoon as compared to the morning.

However, when comparing individual data, 10 out of the 14 subjects had changes in HR that were greater than or equal to 6 beats per minute across the different times of the day.

Effect of Time of Day on Symptom Perception

The final objective of the present investigation was to evaluate the impact of time of day on subjects' perception of dyspnea and leg fatigue at rest and during exercise. It was hypothesized that symptoms would be perceived to be greater in the morning. Our results indicate that symptoms did increase in response to exercise, as expected, but were not affected by testing time.

In COPD, subjects are often limited by leg fatigue and dyspnea prior to attaining a true physiological maximum. Perhaps conducting an endurance test, which could be more sensitive to change, would allow for greater variations to be detected [174]. The stimulus for perceived symptoms is based on the work achieved; it may be more feasible to increase endurance time than to reach a higher work rate on an incremental test [98, 154].

Effect Size

This study is the first of its kind to measure diurnal variations in peak exercise capacity in COPD subjects. As such, sample size calculation was based on peak exercise capacity variations reported in similar studies conducted in other populations. Furthermore, the study was not powered to detect changes in secondary objectives. The negative results obtained for overall time effects on exercise capacity and pulmonary function may suggest that the study was underpowered. Effect sizes observed in the present study will be useful for sample size calculations for future studies investigating diurnal variations in the acute response to exercise in individuals with COPD.

Conclusion

The general aim of the present study was to investigate the impact of time of day on the acute response to exercise in individuals with COPD. Although no overall time effect was found for peak exercise capacity, changes at or beyond the suggested minimal clinically important difference were observed in a majority of the subjects. Our results suggest that diurnal variations in the acute response to exercise may be heterogeneous among COPD patients and may follow more than one pattern. Further analyses will be needed to support this observation.

Given that exercise testing is routinely used in COPD to confirm diagnosis, determine prognosis, and evaluate response to treatment, the clinical implications of our findings are significant. Latest guidelines recommend that repeated exercise tests be conducted at the same time of day to avoid the potential confounding effect of testing time on measured outcomes. Results from the present study did not confirm the presence of such a time effect in COPD patients, but suggest that caution is warranted. Finally, given the limited research conducted to date in the field of chronobiology and COPD, further studies are needed to clarify the role of diurnal variations in resting and exercising outcomes.

Tables

Table 2 - Subject Characteristics*

Male/female, n/n	9/5
Age, yrs	71 ±7
Height, m	1.70 ± 0.08
Weight, kg	78.21 ± 14.77
BMI, kg/m^2	27±5
FEV_1 , L	1.48± 0.4
FEV_1 ,% pred.	58±13
FVC, L	2.83±0.64
FEV_1/FVC ,%	53±11
Chronotype (morning / intermediate), n/n	9/5

*Values in mean ± SD

BMI: Body mass index, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity

Table 3 – Changes in mean physiological response from rest to peak across three times of the day*

Physiological Measure	**8:00**	**12:00**	**16:00**
VO_2 rest (ml/min/kg)	3.6 ± 0.6	3.6 ± 1.2	3.4 ± 0.8
VO_2, peak (ml/min/kg)	13.7 ± 51.4	14.4 ± 79.9	14.1 ± 64
VCO_2 rest (ml/min)	250.2 ± 51.4	234.1 ± 79.9	224.3 ± 64
VCO_2, peak (ml/min)	1057.6 ± 281.7	1102.9 ± 275.8	1086.2 ± 289.5
RER rest	0.9 ± 0.1**	0.8 ± 0.1	0.8 ± 0.1
RER peak	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1
V_E rest (L)	11.8 ± 2.0	11.6 ± 2.7	11.3 ± 3.1
V_E peak, (L)	40.6 ± 8.8	41.8 ± 7.4	42.0 ± 8.9
RR rest, (L/min)	16.4 ± 5.3	18 ± 5.1	18.4 ± 3.2
RR peak, (L/min)	32.4 ± 5.8	32.2 ± 5.9	33.2 ± 4.8
VT rest, (L)	0.9 ± 0.4	0.8 ± 0.4	0.7 ± 0.3
VT peak, (L)	1.3 ± 0.2	1.3 ± 0.3	1.3 ± 0.3
SpO_2 rest, (%)	97 ± 1.1	97 ± 1.4	97 ± 1.3
SpO_2 rest, (%)	95 ±1.4	95 ± 1.6	95 ± 1.6
BP systolic rest, (mmHg)	114 ± 23.1	121 ± 14.7	121 ± 22
BP systolic peak, (mmHg)	176 ± 26.6	183 ± 27.1	173 ± 20.4
BP diastolic rest, (mmHg)	75 ± 7.2	74 ± 7.4	77 ± 10.6
BP diastolic peak, (mmHg)	80 ± 12.9	78 ± 9	81 ± 12.7

*Values are mean ± SD, ** Significantly different from other two time points, $p < 0.05$.
VO_2: oxygen consumption, VCO_2: carbon dioxide production, RER: respiratory exchange ratio, V_E: minute ventilation, RR: respiratory rate, VT: tidal volume, SpO_2: oxygen saturation, BP: blood pressure

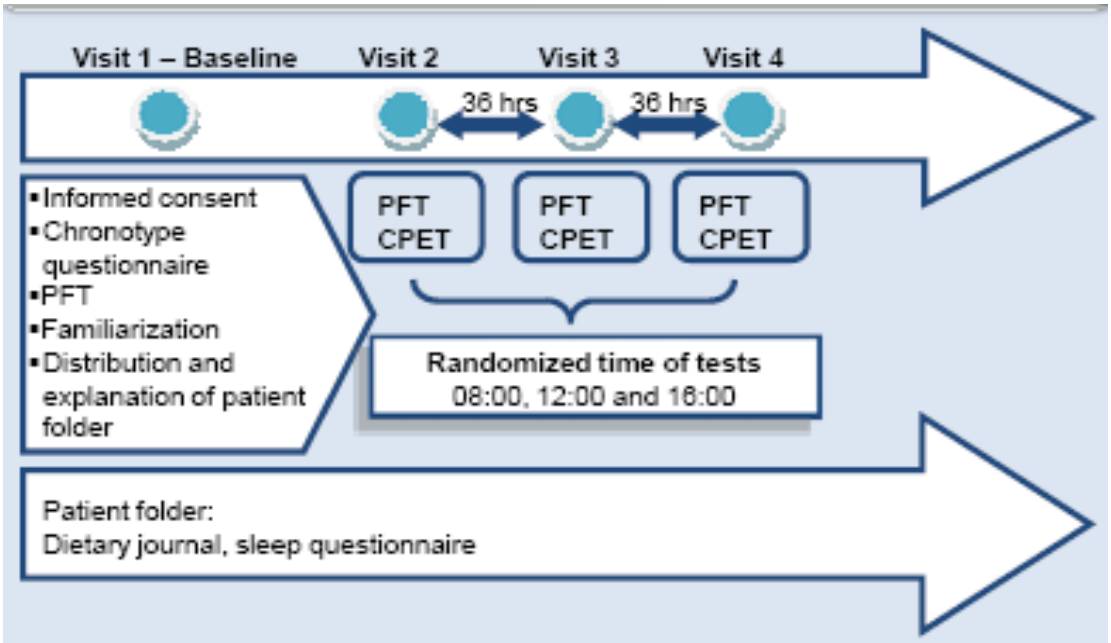
Table 4 – Symptoms of perceived dyspnea and leg fatigue as measured by the modified 10 point Borg scale across three times of day*

Symptoms	**8:00**	**12:00**	**16:00**
Dyspnea rest	0.36 ± 0.6	0.21 ± 0.4	0.14 ± 0.4
Dyspnea peak	6 ± 2.4	6 ± 2.3	6 ± 1.9
Leg fatigue rest	0.14 ± 0.4	0 ± 0	0.07 ± 0.3
Leg fatigue peak	6 ± 2.3	6 ± 1.9	6 ± 2.2

*Values are mean ± SD

Figures

Figure 4 – Study timeline



PFT:,pulmonary function test ,CPET: cardiopulmonary exercise test.

Figure 5 - Individual data and group means (horizontal bars) for peak exercise capacity across the three testing times.

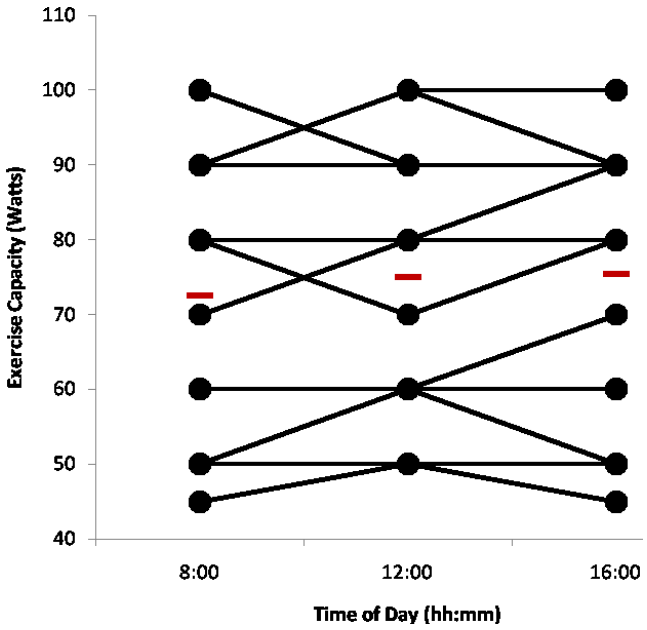


Figure 6 – Interactive effect of time of day and chronotype (Panel A), age (Panel B), sex (Panel C), and BMI (Panel D) on peak exercise capacity

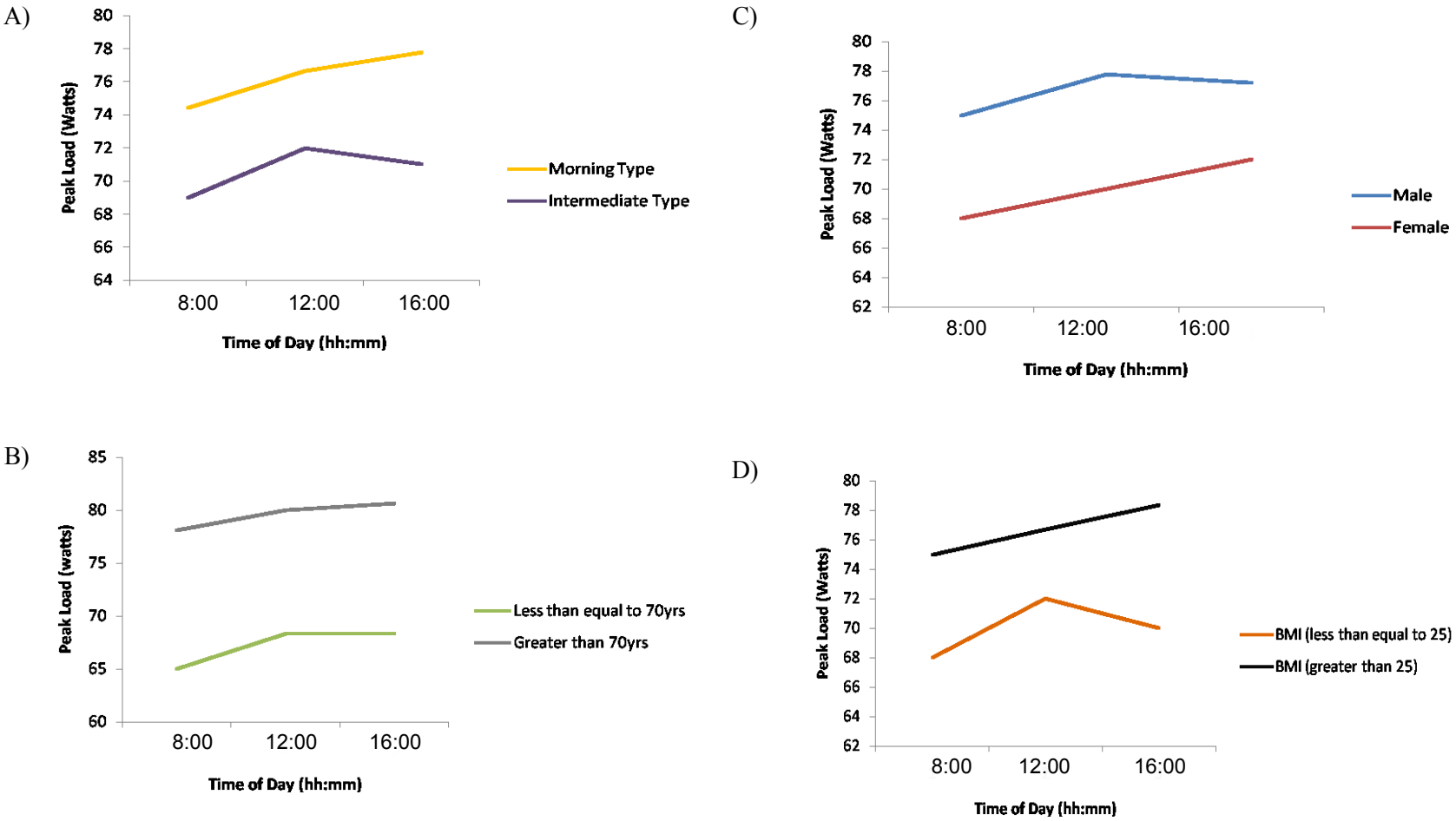
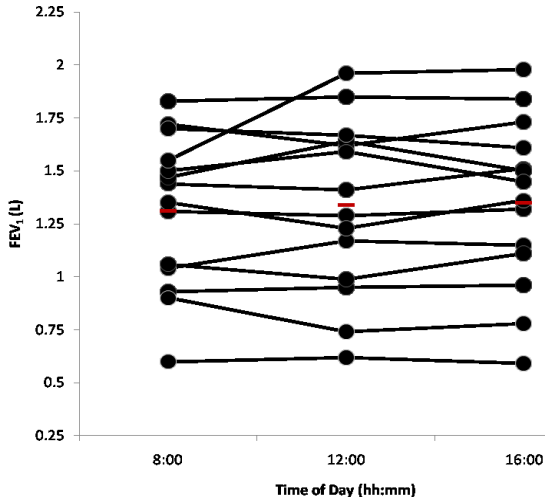
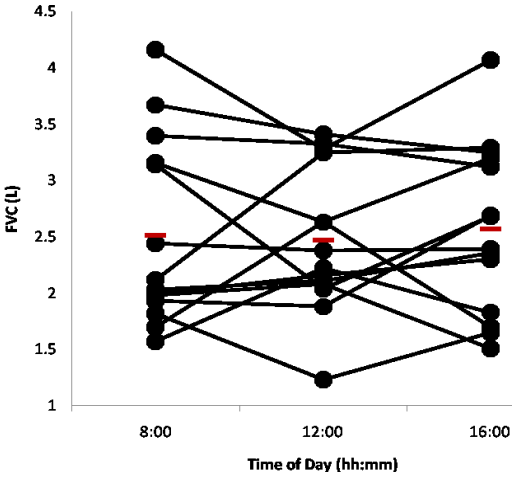


Figure 7 – Individual data and group means (horizontal bars) for FEV_1 (Panel A), FVC (Panel B), and FEV_1/FVC (Panel C) across the three different times of the day.

A)



B)



C)

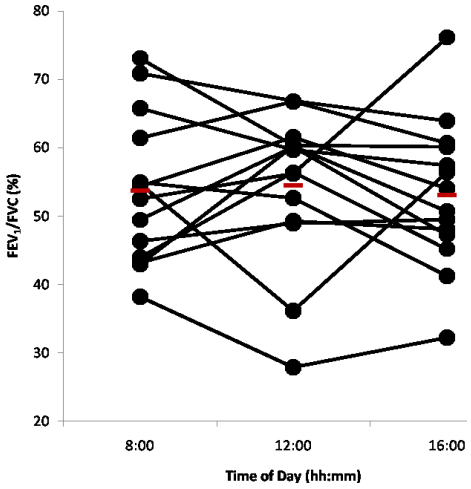
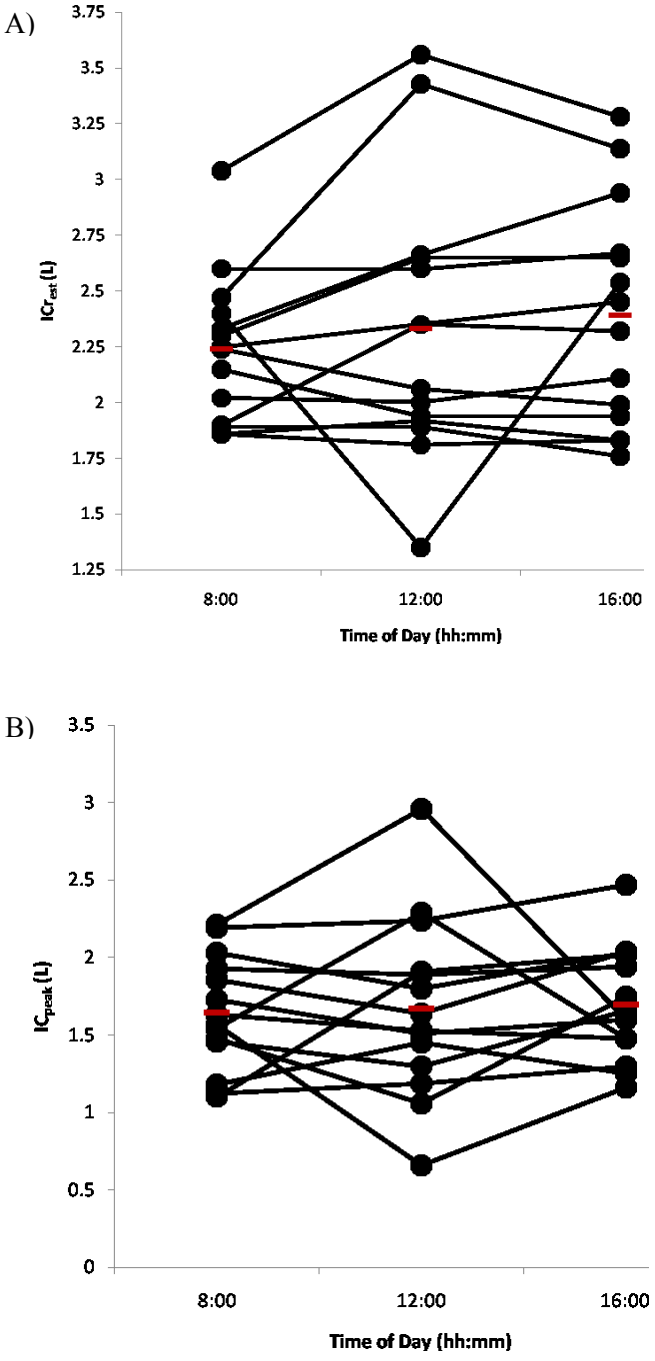


Figure 8 – Individual data and group means (horizontal bars) for inspiratory capacity measures obtained at rest (Panel A) and at peak exercise (Panel B) across the three different times of the day.



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Appendix A – Patient folder

Étude des variations diurnes de la tolérance à l'effort dans la maladie pulmonaire obstructive chronique

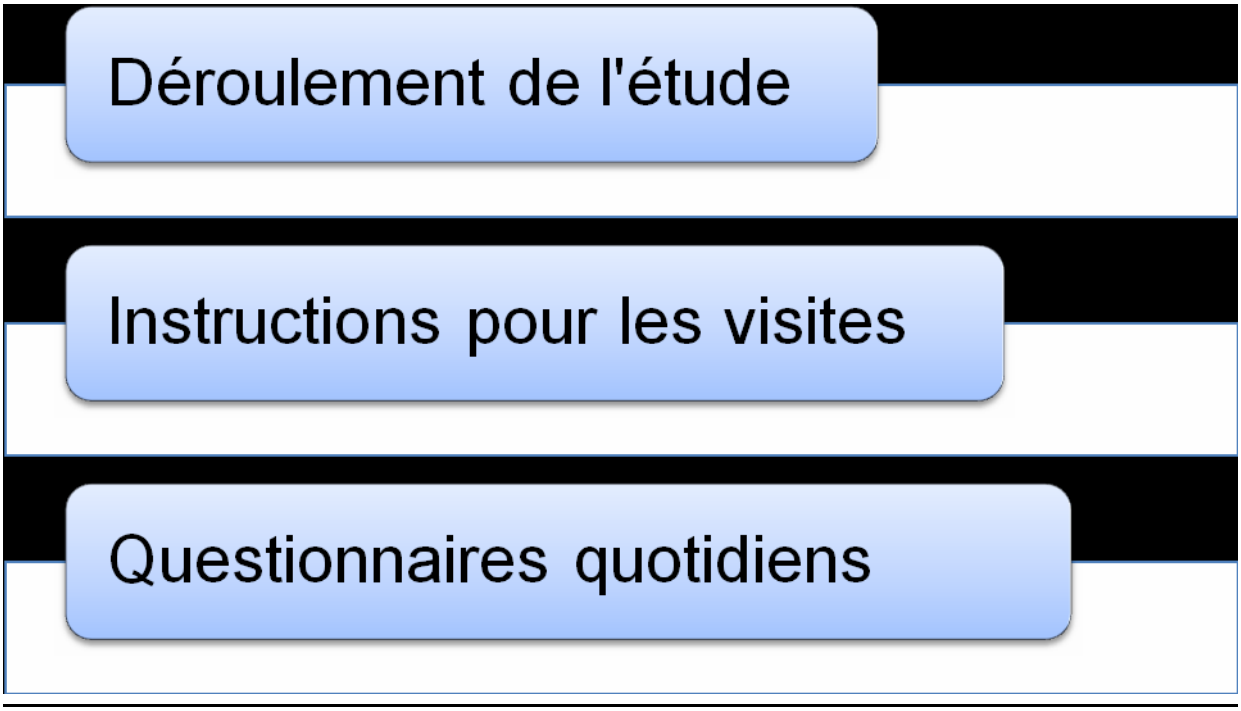
Carnet de suivi

Nom du participant: _____
Date départ: _____
Date de fin: _____

Personne de contact: **Emilie Chan-Thim**
Numéro: **514-338-2222 post 3944**

1er visite: _____ Hr: _____
2e visite: _____ Hr: _____
3e visite: _____ Hr: _____
4e visite: _____ Hr: _____

HSCM
HÔPITAL DU SACRÉ-COEUR
DE MONTRÉAL


Déroulement de l'étude
Instructions pour les visites
Questionnaires quotidiens

Déroulement de l'étude

	1ère visite	Carnet de suivi	2ème, 3ème, et 4ème visite
Durée des visites:	1h30		chaque visite = 2h
Procédures:	Formulaire de consentement Questionnaire de chronotype Questionnaire d'humeur Évaluation des fonctions pulmonaires Familiarisation avec les épreuves d'effort Remise et explication du carnet de suivi	Journal alimentaire Prise des médicaments Questionnaire du matin, midi et soir Questionnaire d'humeur Actigraphie	Évaluation des fonctions pulmonaires Épreuve maximale sur vélo
Compensation:	un versement de $50 à la fin de la 4 ème visite du protocole		

Instructions pour les visites

À suivre avant chaque épreuve d’effort

1- Évitez de manger un repas copieux dans les 3 heures précédant l’épreuve d’effort. Limitez-vous à une collation.

2- Évitez de boire de l’alcool ou tout breuvage avec caféine (café, thé ou boisson gazeuse) 3 heures avant l’épreuve d’effort.

3- Évitez de fumer 3 heures avant l’épreuve d’effort.

4- Évitez de porter du vernis à l’ongle

5- Soyez reposé(e), évitez de faire de l’exercice le jour de l’épreuve d’effort.

6- Portez des vêtements souples et confortables et des chaussures de sport.

7- Il est possible que vous soyez fatigué(e) après l’évaluation; au besoin, prévoyez que quelqu’un vienne vous chercher et vous raccompagne à la maison.

8- Buvez beaucoup (préférablement de l’eau) dans les 24 heures précédant l’évaluation pour vous assurer d’être bien hydraté(e).

9- Si vous êtes diabétique, apportez votre glucomètre et une collation.

10- Apportez votre carnet de suivi à chaque visite du protocole.

11- Apportez vos médicaments "de secours".

12- Suivre les consignes pour le sevrage de vos médicaments.

Sevrage de médicaments avant chacune des visites

Visite 2 :

Date : _____

Médicaments	Ne pas prendre après

Visite 3 :

Date : _____

Médicaments	Ne pas prendre après

Visite 4 :

Date : _____

Médicaments	Ne pas prendre après

Consignes pour remplir le carnet

- Chaque jour, vous avez 3 questionnaires à remplir:
  1. Questionnaires du **matin**: à remplir après le déjeuner
  2. Questionnaires du **midi**: à remplir après le dîner
  3. Questionnaires du **soir**: à remplir après le souper

- Indiquez, en haut de la page, l'heure à laquelle vous remplissez chaque questionnaire.

- Le carnet doit être rempli pendant 7 journées consecutives du _____ au _____ inclusivement.

- Veuillez répondre à toutes les questions, il y a plusieurs parties à remplir :

  Matin :
  Description de l'alimentation
  Heures de la prise de médicaments
  Questions sur le sommeil (7 questions)
  Questionnaire sur l'humeur (6 questions)

  Midi :
  Description de l'alimentation
  Heures de la prise de médicaments
  Questionnaire sur l'humeur (6 questions)

  Soir :
  Description de l'alimentation
  Heures de la prise de médicaments
  Questions sur vos activités (3 questions)
  Questionnaire sur l'humeur (6 questions)

Si vous avez d'autres commentaires ou évènements spéciaux qui pourraient avoir influencé votre état dans la journée, vous pouvez les écrire en bas de la page des questionnaires du soir.

Consignes pour remplir le journal d'alimentation et la liste des médicaments

- Indiquez l'heure de vos repas et de vos collations.
- Donner une description complète de votre alimentation.
- Soyez le plus précis possible.

  Par exemple :
  Produits céréaliers,
  Légumes et fruits,
  Viandes ou substituts,
  Huiles et matières grasses,
  Lait ou substituts,
  Breuvages et produits caffeiné ou alcool,
  Autre

- Indiquez l'heure de la prise des médicaments ainsi qu'une liste de ces médicaments et leur dosage.
- Si vous fumez, indiquez les heures auxquelles vous avez fumé et le nombre de cigarettes (ou cigares et/ou pipes).

Exemple :

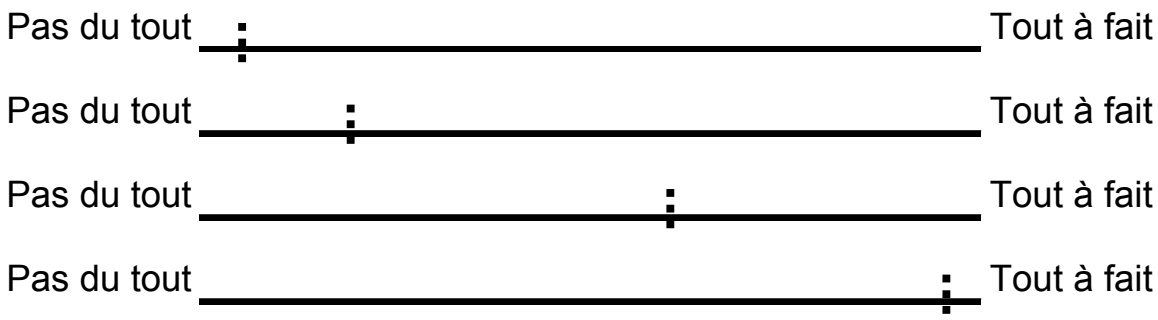
Heure:	Description d'alimentation
Déjeuner:	1 pain pita au blé entier, 1 petit morceau de fromage pour garnir
9h00	Demi tasse thé avec une demi tasse de lait 1%
Collation:	1 banane, 10 amandes sans sel
10h30	

Heure:	Liste de médicaments (dosage)
9h00	Advair (100mcg), Asaphen ec 80mg

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Consignes pour remplir les questionnaires d'humeur

Durant la **semaine de suivi**, nous vous demandons de répondre 3 fois par jour à 5 questions qui correspondent à des sentiments que vous éprouvez sur vous-même. Pour chacune, nous vous demandons de faire **un trait vertical** entre les bornes « pas du tout » et « tout à fait » sur la ligne horizontale en fonction de l'intensité choisie. Il s'agit d'échelle visuelle analogique. Le principe de réponse à ces échelles vous est présenté ci-dessous. Ceci n'est qu'un exemple des multiples réponses possibles.



Aucune réponse n'est juste, elle est avant tout personnelle.

Instructions pour les sujets portant le moniteur Actiwatch

- Vous devez porter un moniteur au poignet _____ de façon continue (autant que possible), 24 heures par jour, incluant la période de sommeil.

- Si vous faites des activités durant lesquelles vous ne pouvez pas garder le moniteur (ex : bain/douche, laver la vaisselle, natation), écrivez dans votre agenda les heures durant lesquelles vous avez retiré le moniteur en indiquant la raison.

- **Les moniteurs sont résistants à l'eau, mais pas imperméables. Ne pas les plonger dans l'eau et veiller à les protéger autant que possible de la pluie.**

- Les moniteurs sont sensibles aux chocs : évitez autant que possible de les cogner ou de les échapper.

- Ne jamais essayer d'ouvrir les moniteurs ou de démonter une de leurs pièces.

- Veuillez indiquer avec le plus de précision possible vos heures de lever et de coucher dans les agendas de sommeil. Cette information nous aidera à interpréter vos données.

- Veuillez presser le marqueur sur l'actiwatch pour préciser quand vous fermer la lumière au coucher et la sortis du lit le matin.

Questionnaires quotidiens

Heure :_____ Questionnaire du Matin 1

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui
   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>réveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**
   1 2 3 4 5
   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondant à votre forme au levé :**
   1 2 3 4 5
   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Midi 1**

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 1

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Avez-vous dormi? _____
2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui
   Si oui: Quoi et à quelle heure: _____
3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

.....
.....
.....
.....
.....
.....

Heure :_____ Questionnaire du Matin 2

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui

   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>réveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**

   1 2 3 4 5

   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**

   1 2 3 4 5

   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Midi 2**

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 2

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui

   Si oui, de quelle heure à quelle heure? De _____ à _____

   Avez-vous dormi? _____

2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui

   Si oui: Quoi et à quelle heure: _____

3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui

   Si oui, de quelle heure à quelle heure? De _____ à _____

   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

.....
.....
.....
.....
.....
.....

Heure :_____ **Questionnaire du Matin 3**

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui

   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**

   1 2 3 4 5

   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**

   1 2 3 4 5

   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Midi 3

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 3

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui

   Si oui, de quelle heure à quelle heure? De _____ à _____

   Avez-vous dormi? _____

2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui

   Si oui: Quoi et à quelle heure: _____

3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui

   Si oui, de quelle heure à quelle heure? De _____ à _____

   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

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Heure :_____ Questionnaire du Matin 4

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de medicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui

   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**

   1 2 3 4 5

   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**

   1 2 3 4 5

   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Midi 4**

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Soir 4**

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Avez-vous dormi? _____
2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui
   Si oui: Quoi et à quelle heure: _____
3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :
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Heure :_____ Questionnaire du Matin 5

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui

   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**

   1 2 3 4 5

   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**

   1 2 3 4 5

   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

Veuillez mettez un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Midi 5**

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 5

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Avez-vous dormi? _____
2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui
   Si oui: Quoi et à quelle heure: _____
3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

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Heure :_____ Questionnaire du Matin 6

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui

   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**

   1 2 3 4 5

   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**

   1 2 3 4 5

   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Veuillez mettez un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Midi 6**

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 6

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui

   Si oui, de quelle heure à quelle heure? De _____ à _____

   Avez-vous dormi? _____

2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui

   Si oui: Quoi et à quelle heure: _____

3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui

   Si oui, de quelle heure à quelle heure? De _____ à _____

   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

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Heure :_____ Questionnaire du Matin 7

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**

   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui

   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**

   1 2 3 4 5

   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**

   1 2 3 4 5

   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Midi 7

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 7

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui

   Si oui, de quelle heure à quelle heure? De _____ à _____

   Avez-vous dormi? _____

2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui

   Si oui: Quoi et à quelle heure: _____

3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui

   Si oui, de quelle heure à quelle heure? De _____ à _____

   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

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Heure :_____ **Questionnaire du Matin 8**

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui

   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**

   1 2 3 4 5

   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**

   1 2 3 4 5

   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Midi 8

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 8

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Avez-vous dormi? _____
2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui
   Si oui: Quoi et à quelle heure: _____
3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Veuillez mettez un trait au centre de la ligne ci-dessous

_____

Autres évènements à indiquer :

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MERCI BEAUCOUP POUR VOTRE COLLABORATION : ELLE EST TRÈS APPRÉCIÉE!