Interaction between circulatory and respiratory exercise adaptation in chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF)

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) patients show a marked reduction in exercise capacity compared to that of healthy age-matched individuals. While inadequate gas exchange and resulting hypoxemia appears as the primary factor in COPD, an impaired cardiac output is the predominant explanation for the reduced oxygen delivery in CHF. However, the extent of the contributions of other systemic factors remains unclear. In light of the potential interactions between cardiac output (Qc) and pulmonary hyperinflation, there is surprisingly little data thus far on ventilatory constraints in CHF and on the role of blood flow delivery in COPD which may further limit the exercise capacity. Thus, the purpose of this study was to compare the slope of the Qc versus oxygen uptake (VO_2) response through several submaximal cycling loads in patients with moderately severe COPD and with that of moderate to severe CHF patients as well as age-matched healthy control subjects (CTRL). Also examined was the possibility that ventilatory constraints such as dynamic hyperinflation contribute to an abnormal stroke volume response in both diseases. Cardiac output was measured using the CO_2-rebreathing equilibrium technique during baseline conditions and cycling at 20, 40 and 65% of peak power in 17 COPD (Age: 64 ± 8 yrs; FEV_1/FVC: 37 ± 11%; FEV_1: 41 ± 15 % predicted), 10 CHF (Age: 57± 10 yrs; FEV_1/FVC: 73.8 ± 5.6%; FEV_1: 93 ± 13% predicted) and 10 age-matched CTRL subjects. Inspiratory capacity (IC) was also measured for the determination of dynamic hyperinflation during the steady state exercise bouts. The results indicate that while the absolute Qc values are lower in COPD and in CHF than in CTRL during 65% peak power cycling (11.30 ± 2.38 *vs* 12.40 ± 2.08 *vs* 15.63 ± 2.15 $L \cdot min^{-1}$ respectively, $p < 0.01$), likely due to their lower exercise metabolic demand. The Qc/VO_2 response to increasing levels of exercise intensity was lower or normal in CHF patients compared to CTRL, while normal or hyperdynamic in most COPD patients. Indeed, the majority of patients with COPD exhibited Qc/VO_2 slopes greater than 7.0, which may be indicative of a peripheral muscle bioenergetic disturbance that may drive the need for greater oxygen delivery, and thus result in an exaggerated central circulatory response.

RÉSUMÉ

Les patients atteints de maladie pulmonaire obstructive chronique (MPOC) et d'insuffisance cardiaque chronique (ICC) démontrent une diminution marquée de la capacité d'exercice comparativement à des individus de même âge. Tandis que la détérioration des échanges gazeux et l'hypoxémie qui en résulte semblent être le facteur primaire chez les MPOC, la diminution du débit cardiaque (Qc) explique principalement la diminution de l'apport en oxygène chez les ICC. Toutefois, l'importance de la contribution de facteurs systémiques autres demeure nébuleuse. Considérant l'interaction potentiel entre l'hyperinflation pulmonaire et le débit cardiaque, à ce jour il existe que peu de données sur le rôle des contraintes ventilatoires chez les ICC et la distribution des flux périphérique chez les MPOC comme facteurs aggravants la diminution de la capacité à l'effort. Donc, le but de cette étude était de comparer la pente du Qc versus la réponse en consommation d'oxygène (VO_2) à trois niveaux différents d'effort constant et sous-maximal sur ergocycle chez des patients avec une MPOC modéré à sévère ainsi que des patients avec une ICC modéré à sévère à celle de sujets témoins en bonne santé d'âge comparable (CTRL). Les contraintes ventilatoires tel que l'hyperinflation dynamique et sa contribution possible à une réponse anormale de Qc a aussi été examinée chez ces deux groupes de patients. Le Qc a été mesuré en utilisant la technique d'équilibre de réinhalation de CO_2 au repos et à l'effort à une intensité correspondant à 20, 40 et 65% de la puissance maximale chez 17 sujets MPOC (Age: 64 ± 8 ans; FEV_1/FVC: 37 ± 11%; FEV_1: 41 ± 15 % prédit), 10 ICC (Age: 57± 10 ans; FEV_1/FVC: 73.8 ± 5.6%; FEV_1: 93 ± 13% prédit) et 10 sujets CTRL. La capacité inspiratoire a également été mesurée pendant les trois niveaux d'effort constant en état stable, afin de chiffrer l'hyperinflation dynamique. Les résultats indiquent que les valeurs absolus de Qc (à une intensité d'effort correspondant à 65% de la puissance maximale) sont inférieures chez les MPOC ainsi que les ICC comparés aux CTRL (11.30 ± 2.38 *vs* 12.40 ± 2.08 *vs* 15.63 ± 2.15 $L \cdot min^{-1}$ respectivement, $p < 0.01$), vraisemblablement parce que leur demande métabolique est inférieure. La réponse Qc/VO_2 correspondant aux niveaux croissants d'intensité est diminuée ou normale chez les patients ICC

comparativement au CTRL, tandis qu'elle est normale ou hyperdynamique chez la majorité des patients MPOC. En effet, la majorité des patients atteints de MPOC a démontré des pentes de Qc/VO_2 plus grandes que 7.0; ce qui indique possiblement une perturbation bioénergétique en provenance des muscles périphériques engendrant une plus grande demande en oxygène, et créant ainsi une réponse circulatoire centrale exagérée.

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PART II: EXPERIMENTAL ARTICLE

PART I: REVIEW OF LITERATURE

The prevalence of chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) is rapidly increasing worldwide such that in North America and Europe, heart disease is the first leading cause of death while COPD is fourth. In addition to being both chronic diseases, chronic obstructive pulmonary disease and chronic heart failure, share common elements with respect to their physiological and functional repercussions on patients' clinical status and quality of life. Physiological examples of common features in both diseases include great resemblance in histological and biochemical skeletal muscles characteristics, similar exaggerated ventilatory response for any given level of oxygen consumption and comparable reduction in maximal exercise capacity. In both COPD and CHF, reduction in muscle mass, muscle strength and muscle endurance are observed (H. R. Gosker, Wouters, E.F.M.,van der Vusse, G., Schols, A.M.W.J., 2000). At the cellular level, changes in muscle phenotype include a reduction in the proportion of type I fibers and an increase in the proportion of type IIb fibers as well as atrophy of type I and type IIa fibers (H. R. Gosker, Wouters, E.F.M.,van der Vusse, G., Schols, A.M.W.J., 2000). In line with the fiber-type profile described above, activity of oxidative enzymes (citrate synthase and 3-hydrozyacil-CoA dehydrogenase) has been reported to be low in COPD and CHF (Jakobson, 1995; Maltais F., 1996; M. J. Sullivan *et al.*, 1990). In addition, the muscle capillarization is reduced when compared to age-matched healthy subjects (H. Drexler *et al.*, 1992; M. J. Sullivan et al., 1990; Whittom, 1998). Furthermore, both COPD and CHF patients exhibit markedly reduced maximal exercise capacity and peak oxygen consumption (VO_2peak) and an exaggerated ventilatory response during exercise. Exaggerated ventilation for a given level of oxygen consumption (VE/VO_2 ratio) may be the result of the reduced exercise oxygen delivery as dictated by peripheral muscle signaling. While an impaired cardiac output is the predominant explanation for the reduced oxygen delivery in CHF, inadequate gas exchange and resulting hypoxemia appears as the primary factor in COPD. Recent data indicates that patients with

CHF have a restrictive ventilatory defect and reduced lung diffusion capacity (Dimopoulou, 1998). The extent to which pulmonary limitation in CHF also contribute to the impaired exercise oxygen delivery is increasingly being examined (Schroeder, 2003; Wensel, 2004). On the other hand, circulatory factors have not been closely studied in COPD. Hyperinflation is commonly observed in moderate to severe COPD patients (O'Donnell, 2001; O'Donnell *et al.*, 2001b). Inasmuch as lung hyperinflation may affect the intrapulmonary pressure and thus could impinge on venous return and ventricular filling, lung hyperinflation possibly would impact on the exercise cardiac output in COPD. However, the extent to which dynamic hyperinflation influences cardiac output response to exercise has not been examined. It is beyond the scope of this thesis to provide a thorough review of the pathophysiology of COPD and CHF. This literature review will therefore briefly contrast the major elements of pathophysiology of both COPD and CHF and will explore the physiological mechanisms involved in the oxygen transport limitation during systemic exercise in these diseases.

1. PATHOPHYSIOLOGY OF COPD

1.1. Definition and diagnosis

Most recently, an international workshop on COPD, the Global Initiative for Lung Disease (GOLD) established a definition based on physiology, etiology and pathology: "COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow obstruction is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles of gases."(Pawels *et al.*, 2001). In COPD, the abnormally enhanced inflammation of the lungs primarily caused by cigarette smoking, results in marked expiratory flow limitation and decreased lung diffusion capacity. The term COPD includes both chronic bronchitis and emphysema.

The relative contribution of chronic bronchitis and emphysema to the COPD disease process is often difficult to discern (Calverley, 2003). Chronic

bronchitis is defined as the presence of chronic productive cough for three months in each of two successive years in a patient in whom other causes of productive chronic cough have been excluded (ATS, 1995). It is associated with mucus hypersecretion due to an increase in the volume and number of submucosal glands and the number of goblet cells in the mucosa. Emphysema is defined as the presence of permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis (G. Snider, Kleinerman J, Thurlbeck WM, Bengali ZK., 1985). In emphysema, the first symptom may be the development of breathlessness and dyspnea with previously tolerated activities. While in chronic bronchitis, persistent cough often precedes the development of airflow limitation and breathlessness (Pawels *et al.*, 2001). Often time, in both emphysema and chronic bronchitis there coexists bronchoconstritor tone that may be attributed to an asthmatic component. The diagnosis of COPD is confirmed when airflow limitation is not fully reversible with the use of bronchodilators. Otherwise, a reversibility greater that 15% is usually reflective of transient bronchoconstriction typically seen in asthma (Halpin, 2002).

1.2. Classification of disease severity

The assessment of forced expiratory volume in one second (FEV_1) and the ratio of this to the forced vital capacity (FEV_1/FVC) are used to diagnose and quantity the expiratory flow limitation when compared to predicted values for age, gender, height and race (ATS, 1995; BTS, 1995; Pawels et al., 2001; Siafakas *et al.*, 1995). The classification of COPD severity is determined by the degree of airflow limitation. Table 1 shows severity classification guidelines for diagnosis of COPD based on FEV_1 and FEV_1/FVC. As can be seen in this table, there is currently four system of classification. The American Thoracic Society (ATS), the European Respiratory Society (ERS), the British Thoracic Society (BTS) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classify of the COPD disease into three categories: mild, moderate and severe.

Table 1: Classification of mild, moderate and severe COPD

	Stage 1 (Mild)	Stage II (Moderate)	Stage III (Severe)
ATS[1] FEV_1/FVC: <70%	FEV_1 % predicted: ≥ 50%	FEV_1 % predicted: 35-49%	FEV_1 % predicted: <35%
ERS[2] FEV_1/FVC: <88%	FEV_1 % predicted: ≥ 70%	FEV_1 % predicted: 50-69%	FEV_1 % predicted: <50%
BTS[3] FEV_1/FVC: <70%	FEV_1 % predicted: 60-79%	FEV_1 % predicted: 40-59%	FEV_1 % predicted: <40%
GOLD[4] FEV_1/FVC: <70%	FEV_1 % predicted: ≥ 80%	FEV_1 % predicted: 30-79%	FEV_1 % predicted: <30%

(ATS=American Thoracic Society; ERS=European Respiratory Society; BTS=British Thoracic Society; GOLD=Global Initiative for Chronic Obstructive Lung Disease)

According to ATS (ATS, 1995), the severity of COPD is categorised into three stages in terms of percent of predicted norms: stage I is $FEV_1 \geq 50\%$; stage II is FEV_1 35 to 49%; and stage III is $FEV_1 < 35\%$. The ERS (Siafakas et al., 1995) uses slightly different categories, where mild COPD is $FEV_1 \geq 70\%$; moderate is FEV_1 50 to 69%; and severe is $FEV_1 < 50\%$. The BTS (BTS, 1995) classify mild COPD as $FEV_1 \geq$ 60-79%; moderate is FEV_1 40 to 59%; and severe is $FEV_1 < 40\%$. The GOLD (Pawels *et al.*, 2001) staging system is also slightly different, where stage I is $FEV_1 \geq 80\%$; stage II is FEV_1 30 to 79%; and stage III is $FEV_1 < 30\%$ (Iqbal *et al.*, 2002). As can be seen, at this moment in time there is still no consensus in the classification criteria among the different expert panels. These discrepancies may reflect the fact that FEV_1 poorly represents the degree of impairment and incompletely reveal the complexity of COPD. In North America,

the ATS guidelines are often used; however the GOLD guidelines may become preferred (Minkoff, 2005).

1.3. Resting lung volume in COPD

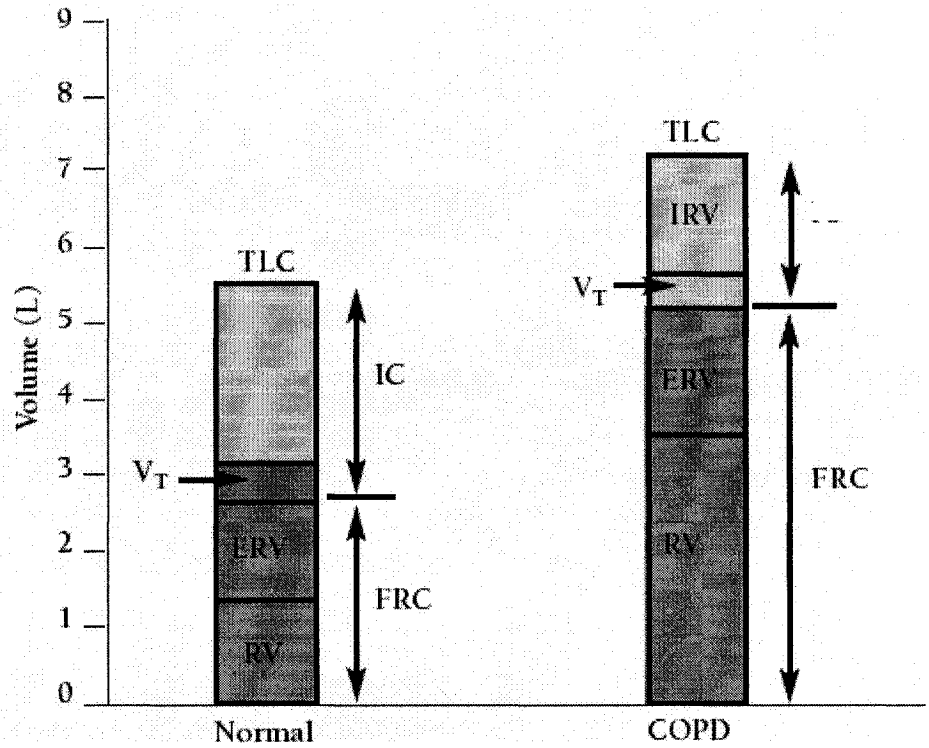

Figure 1: Relative proportions of lung volumes at rest in the normal lung and the lung with COPD. TLC= total lung capacity; IC= inspiratory capacity; FRC=functional residual capacity; IRV= inspiratory reserve volume; TV=tidal volume; ERV= expiratory reserve volume; RV= residual volume; VC= vital capacity. Adapted from (Minkoff, 2005).

Typical spirometry tracing of lung volumes at rest in COPD patients compared to normal healthy individuals is illustrated in Figure 1. Total lung capacity (TLC) is the sum of the vital capacity (VC) and the residual volume (RV). The RV is the volume of air that remains in the lung after a maximal forced expiration. COPD patients, especially the emphysematous type, have elevated RV due to air trapping as a result of their expiratory flow limitation. Residual volume as high as 327% of the predicted values for age, height, race and sex has been reported in severe patients prior to lung volume reduction surgery (Kubo, 1997). In COPD patients, the RV/TLC ratio, which is an indicator of air trapping called

lung hyperinflation, is increased due to their marked increase in RV. The TLC may also be increased in COPD (Calverley & Pearson, 2003; Pellegrino & Brusasco, 1997). TLC normally ranges between five and six litres, however in COPD it can exceed eight litres (Guyton & Hall, 2000c; Kubo, 1997). The vital capacity (VC) is the amount of air that can be exhaled after a maximal inspiration. It is the sum of the inspiratory reserve volume (IRV), tidal volume (V_T) and the expiratory reserve volume (ERV). The VC may be preserved or slightly decreased depending if both TLC and RV are proportionally increased or not (Calverley & Pearson, 2003). V_T is the volume ventilated per breath. V_T usually remains normal, but severe COPD patients tend to have smaller V_T (Sorli, 1978). The IRV is the volume of air that can be inspired in addition to normal tidal breathing, while ERV is the volume of air that can be expired in addition to tidal expiration. The inspiratory capacity (IC) is the amount of air that can be taken in after a normal tidal expiratory breath. The IC is calculated as the sum of the V_T and IRV and it is often diminished in COPD compared to healthy individuals. Reduced IC is often coupled with an augmented functional residual capacity (FRC) (J. Milic-Emili, 2000b). The FRC is the total amount of air remaining in the lungs at the end of a normal expiration, and it comprises the sum of ERV and RV. The ERV is usually similar in both healthy and COPD (Pride & Milic-Emili, 2003).

1.4. Lung mechanics in COPD

In COPD, the airway resistance, the elastic recoil and the compliance of the lung are changed. In pulmonary emphysema, the destruction of the lung parenchyma results in loss of alveolar attachments (Shapiro, 2000) and increases the dynamic compliance of the lungs. The alveolar damage is often combined with fibrosis and scaring due to disturbances in elastin and collagen synthesis. These modifications of the lung parenchyma diminish the normal elastic recoil property of lungs. In chronic bronchitis, alteration in mucus production and mucocillary clearance as well as development of fibrosis in the airway epithelial wall result in static airway narrowing. Narrowing of the small airways can

compromise airflow since it increases the airway resistance. Therefore, the overall mechanical properties of the lung are changed in COPD. Airflow during forced exhalation is the result of the balance between the elastic recoil of the lungs and the resistance of the airways limiting flow. During expiration, as the lung parenchyma provides progressively less elastic recoil and the cross-sectional area of the airways falls, the resistance to airflow increases. Evidence of the mechanical property changes can be reflected in a maximal flow-volume curve, as the decrease in flow, which coincides with the decrease in lung volume, is readily apparent in the expiratory portion of a flow-volume curve as can be seen in figure 2.

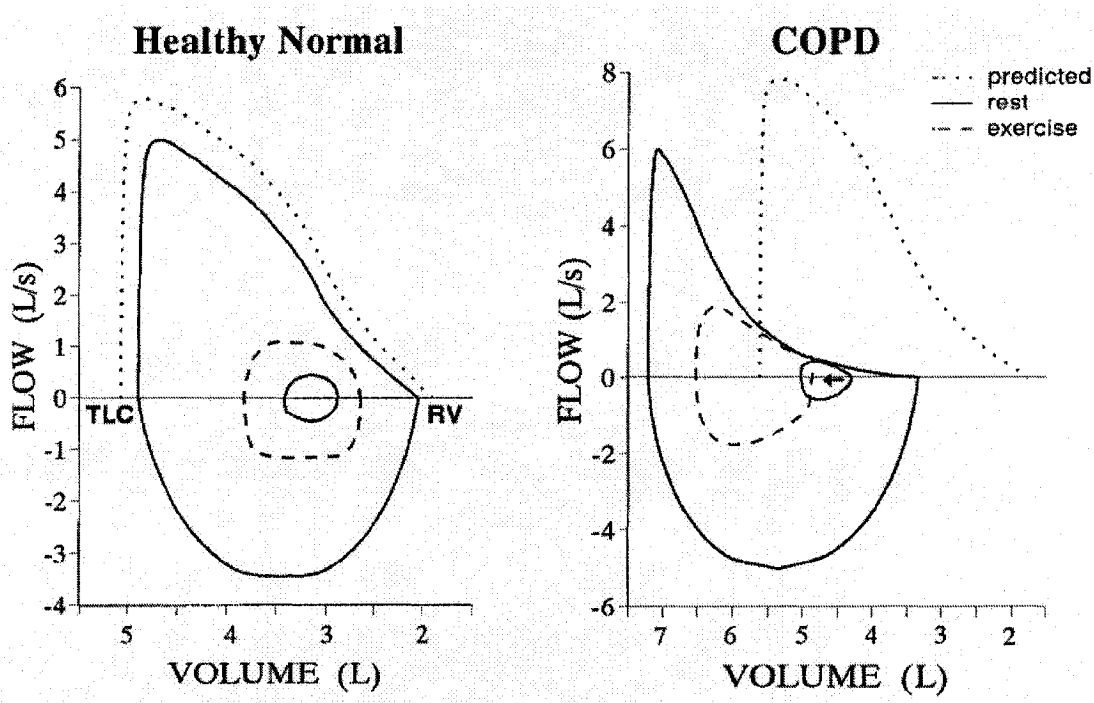

Figure 2. Comparison of maximal and tidal flow-volume loops in a healthy subject and patient with COPD, at rest and during exercise. Volume compartments of the VC are also depicted (O'Donnell, 2000).

During tidal breathing, the balance between the elastic recoil of the lungs and the chest wall determines the resting volume of the thorax. In healthy individuals during inspiration, the diaphragm contracts to lengthen the chest

cavity; then during expiration, the diaphragm simply relaxes, and the elastic recoil of the lungs and chest wall compresses the lungs. In the presence of airway obstruction, hyperinflation during tidal breathing is a compensatory mechanism to facilitate expiratory airflow, because as the lung volume increases, elastic recoil pressure increases, airways enlarge and airway resistance decreases. On the other hand, hyperinflation places the respiratory muscles at a mechanical disadvantage (Larson, 2002).

In COPD, air trapping places the diaphragm muscle in a flattened position and its ideal length-tension property is loss (Gorman *et al.*, 2002). The diaphragm radius of curvature (r_{di}) is increased and the diaphragm must generate greater tension in order to create sufficient change in thoracic pressure for tidal breathing as described by Laplace's law: $P_{di} = 2T_{di} / r_{di}$ (Marino, 1998). In some patients the ability of the diaphragm to generate necessary tension to expand the rib cage is also reduced (De Troyer, 1997; Krachman & Tobin, 2001; Singh *et al.*, 2001). As a result, accessory respiratory muscles may also be activated in COPD to assist ventilation by elevating and depressing the ribs to increase the anteroposterior diameter of the chest cavity. During inspiration, contraction of the external intercostal muscles help raising the rib cage and during expiration, the internal intercostals and the abdominal recti muscles may be activated to provide assistance to airflow. In severe patients, with marked airway resistance in which accessory respiratory muscles are activated, the work of breathing is increased (McIlroy, 1954; Joseph Milic-Emili, 2000a; West, 2000).

1.5. Pulmonary gas exchange in COPD

In COPD, altered lung mechanics coupled with impaired gas exchange are responsible for the deficiency of the lungs as exchanger of oxygen (O_2) and carbon dioxide (CO_2). The pulmonary diffusion capacity, which is defined as the volume of gas that diffuses through the membrane each minute for a pressure difference of 1 mmHg (Guyton & Hall, 2000b), is a marker of the integrity of the

respiratory membrane where the gas exchange takes place. The most commonly used diffusing capacity technique is the single-breath-hold diffusing capacity for carbon monoxide (D_LCO) technique, in which the transfer of inspired CO to the alveoli is measured. COPD patients, especially those with predominant emphysema may exhibit a reduced pulmonary diffusion capacity of less than 55% of predicted values (McIvor, 2002; G. L. Snider, 1998) since destruction of alveolar walls and pulmonary capillary membranes impede gas exchange. Widespread airway narrowing with varying degrees of parenchymal and vascular structural destruction are at the root of the misdistribution of alveolar ventilation (V_A) and pulmonary blood flow. Within the same individual, areas of low and high V_A/Q ratio are found. In COPD, the areas of ventilation-perfusion mismatch are exaggerated. In both extremes of the lung, inequalities of ventilation and perfusion decrease the effectiveness of the lung for exchange of O_2 and CO_2. For instance, in areas of physiologic shunt where small airways are obstructed, some alveoli may be poorly ventilated or not ventilated at all causing a V_A/Q ratio that approaches zero. In contrast, in those areas of exaggerated physiologic dead space (V_D), where the alveolar walls have been mainly destroyed, but there is still alveolar ventilation, most of the ventilation is wasted because of inadequate blood flow to transport the blood gases and the V_A/Q ratio is high. The size of the V_D can be calculated from the mixed expired ($P_{ET}O_2$) and arterial carbon dioxide tensions (PaCO2) and the tidal volume:

$$V_D = V_T (1 - (P_{ET}CO_2/PaCO_2))$$

The general effectiveness of ventilation and gas exchange can be estimated with the calculation of the deadspace to tidal volume ratio V_D/V_T. A rise in V_D will elevate $PaCO_2$ since ventilation of unperfused area is wasted. Most patients with COPD maintain their CO_2 tension within the normal range, despite a large V_D. However, when the airflow obstruction becomes severe, hypercapnia may develop (ATS, 1995). The result of the exaggerated misdistribution of inspired gas and blood flow in COPD result in abnormal respiratory arterial blood gases. The alveolar-arterial gradient ($A\text{-}aPO_2$) is markedly elevated since typically in COPD partial pressure of oxygen in arterial blood (PaO_2) is reduced. In healthy

individuals, PaO_2 at rest is about 100 mm Hg.(Guyton & Hall, 2000b) Yet, with increasing disease severity PaO2 values at rest as low as 55 mmHg can be observed (Calverley, 2003). The oxygen content in arterial blood depends on the level of oxyhemoglobin saturation (SaO2). For pressures below PaO2 of 60 mmHg a small decrease in PaO2 results in a significant reduction in SaO2 and hypoxemia is more pronounced.

2. PATHOPHYSIOLOGY OF CHF

2.1. Definition and classification of disease severity

According to The European Society of Cardiology (ESC) no simple objective definition for CHF is entirely satisfactory because there is no cut off value of cardiac or ventricular dysfunction or change in flow, pressure, dimension, or volume that can be used reliably to identify patients with heart failure (Swedberg *et al.*, 2005). The American College of Cardiology (ACC)/American Heart Association (AHA) define CHF as a complex clinical syndrome that can result from any structural or functional cardiac disorder that, impairs systolic or diastolic function or more frequently a combination of both (Hunt *et al.*, 2001). These functional impairments can result from a number of valvular or myocardial diseases such as myocardial infarction, arterial hypertension, as well as pericardial or infiltration disease and viral or bacterial infection. Typically, systolic dysfunction arises from abnormalities in myocardial contractility with left ventricular ejection fraction generally less than 40% (Hunt et al., 2001; Swedberg et al., 2005). In contrast, in diastolic dysfunction the contractility of the myocardium and thus the ejection fraction is preserved, however myocardial relaxation is impaired. Patients with predominant diastolic dysfunction have one or more indices of impaired ventricular filling as shown by evidence of abnormal left ventricular dysfunction, increased stiffness of the ventricles and reduced distensibility (Swedberg et al., 2005). Nevertheless, both systolic and diastolic dysfunction result in a reduction in stoke volume with a concomitant decrease in cardiac output (Hunt et al., 2001). The New York Heart

Association (NYHA, 1994) classification system is commonly used to quantify the degree of functional limitation in heart disease including CHF. Patients are classified into four categories as can be seen in table 2.

Functional capacity	Objective assessment
Class1: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class 2: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease
Class 3: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease
Class 4: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of the heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease

Table 2: New York Heart Association classification of functional capacity and objective assessment (NYHA, 1994)

2.2. Diagnosis

The clinical recognition of heart failure is possible when signs and symptoms of exercise intolerance, fluid retention, abnormal ECG or chest X-ray and elevated levels of atrial natriuretic peptide are present. However, the single most widely recognized tool to objectively diagnose CHF is the two-dimensional echocardiogram coupled with Doppler flow evaluation. The echocardiographic examination allows quantitative assessment of the dimensions, geometry, thickness, and motion of the right and left ventricle and the qualitative evaluation of the atria, pericardium, valves and vascular structures. Measurement of several

indices of myocardial contractility or diastolic function can therefore be easily performed to closely monitor changes in the evolution of disease (Hosenpud, 2000).

2.3. Compensatory mechanism in CHF

CHF is a complex syndrome in which compensatory mechanisms for the chronic reduction in cardiac output are intricately activated. Hemodynamic circulatory factors are regulated by baroreflexes through the relationship between flow, pressure and resistance as given below by $\Delta P = Qc \times R$, where ΔP is the difference between mean arterial and mean venous pressures, Qc is the systemic blood flow, and R is the resistance to flow, termed vascular resistance. In an attempt to maintain adequate flow and perfusion to vital organs, the adrenergic nervous system, as well as the rennin-angiotensin system, vasopressin, endothelins, and cytokines work together to maintain systemic perfusion pressure through an increase in vascular resistance to offset the reduction in systemic flow or cardiac output.

2.3.1. Sympathetic nervous system

Alteration in systemic vascular resistance primarily serves the function of regulating mean arterial and venous pressure to insure adequate flow. When cardiac output (Qc) is reduced, sympathetic mediated increase in contractility and peripheral vasoconstriction compensate at least partially for the cardiac failure (Guyton & Hall, 2000a). Neuronal sympathetic stimulation of the β-adrenoceptor of the myocardium increases cardiac contractility as well as heart rate (HR) and thus Qc is improved. However, prolonged sympathetic stimulation of the ventricular myocytes can lead to β-adrenergic receptor desensitization, which in turn further reduces myocytes contractility (Hosenpud, 2000). Sympathetic-mediated constriction of endothelial smooth muscles of blood vessels through α-adrenoceptor stimulation results in an

increase in vascular resistance. Zelis et al. demonstrated that vascular resistance is higher in CHF patients by showing that peak forearm flow related to a hyperdynamic response after 10 minutes of arterial occlusion is markedly reduced in CHF compared to healthy normal individuals (Zelis *et al.*, 1968). Sympathetically mediated venoconstriction enhances venous return and thus cardiac preload through the Frank-Starling mechanism to support stroke volume and cardiac output. However, the increase in venous return may lead to an increase in left atrial pressure resulting in an exaggerated pulmonary hydrostatic capillary pressure and pulmonary oedema (Navas & Martinez-Maldonado, 1993). The stimulation of α-adrenoceptor also mediates arterial vasoconstriction, which increases systemic vascular resistance and raises arterial pressure.

On the other hand, this may increase left ventricular afterload, which can further worsen heart failure (McPhee, 2003). In addition, peripheral vasoconstriction, particularly in the smaller arterioles, has been shown to limit muscle perfusion during exercise in patients with CHF thereby contributing to the decrease in exercise capacity (H. Drexler, 1991). Similarly, sympathetic-mediated constriction of the coronary arteries in CHF could also impair coronary blood flow (Bigger, 1987).

2.3.2. Hormonal system

The Renin-Angiotensin-Aldosterone cascade is another compensatory mechanism for the reduction in circulating blood volume (Guyton & Hall, 2000a). Reduction in circulating blood volume results in a reduction in glomerular pressure due to a combination of both reduced arterial pressure and sympathetic constriction of the afferent arterioles. The glomerular filtration rate decreases and markedly decreases urine output. The juxtaglomerular cells of the kidneys perceive the reduction in renal perfusion pressure as a decreased stretch on the

afferent arteriolar walls, which stimulates renin release. Renal renin acts on angiotensinogen to form angiotensin I. Angiotensin I is in turn transformed to angiotensin II, by the action of the angiotensin-converting enzyme (ACE). While angiotensin I has little known biological effect in humans, angiotensin II can exert several systemic effects through specific angiotensin II receptors. A major direct effect of Angiotensin II on arterial smooth muscles is its pressor action, which leads to vasoconstriction and increased peripheral resistance and therefore contributes to blood pressure regulation. This results in an increased left ventricular afterload, which could reduce ventricular ejection and results in greater end-systolic volume, in turn, enhancing ventricular preload (R. D. Smith *et al.*, 1992). Secondly, angiotensin II has a direct effect on the arterioles of the kidneys to promote reabsorption of both water and sodium from the renal tubules. As a result, extracellular fluid volume augments, which in turn raises the arterial pressure. Angiotensin II stimulates aldosterone secretion from the adrenal cortex and elevated aldosterone levels further increase reabsorption of sodium from the renal tubules. The resultant elevated plasma osmolarity and sodium concentration will stimulate the posterior pituitary gland to secrete arginine vasopressin (also called antidiuretic hormone). The release of vasopressin will rise the blood pressure by directly promoting the reabsorption of water in the renal tubules. The resultant increase in plasma volumes and filling pressures help to maintain blood pressure and Qc (Eichhorn, 1996).

However, excessive elevation of left atrial pressure may lead to transudation of fluid into the lungs causing pulmonary congestion and oedema that leads to dyspnea (Hosenpud, 2000). It is therefore not surprising to see reports of reductions in pulmonary diffusion capacity in CHF patient that becomes worsen during exercise (P. Agostoni *et al.*, 2003). Yet, a vicious cycle is initiated since continued hyperactivity of the renin-angiotensin system leads to marked vasoconstriction, increased afterload, and further reduction in cardiac output and glomerular filtration rate.

2.3.3. Ventricular remodelling

Another compensatory mechanism to the reduced cardiac output is the increase in end-diastolic volume through an increase in heart chamber dilation. Neurohormonal mediators trigger a chain of event that exert direct effect on the myocardium and promote growth factors to increase the number of contractile element in the heart and cause hypertrophy. The α1-adrenergic receptors, which are important for induction of myocardial hypertrophy, are increased in HF patients (McPhee, 2003). Overtime, progressive left ventricular remodelling occurs. The left ventricular chamber enlarges and becomes more spherical as a result of changes in various mechanical, biochemical and molecular signals (Hosenpud, 2000). Increases in chamber size exacerbate the hemodynamic stresses on the myocardial walls, reducing mechanical performance and potentially increasing the amount of regurgitant flow through the mitral valve, perpetuating the remodelling process (Liu *et al.*, 2001). Angiotensin II, norepinephrine, cytokines and endothelins active pathways have been suggested to play a role in the stimulation of fibroblasts and myocytes proliferation. The fibroblast synthesis stimulation increase the amount of collagen deposition and fibrous tissue in the interstitial spaces of the myocardium, which results in stiffness of the heart chambers (K. B. Weber, CG, 1991). In addition, Angiotensin II and norepinephrine may have direct effects on myocytes leading to fibrosis and further cell necrosis introducing a negative spiralling effect on ventricular function (Francis, 2001). The mechanism by which remodelling takes place is highly complex and still remains poorly understood.

3. PHYSIOLOGICAL MECHANISMS CONTRIBUTING TO EXERCISE INTOLERANCE IN COPD AND CHF

3.1. EXTENT OF EXERCISE INTOLERANCE IN COPD AND CHF

In COPD and CHF patients evidence of exercise intolerance is common. In both diseases, they are limited in the amount of physical activity they can

perform and they exhibit a reduced maximal exercise capacity due to the inability to meet the oxygen demands of the tissues.

3.1.1. Reduced maximal exercise capacity

The decline in peak aerobic power (VO_{2peak}) with advancing age in healthy normal individuals is about 1% per year (I. Astrand *et al.*, 1973; Tanaka & Seals, 2003). Patients with COPD or CHF typically demonstrate a reduced maximal exercise capacity compared to controls matched for age. In general, VO_{2peak} seems to be related to disease severity. Patients with mild COPD and CHF typically show a VO_{2peak} close to predicted values for healthy age and sex matched individuals (T. G. Babb et al., 1991; K. T. Weber et al., 1982), while severe patients show values below 10 ml•kg•min^{-1} (Oelberg *et al.*, 1998a; K. T. Weber *et al.*, 1982). The magnitude of the reduction in maximal oxygen consumption compared to healthy age-matched controls is very much alike in moderate to severe COPD and patients with CHF. For instance, Gosker *et al.* compared in the same study COPD and CHF patients and showed that VO_{2peak} during cycling exercise in moderate to severe COPD and CHF to be about 50% of that in healthy aged-matched controls (H R. Gosker *et al.*, 2003). Results also show that the difference between the COPD and CHF groups was small and statistically not significant, with mean VO_{2peak} values of 0.8L•min^{-1} in COPD, 1.1 L•min^{-1} in CHF and 2.1 L•min^{-1} in the group of healthy control subjects. Similarly, the study by de Castro comparing VO_{2peak} values of moderate to severe COPD and CHF patients on a treadmill and showed that VO_{2peak} was 1.2 L•min^{-1} for both groups (de Castro Cesar *et al.*, 2003).

3.1.2. Submaximal exercise testing

Evidence of exercise intolerance is also present during submaximal exercise both in COPD and CHF. Submaximal exercise tests are generally

conducted in a laboratory on an exercise ergometer, on which the subjects exercise at a constant power output. The main outcome of these tests is generally the time to exhaustion and dyspnea scores and has been termed endurance testing. Most of the studies using this approach in the COPD and CHF population have been performed in the context of therapeutic interventions, such as pharmaceutical interventions or pulmonary rehabilitation (Lloyd-Williams *et al.*, 2002; O'Donnell, 2000; Rochester, 2003). For instance, studies generally found significantly lower endurance times during endurance steady-state cycling at 50-80% of pre-determined maximal exercise capacity in COPD as well as CHF compared to aged-matched healthy control (Gething *et al.*, 2004; Neder *et al.*, 2000; A. Somfay *et al.*, 2001a).

The 6-min walking distance test is also often used before and after a training program or a pharmaceutical trial as an assessment of the effectiveness of the intervention. It is not a maximal test, thus it is not used exclusively as a measure of exercise capacity but rather used as an indicator of functional status (ATS, 2002). For this reason, the 6-min walking distance is not a good indicator of the physiological determinants of exercise capacity. Several studies have shown that 6-min walking distance is markedly reduced in COPD and CHF compared to healthy age-matched controls. Typical 6-min walking distance values in healthy older adults range from 500 to 700 meters (Enright & Sherrill, 1998; Gibbons *et al.*, 2001; Miyamoto *et al.*, 2000; Troosters *et al.*, 1999). In moderate to severe COPD patients, measures of 6-min walking distance ranges from 175 to 595 meters (Celli *et al.*, 2004; Chuang *et al.*, 2001; Marin *et al.*, 2001; Oga *et al.*, 2002; Stevens *et al.*, 1999; Troosters *et al.*, 2002). Olsson et al. recently reviewed 63 randomized, blinded controlled trials that have used the 6-min walking distance as an outcome measure in moderate to severe CHF patients. Results show that the 6-min walking distance typically ranges from 165 to 499 meters (Olsson *et al.*, 2005). Without any doubt, COPD and CHF patients undergo very similar decreases in their exercise capacity in the course of their disease.

However, it remains unclear how much of the reduction in exercise capacity is related to the impairment in oxygen delivery capacity, as the expiratory flow limitation in COPD and the reduced Qc in CHF does not explain in full the reduction in exercise capacity. For instance, pharmacological interventions such as vasodilators and inotropic drugs that improve central hemodynamic have inconsistent acute effects on exercise performance in CHF patients (Pina & Fitzpatrick, 1996). After eight weeks of rehabilitation training program, exercise capacity is increased despite the fact that improvements in FEV_1 in COPD or in resting left ventricular function in CHF are not seen (Gosselink *et al.*, 1997; J. Myers *et al.*, 1999; Rochester, 2003; Stevenson, 1995). Hence, limitation in exercise capacity in patients with COPD and CHF can be in part attributed to the result of a sedentary lifestyle and deconditioning. Evidence of altered skeletal muscle physiology as well as respiratory and circulatory physiological response in both COPD and CHF also contributes to the exercise intolerance.

3.2. Role of skeletal muscle in the exercise intolerance in COPD and CHF

The last decade has brought forward an interest for the role of peripheral skeletal muscle in the exercise limitation of patients with COPD and CHF. It is beyond the scope of this section to provide a detailed account of the experimental evidence accumulating to suggest the existence of skeletal muscle alterations in patients with CHF and COPD. Instead, the reader is referred to several in-depth reviews providing detailed evidence for the morphological, functional, histological and metabolic skeletal muscle impairment in CODP (Couillard & Prefaut, 2005) and CHF (Ventura-Clapier *et al.*, 2004) or both (F.M. Franssen *et al.*, 2002b; Troosters *et al.*, 2004). The extent to which each of these factors specifically contributes to the exercise intolerance of patients remains unclear. The fact that similar skeletal muscle alterations are seen in both chronic lung and

heart diseases point to the involvement of a similar impairment in oxygen delivery common to both conditions although as a result of a different mechanism.

3.2.1. Skeletal muscle wasting in COPD and CHF

Experimental evidence concur to show reductions in lean body mass in COPD and CHF (ATS & ERS, 1999; Filippatos *et al.*, 2005; H. R. Gosker et al., 2000). Fat free mass measurements in both diseases were 11-34% lower when compared to that in healthy control groups (F. M. Franssen *et al.*, 2005; H R. Gosker et al., 2003; Jagoe & Engelen, 2003; Minotti *et al.*, 1993; Schulze *et al.*, 2004). Only one study compared simultaneously the extent of muscle atrophy in aged-matched COPD and CHF patients in comparison to aged-matched control subjects. Results show that moderate to severe COPD and CHF exhibited an equal reduction of 11% in fat free mass assessed by bioelectrical impedance in comparison to the control group (H R. Gosker et al., 2003). It must be recognized however that not all studies present patients with similar disease severity, which limits the possibility to generalize on this issue.

Results of fat free mass measurements obtained from assessment of body composition, magnetic resonance imaging or dual emission of X-ray absorptiometry show that a reduced muscle mass may be present in 21 to 49% of mild to severe COPD patients compared with healthy age-matched controls (Debigaré et al., 2001; Engelen *et al.*, 1994; Jagoe & Engelen, 2003; A. M. Schols *et al.*, 1993). Results also show a wide distribution of lean and fat mass which may be related to disease severity such that cachexia i.e. low fat free mass and low total body mass index is more prevalent in more advanced disease state (A. M. W. J. Schols *et al.*, 2005).

In CHF, there is little quantitative direct evidence of the prevalence in reduction in fat free mass in relation to disease severity or its evolution. Indirect evidence of reduced fat free mass, such as reduced body weight or BMI, is more

prominent in more advanced stages of disease (Filippatos *et al.*, 2005). Such evidence of muscle wasting has been reported to be present in 12-16% of CHF outpatients (Anker *et al.*, 2003; Anker *et al.*, 1997a) and up to 47-68% in severe CHF patients when compared to healthy aged-matched control groups (Adams *et al.*, 1999; Filippatos *et al.*, 2000; D. M. Mancini *et al.*, 1992). In addition, a cohort study of 1929 CHF patients class I-IV followed over a two years period revealed that there is an increase in the prevalence of non-intentional weight loss overtime, such that in 12% of the subjects experienced non-intentional weight loss greater that 6% at 9 months *vs* 34% of the subjects at 48 months (Anker et al., 2003).

3.2.2. Skeletal muscle function in COPD and CHF

Fat-free mass is known to be a strong predictor of muscle strength (Gosselink *et al.*, 1996) Likely as a result of the reduced lean body mass found in both COPD and CHF patients, reduced muscle strength and endurance has been reported (F.M. Franssen et al., 2002b; H. R. Gosker et al., 2000; Serres et al., 1998). Studies of CHF patients have shown that fat-free mass is a strong predictor of exercise capacity in this population, presumably because of greater locomotor muscle strength (H R. Gosker et al., 2003; Senden *et al.*, 2004). However, it remains unclear whether the loss in fat-free mass alone could explain entirely the observed reduction in muscle strength. In an attempt to find an answer, Degens et al. carefully selected sedentary COPD patients with preserved fat free mass and compared maximal isometric voluntary quadriceps muscles strength to aged- fat free mass- and activity-matched control group. Results show that patients with moderate COPD with preserved fat-free mass (n=9) had a quadriceps muscles strength of approximately 400 N, which was not statistically different from the 450 N measured in the control group (n=9) (Degens *et al.*, 2005). Similarly, Franssen et al. recently investigated leg muscle function in COPD patients GOLD stage III with preserved fat-free mass and in COPD patients with similar disease severity but with reduced fat free mass relative to age- and sex-matched healthy control subjects. They found that isokinetic quadriceps strength was significantly

lower in fat-free mass depleted compared with non-depleted patients (F. M. Franssen et al., 2005). Together, these results suggest fat-free mass and deconditioning are involved in the reduction of muscle strength. It is well established that chronic disability introduces a negative spiral in which the disease factor negatively impacts on the ability to move which in turn leads to sedentarity and further debilitation. Because activities of daily living involve primarily the upper limb skeletal muscles, the selective assessment of strength and endurance of lower and upper limbs has been carried out in patients with chronic diseases compared to healthy controls.

Some studies have proposed to use force measurement of the adductor pollicis muscle to investigate strength impairment in both COPD and CHF. Results show no statistical difference between groups, such that twitch amplitudes measured by supramaximal magnetic stimulation is 6.5 N in COPD and 6.8 N in healthy aged-matched controls (W. D. Man *et al.*, 2003). Similarly in CHF, results show that isometric force production is not significantly different compared to healthy subjects (Buller *et al.*, 1991).

Other researchers have proposed to use the grip strength measured by maximal voluntary contraction with a handgrip dynamometer to investigate the strength of the upper limb skeletal muscle in both diseases. Handgrip strength in both COPD and CHF patients has been reported to be either normal (Degens et al., 2005; Heijdra *et al.*, 2003; Lavietes *et al.*, 2004) or about 20% (Andrews *et al.*, 1997; F. M. Franssen et al., 2005; Gosselink *et al.*, 2000) reduced compared to healthy aged-matched controls. Gosselink et al. results show the isometric peak handgrip muscle force to be 366 N in COPD and to be 466 N in healthy aged matched controls. Similarly, maximal voluntary handgrip force was 34kg in CHF patients class II-III *vs* 42 kg in healthy aged-matched controls (Andrews et al., 1997). Recently, Franssen et al. reported handgrip force reduction of the same magnitude in COPD patients. Results show the maximal handgrip force to be 32-35 kg in COPD and 41 kg in healthy aged-matched controls. On the other hand,

other studies showed reduction in handgrip strength, which was not statistical different between patient groups when compared to aged-matched control groups. Heijdra et al. reported handgrip strength to be 97% of predicted value in COPD patients and 106% of predicted value in aged-matched healthy controls (Heijdra et al., 2003). Similarly, Lavietes et al. results shows no statistical difference in handgrip strength in CHF, as mean handgrip strength was 114% of the predicted value in the CHF group and 125% of the predicted value in the healthy aged-matched control group (Lavietes et al., 2004).

In a more global perspective, many investigations have examined leg strength using either isometric or isokinetic knee extension and measured vastus lateralis strength. Hamilton and colleagues in a very large study of 4617 subjects showed that patients with mild to severe chronic respiratory or cardiovascular disease had on average a quadriceps muscle strength 20-30% lower of that in healthy aged-matched controls (Hamilton *et al.*, 1995). Results also show that a two-fold decrease in muscle strength was associated with a 1.4 to 1.6 fold decrease in work capacity compared to aged-matched control subjects (Hamilton et al., 1995). Similar findings are reported in a study done recently by Gosker et al. where maximal isokinetic muscle strength was assessed as peak torque in the quadriceps of COPD, CHF and healthy aged-matched controls. Results showed that the quadriceps strength was 84 Nm in CHF, 85 Nm in COPD and 118 Nm in controls (H R. Gosker et al., 2003). Other researchers reported comparable reduction in quadriceps strength in patients with moderate to severe COPD and CHF disease (Anker *et al.*, 1997b; Bernard *et al.*, 1998; Gosselink et al., 2000; Hamilton et al., 1995; Lipkin *et al.*, 1988; W. D. Man *et al.*, 2005; W. D. Man et al., 2003; Schulze et al., 2004).

Although, the upper body muscle function seems to be somewhat better preserved than the lower body muscle strength, such inference is dubious since upper and lower limb strength measuring tools are not easily comparable. A clear

explanation for the reduced skeletal muscle force in patients with chronic diseases has still not been provided.

3.2.3. Skeletal muscle cells in COPD and CHF

Results from histological and gel electrophoresis analysis of skeletal muscle biopsies in the vastus lateralis of moderate to severe COPD and CHF patients exhibit a lower percentage of type I (slow twitch, oxidative) fibers combined with a higher percentage of type II (fast twitch, glycolytic) fibers, with a reduction in muscle fiber size compared to healthy aged-matched controls (H. Drexler et al., 1992; F.M. Franssen et al., 2002b; Hildebrand *et al.*, 1991; Jakobsson *et al.*, 1990; Jobin *et al.*, 1998; Lipkin et al., 1988; F. Maltais *et al.*, 1999; D. M. Mancini *et al.*, 1989; Satta *et al.*, 1997; Schaufelberger *et al.*, 1995; M. J. Sullivan *et al.*, 1997; M. J. Sullivan et al., 1990; Whittom, 1998).

This shift in fiber type is accompanied by a decrease in oxidative metabolism and an increase glycolytic activity in peripheral muscles of both diseases. There is accumulating evidence of a decrease in oxidative enzyme markers such as citrate synthase and succinate dehydrogenase in the locomotor skeletal muscles of COPD and CHF, with a concomitant increase in glycolitic enzymes such as hexokinase and phosphofructokinase (Clark AL, 1996; Serres et al., 1998). Because, these enzyme activities depend largely on the fiber type, it is likely that it may be related to the shift in fiber type distribution (H. R. Gosker et al., 2000). Marking of skeletal myocytes for the presence of apoptosis using terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling showed the vastus lateralis of patients with class I-III CHF to exhibit apoptosis 47% of myocytes. None of the healthy aged-matched control subjects had evidence of apoptosis suggesting that muscle wasting is also present at the cellular level (Adams et al., 1999). Most interestingly, the maximal cycling exercise capacity was much lower in those patients in which muscle apoptosis was present (12.0 ± 3.7 ml•kg•min^{-1}), compared to the apoptotic-negative patients (18.2 ± 4.4 ml•kg•min^{-1}) (Adams et al., 1999).

Similar enzymatic and fiber type changes in muscle physiology and structure with disuse and aging are well documented (Fitts *et al.*, 2000; Stein & Wade, 2005). In cases of microgravity, such as prolonged bed rest and human space flight, skeletal muscle fibers undergoes an adaptive response where muscle fibers type I and II become atrophied and where there is a decrease in the expression of type I fibers and an increase in the proportion of type II fibers (Berg *et al.*, 1997; Fitts *et al.*, 2001). On the other hand, it is commonly accepted that ageing leads to preferential type II fiber atrophy leading to an increase percentage of type I fibers in older adults (Lexell, 1995; G. N. Williams *et al.*, 2002). This observation is in opposition of the fiber type shift currently observed in both COPD and CHF muscle fibers. Despite being two diseases that are often seen in older individuals, it seems controversial that the remodelling in skeletal muscle fibers occurs in the opposite direction (F. M. Franssen et al., 2005). It appears likely however that the histological pattern may vary with the stages of ageing such that type II fiber atrophy may only occur in advanced aging whereas the samples of CHF and COPD patients typically range in age between 50 and 65 years old.

Results from studies that examined the capillary density and the capillary to muscle fiber ratio in COPD and CHF patients have been reviewed by Gosker et al. and Franssen et al (F.M. Franssen et al., 2002b; H. R. Gosker et al., 2000). In COPD patients the ratio has been reported as normal (Whittom, 1998) or reduced (Jobin et al., 1998). In a recent study by Saey et al., capillary to fiber ratio was lower in the vastus lateralis muscle of COPD patients classified as fatiguers (n=22) compared with the non-fatiguers subgroup (n=10) of patients (Saey *et al.*, 2005). Patients were classified as fatiguers when post-exercise quadriceps twitch force reduction was greater than 15% of resting values. These data suggests that perhaps a lower capillary to fiber ratio contributes to the lower exercise tolerance of "fatiguers".

Most studies in CHF patients demonstrated a reduction of capillary to fiber ratio of about 20% and no difference in capillary density when compared to aged-matched controls (Lipkin et al., 1988; Schaufelberger et al., 1995, 1997; A. D. Williams *et al.*, 2004) and also when compared to sedentary aged-matched controls (Duscha *et al.*, 2002). However, two studies reported a decreased in capillary density (H. Drexler et al., 1992; Duscha *et al.*, 1999), while one study reported a higher capillary density (D. M. Mancini et al., 1989). Despites similar disease severity within studies, capillary to fiber ratio and capillary density data in COPD and CHF remain contentious. These discrepancies could reflect the possibility that these changes may only be seen months after initiation of the disease process, which was not taken in consideration in theses studies.

3.2.4. Skeletal muscle bioenergetics in COPD and CHF

In the past decade, much ^{31}P-nuclear magnetic resonance spectroscopy metabolic and bioenergetics data became available on skeletal muscle metabolism in patients with COPD or CHF. This approach enables direct and non-invasive assessment of variations in muscle concentrations of adenosine triphosphate, adenosine diphosphate, phosphocreatine and inorganic phosphate during repeated contraction of an isolated muscle mass. At rest, these concentrations in patients with COPD and CHF are not different from to those of healthy control subjects (F.M. Franssen et al., 2002b). In moderate to severe COPD and CHF patients, an increase in the rate of depletion of intramuscular phosphocreatine is observed in the calf muscles during submaximal dynamic plantarflexion exercise compared to aged-matched controls (Kemp *et al.*, 1996; D. M. Mancini et al., 1989; Wuyam *et al.*, 1992). This may be taken to reflect an enhanced phosphate potential which acts to enhance mitochondrial respiration to maintain a given oxygen flux. Furthermore, during recovery after exercise there is a prolonged half-life of phosphocreatine rephosphorylation in COPD (Thompson *et al.*, 1993) and CHF (Tada *et al.*, 1992) compared to aged-matched control groups, which could suggest a reduced turnover rate of clearance.

Chati et al. compared the ^{31}P-nuclear magnetic resonance spectra of patients with CHF class II-III during fixed workloads of calf muscle exercise with both sedentary and trained aged-matched controls (Chati *et al.*, 1996). Results show that the trained controls had a slower phosphocreatine depletion rate and lower adenosine diphosphate levels during exercise compared to the healthy sedentary controls and the CHF subjects (Chati et al., 1996). Results show no significant difference in these parameters between the CHF patients and the sedentary healthy control group, again suggesting that deconditioning itself plays a role in the energy metabolism in skeletal muscle (Chati et al., 1996).

There is a current debate as to whether these muscle alterations are simply the consequence of a sedentary lifestyle associated with chronic disease and the concomitant deconditioning or whether there is an actual muscle dysfunction where intrinsic abnormalities would be induced by the chronic disease. Other possible contributors to the skeletal muscle alteration such as oxidative stress, hypoxia, nutritional status and medication are currently under investigation (Couillard & Prefaut, 2005).

3.3. Role of ventilation and gas exchange in the exercise intolerance in COPD and CHF

Respiratory function is of course altered in COPD. There is however growing evidence that this respiratory dysfunction may co-exist with the primary heart disease in CHF to contribute to their exercise intolerance. This section will review the ventilatory pattern and the exercise gas exchange responses in patients with COPD and CHF.

3.3.1. Ventilatory and gas exchange response to acute dynamic exercise in healthy individuals

3.3.1.1. Normal ventilatory response to acute dynamic exercise

Minute ventilation (V_E) refers to the volume of air moved in and gas moved out of the lungs per minute. The normal minute ventilation response to incremental exercise is a linear increase from the onset of exercise up to a point called ventilatory threshold, after which V_E increases exponentially with regards to VO_2. Hyperventilation is defined as a ventilation regime in excess of that of metabolic requirements or VO_2. During a progressive incremental maximal exercise, hyperventilation is thus typically found beyond the point of ventilatory threshold, which defines an exaggerated increase in VE for the increase in VO_2. As a result of hyperventilation of the alveolar spaces, more CO_2 is expelled through expiration resulting in a fall in the alveolar CO_2 partial pressure. The anatomic dead space (V_D) tends to increase slightly during incremental exercise as a result of bronchodilation and recruitment of additional airway (Jones, 1997). Yet, the exercise-induced increase in V_D is negligible compared to the large increase in V_T. As a result, the ratio of V_D over V_T diminishes with incremental exercise and alveolar ventilation is not compromise.

Minute ventilation generally increases from resting values of approximately 5 to 6 $L \cdot min^{-1}$ up to 100 to 150 $L \cdot min^{-1}$ at peak during maximal incremental exercise in healthy individuals (Brooks *et al.*, 2005). As exercise intensity increases, V_E approaches but does not reach maximal voluntary ventilation (MVV), which can be estimated as 35 or 40 x FEV_1 ($L \cdot min^{-1}$) in healthy individuals (T.G. Babb, 1999). The difference between MVV and maximal exercise V_E is termed respiratory reserve volume. At peak exercise, healthy asymptomatic individuals exhibit a respiratory reserve volume between 20 to 40% of MVV and ratios of maximal V_E over MVV between 60 to 80% (Wasserman *et al.*, 1987). A ratio of maximal V_E over MVV above 90% often indicate the presence of ventilatory constraints (T.G. Babb, 1999; Wasserman et al., 1987).

The exercise intensity-related increase in V_E is caused by an increase in both tidal volume (V_T) and breathing frequency (Fb). At the start of a progressive maximal exercise both V_T and Fb increase proportionately. Breathing frequency increases steadily in a linear pattern from rest up to the ventilatory threshold, typically observed at 60-75% VO_{2max} (P.O. Astrand *et al.*, 2003), where thereafter the increase in Fb follows a sharper increase. Generally, the Fb increases from 10 to 20 breaths per minute at rest, up to 40 to 45 breaths per minute at maximal exercise in healthy normal individuals (P.O. Astrand et al., 2003). As Fb increases with increasing exercise demands, the total respiratory time reduces. The inspiratory time falls from resting values of approximately 1.6 seconds to 0.7 seconds at peak ventilation in healthy individuals during maximal cycling exercise, whereas expiratory time falls to a greater extent, in a curvilinear manner from 2.2 seconds to 0.5 (Brooks et al., 2005).

During incremental exercise as exercise intensity increases, V_T reaches a plateau and the continued increase in VE is essentially related to the increase in Fb (Brooks et al., 2005). Tidal volume during quiet breathing typically represents 15% of the vital capacity of healthy normal individuals, while at peak exercise, the increase in tidal volume reaches approximately 50-60% of vital capacity (Vogiatzis *et al.*, 2005), which represents about 450 ml at rest up to approximately 3 litres at peak exercise capacity. Tidal volume is the difference between end-inspiratory lung volume (EILV) and end-expiratory lung volume (EELV). Assuming that the total lung capacity (TLC) remains constant during exercise, measuring the inspiratory capacity during steady state exercise allows the measurement of the operating lung volumes. In healthy individuals, the increase in V_T seen during incremental exercise is accounted for both by an increase in the EILV and a decrease in the EELV. End-inspiratory lung volume typically increases linearly during maximal incremental exercise in individuals without ventilatory limitations, approaching but never reaching total lung capacity (T.G. Babb, 1999; McClaran *et al.*, 1999; O'Donnell & Webb, 1993a; Sharratt *et al.*, 1987). The increase in end-inspiratory lung volume from rest to peak exercise

represents approximately 20 to 30% of total lung capacity; while there is a slight decrease in EELV of about 10 % of total lung capacity, or approximately 500ml on average (J. A. Alison *et al.*, 1998b).

3.3.1.2. Normal exercise gas exchange response

Ventilatory efficiency relates to both ventilation and the adequacy of gas exchange across the alveolar-capillary membrane or pulmonary diffusion. The pulmonary diffusion capacity generally increases two-fold from rest to peak exercise. Lung diffusion capacity is most frequently assessed by the single-breath-hold D_LCO technique. With increasing exercise intensity, D_LCO increases linearly from resting values of about 25 $mL \cdot min^{-1} \cdot mmHg^{-1}$ to approximately 50 $mL \cdot min^{-1} \cdot mmHg^{-1}$ at peak exercise (Hsia, 2000; Huang *et al.*, 2002).

During incremental exercise, exercise-induced hyperventilation results in an increase in alveolar O_2 partial pressure (P_AO_2), which leads to a widening of the alveolar-arterial O_2 gradient. At VO_{2max}, the alveolar-arterial O_2 gradient typically reaches 15 to 30 mm Hg. The alveolar-arterial O_2 difference may however be seen to contribute to ensure that PaO_2 is maintained during intensive exercise even with shorter pulmonary transit time (Dempsey, 1986; Dempsey & Wagner, 1999; Sharratt et al., 1987). Despite an exercise-induced hyperventilation, some healthy elite athletes show a significant fall in PaO_2 at near maximal exercise, which has been termed exercise-induced arterial hypoxemia (Dempsey & Wagner, 1999; Nielsen, 2003; Richards *et al.*, 2004). A clear explanation for the decrease in O_2 saturation is still lacking although potential contributors are a "relative hypo-hyper-ventilation", an excessively reduced pulmonary transit time, interstitial pulmonary oedema or micro lesions of small airways. A review of these factors is however beyond the scope of this thesis.

3.3.2. Ventilatory and gas exchange response to acute dynamic exercise in patients with COPD

COPD patients exhibit significant gas exchange limitations as a result of the expiratory flow limitation and the ensuing static lung hyperinflation. During exercise, many of these ventilatory and gas exchange limitations become amplified.

3.3.2.1. Ventilatory response to acute dynamic exercise in patients with COPD

The ventilatory response to incremental exercise of patients with COPD is similar to that of healthy individuals with an initial linear increase in V_E followed by a curvilinear exponential increase after reaching the ventilatory threshold. Peak exercise minute ventilation (V_{Epeak}) achieved by COPD patients is however significantly lower than that of healthy controls with V_{Epeak} values ranging from 20 to 80 $L \cdot min^{-1}$ (T. G. Babb et al., 1991; Neder et al., 2000; O'Donnell *et al.*, 2001a; Oelberg et al., 1998a). The extent of increase in ventilation may be related to the disease severity and the degree of expiratory flow limitation. Thus, in a study by Matthews *et al.* (1989), patients with moderate COPD exhibited a 4.3-fold increase in V_E compared to a V_{Epeak} that was 7 times resting V_E in control subjects. In more severe patients, O'Donnell and Webb (1993a) reported an increase in V_E from rest of only 2.6-fold. Ratio of V_E to MVV as high as 115% has previously been reported in COPD moderate to severe patients (O'Donnell & Webb, 1993b; Oelberg et al., 1998a; Turner *et al.*, 2004).

COPD patients also ventilate significantly less than controls for the same relative intensity of exercise in terms of percentage of peak VO_2 (Covey *et al.*, 1999; F.M. Franssen *et al.*, 2002a; Matthews et al., 1989; A Somfay *et al.*, 2001b). Mild to moderate COPD patients cycling at 50% peak VO_2 have similar

V_E to that of controls (Covey et al., 1999; Matthews et al., 1989). However at 75% of peak VO_2, these patients had significantly lower V_E than controls (61 ± 13 versus 80 ± 14 $L \cdot min^{-1}$, respectively) (Matthews et al., 1989). On the other hand, in more severe COPD patients, V_E is already significantly lower when cycling at 50% of peak VO_2 when compared to healthy aged-matched individuals (F.M. Franssen et al., 2002a).

The limited exercise-induced increase in V_E in patients with COPD results from their expiratory flow limitation, which alters the normal V_T and Fb pattern of response to exercise. A number of COPD patients already exhibit static hyperinflation at rest, thus already exhibit a reduced inspiratory reserve volume. These patients are thus limited in their ability to increase V_T during incremental exercise such that peak V_T is significantly reduced in COPD (Matthews et al., 1989; A. Somfay et al., 2001a). As shown by several studies, peak Fb does not appear to be significantly different in COPD patients compared to healthy control subjects (T.G. Babb & Rodarte, 1991; Matthews et al., 1989; Neder et al., 2000; O'Donnell *et al.*, 2001c; O'Donnell & Webb, 1993a). However, for a given relative submaximal exercise intensity, COPD patients exhibit an increased Fb and thus, the total respiratory time and more importantly, expiratory time is shorter in patients compared to controls (F.M. Franssen et al., 2002a; Matthews et al., 1989). An exaggerated submaximal exercise breathing frequency can partially compensate for the limited V_T. However, as a result of the ensuing decrease in expiratory time, the tachypneic response also contributes to lung hyperinflation. Thus, the reduced expiratory time, added to an already limited expiratory flow rate initiate a spiral where progressive air trapping arises. The volume of air trapped in the lungs increases above that under resting conditions (Pecchiari *et al.*, 2004) is referred to the dynamic hyperinflation volume. The progression of dynamic hyperinflation is reflected by the changes in operational lung volumes at the different exercise intensities. An increase in EELV above resting values indicates progressive air trapping during incremental exercise (O'Donnell, 2001). In the limited number of studies that have reported operating lung volumes from

rest to peak cycling exercise in COPD patient, results show a range of increases in EELV with changes ranging from one to seven % of TLC (Belman *et al.*, 1996; Gelb *et al.*, 2004; Martinez *et al.*, 1997; Murciano *et al.*, 2000; O'Donnell & Webb, 1993b; Sinderby *et al.*, 2001). As a result of static hyperinflation at rest, the baseline end-inspiratory lung volume (EILV) is shifted upward in patients as it corresponds to approximately 80% of total lung capacity in COPD compared to 60% in controls. In COPD patients a plateau in EILV is reached before peak exercise capacity is achieved; results show that EILV during submaximal steady state exercise of 50-80% of VO_{2peak} almost reach TLC, such that the IRV becomes very much reduced (Koulouris *et al.*, 1997; W. D. C. Man *et al.*, 2004; O'Donnell et al., 2001b; A. Somfay et al., 2001a).

3.3.2.2. Gas exchange response in patients with COPD

The greater physiological dead space, typical of emphysema or chronic bronchitis, remains elevated during incremental cycling exercise (Diaz *et al.*, 2001; Oelberg et al., 1998a; Palange *et al.*, 2000).

In COPD patients, the inappropriate gas exchange across the alveolar-arterial capillary membrane typically worsens during incremental exercise as reflected by the abnormal pattern of response of blood gases. The shorter pulmonary transit time coupled with an already reduced diffusion capacity of alveolar-capillary membrane is responsible for the abnormally widened alveolo-arterial O_2 gradient of COPD patients. The alveolo-arterial O_2 gradient typically exceeds 25mm Hg even at rest, and can reach up to 38 mm Hg at peak exercise in patients with severe disease (Oelberg *et al.*, 1998b). The increased gradient may be related to both an effect of hyperpnea and hypoxemia. In patients with COPD, PaO_2 which is already reduced at rest further decreases during exercise to values as low as 54 mm Hg in severe disease (Oelberg et al., 1998a; Oelberg et al., 1998b; Stewart & Lewis, 1986a). Consequently, the arterial oxygen saturation, or SaO_2, can fall to levels below 90% in patients during exercise.

3.3.3. Ventilatory and gas exchange response to acute dynamic exercise in patients with CHF

In CHF, the pulmonary response to exercise has not been fully examined. There is however growing evidence suggesting an abnormal ventilatory and gas exchange response in CHF patients during exercise.

3.3.3.1. Ventilatory response to acute dynamic exercise in patients with CHF

Figure 3 shows exercise minute ventilation in patients with mild, moderate or severe CHF. Results demonstrate that patients exhibit a higher V_E than healthy age-matched control subjects for any given level of VO_2 suggesting a hyperventilation response (J. Myers, Salleh A, Buchanan N, Smith D, Neutel J, Bowes E, Froelicher VF., 1992). However, the V_{Epeak} achieved by CHF patients at maximal exercise can be significantly lower than in healthy controls ranging from 29 to 65 $L \cdot min^{-1}$ (K. T. Weber et al., 1982; Witte *et al.*, 2003), which is in line with the reduced peak power output observed in these patients.. Figure 3 also shows that the most severe CHF patients have the most pronounced exaggeration in V_E response to exercise. The exaggerated ventilation serves to maintain PaO_2 as a result of the impairment oxygen delivery.

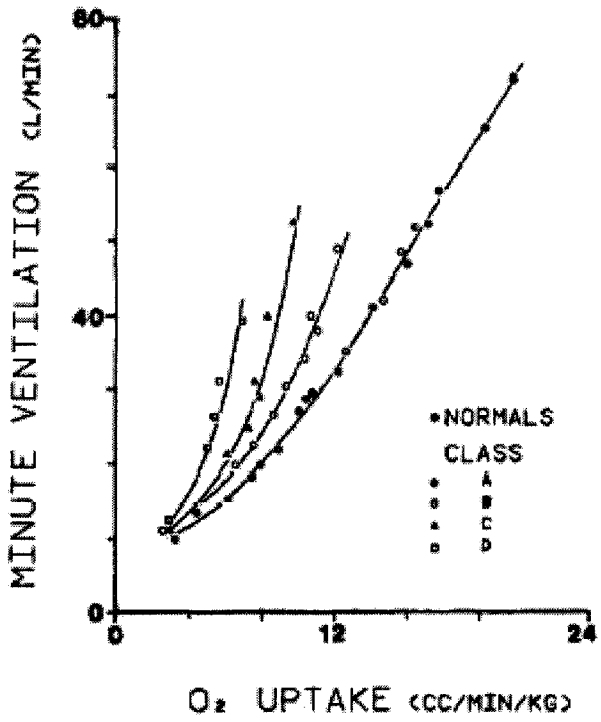

Figure 3: The relationship between V_E and VO_2 ($ml \cdot kg \cdot min^{-1}$) for the four NYHA functional classes of CHF patients, where class D represents the most severe patients (K. T. Weber et al., 1982).

In CHF, as opposed to COPD patients, V_{Epeak} approaches only 50 to 70% of MVV, which is similar to that of healthy controls. Thus even in most moderate to severe CHF patients the ventilatory reserve is usually well preserved (M. J. Sullivan, Higginbotham MB, Cobb FR., 1988; K. T. Weber et al., 1982).

The relation of Fb and V_T to total V_E response in CHF has been described only in a limited number of studies (M. J. Sullivan, Higginbotham MB, Cobb FR., 1988; Witte et al., 2003). In general, the hyperventilatory response observed in CHF patients follows a normal pattern of increase, such that during incremental exercise at low level of work the increase in V_E is mainly due to an increase in V_T and at higher workloads, it is the Fb that becomes mainly responsible for the increase in V_E(Witte et al., 2003). CHF patients ventilate

significantly more than controls for the same relative intensity of exercise which may be explained by a higher Fb and a lower V_T compared to normal aged-matched individuals or CHF patients with a milder disease severity (K. T. Weber et al., 1982). As a result of the reduction in absolute peak work capacity, the V_{Tpeak} in moderate CHF patient ranges 1.6 to 1.8 L, which is significantly reduced compared to healthy aged-matched controls who usually have a V_{Tpeak} of 2.5-2.8 L (Johnson BD, 2000; J. Myers, Salleh A, Buchanan N, Smith D, Neutel J, Bowes E, Froelicher VF., 1992; Witte et al., 2003). Maximal V_T occupies approximately 40 to 50% of vital capacity in mild to moderate CHF patients (K. T. Weber et al., 1982). The mechanisms causing the increase in ventilation to be achieved by an increase in Fb more that V_T in CHF are unknown. It remains to be determined if the reduced V_{Tpeak} observed in CHF patients is linked to an inability to modify the operating lung volumes to match the exercise intensity or if it is simply reflective of their higher Fb and shorter respiratory time.

The operating lung volumes and its relation to exercise intolerance has not been well characterized in CHF patients. Despite trivial differenced in resting lung function between the CHF and aged-matched control group, flow-volume loops during incremental exercise have been shown to be evidence for expiratory flow limitation in the CHF patients (P. Agostoni *et al.*, 2002). Furthermore, it has been shown that the exercise induced tachypnea during exercise in CHF was inversely correlated to dynamic resting lung compliance, suggesting that lung stiffness may lead to a preferential increase in Fb as opposed to V_T as a strategy to increase VE (P. Agostoni et al., 2002). In the few studies that reported EELV measurements in CHF, EELV did not decrease with increasing exercise intensity and either stayed the same (Ben-Dov *et al.*, 1992; Johnson BD, 2000; Schroeder, 2003) or showed a slight increase (O'Donnell *et al.*, 1999) compared to healthy aged-matched controls, suggesting the occurrence of dynamic hyperinflation. Collectively, data may be taken to suggest that expiratory flow limitation and dynamic hyperinflation may be become present in moderate to severe CHF patient during acute exercise.

3.3.3.2. Gas exchange response to acute dynamic exercise in patients with CHF

As recently reviewed by Guazzi, gas exchange both at rest and during exercise may be impaired in a number of CHF (M. Guazzi, 2003). At rest, DL_{CO} in moderate to severe CHF patients was found to be on average 78% of predicted values with a range of 63 to 90% (Bussotti *et al.*, 2004; M Guazzi et al., 2001). Smith et al. measured carbon monoxide transfer factor and pulmonary blood flow by a rebreathing technique in CHF patients and control subjects at rest and during steady-state cycling at 30 W (A. A. Smith et al., 1999). Results show that the CHF patient group had a lower diffusion for a given blood flow both at rest and during exercise. Results also show that both CHF patients and control subjects were able to raise carbon monoxide transfer factor (TLCO) and pulmonary blood flow during steady-state cycling at 30W, suggesting that patients with CHF are able to recruit reserves of diffusion capacity. Lung diffusion capacity measurements have never been reported during high intensity exercise in CHF. However, given that the increase in cardiac output may be limited in severe patients during incremental exercise, the ability to recruit functional reserve of diffusion capacity might possibly be impaired at high intensity exercise. Furthermore, the reduction in diffusion capacity observed in some patients with CHF may be related to the presence of various degrees of pulmonary interstitial oedema resulting from of a rise in pulmonary capillary pressure secondary to an elevation of left atrial pressure. For instance, Agostoni et al. measured diffusion capacity (DLCO), capillary volume (V_C) and alveolar-capillary membrane conductance (D_M) in twenty CHF patients (n=10 moderate and 10 severe) and 10 age-matched controls at rest, two and 60 minutes after a peak cycling incremental exercise. Results showed reductions in D_M and in D_M / V_C with a concomitant decrease in DLCO immediately after exercise despite an increase in V_C in both modetate and severe CHF patients. Results also show that 60 minutes post-exercise values returned to pre-exercise resting values, suggesting exercise-induced impairment in DLCO in CHF seems to be related to transient pulmonary oedema since capillary recruitment was adequate and membrane conductance was temporarily

diminished. These findings are reinforced by the fact that the reductions were more pronounced in the most severe patients group (P. Agostoni et al., 2003). Similar findings showing that the TLCO and TLVO/VA were significantly reduced immediately after exercise had previously been reported in moderate CHF compare to age-matched controls (Messner-Pellenc *et al.*, 1995), however membrane conductance and capillary volume was not measured .

Patients with mild as well as severe CHF have been shown to exhibit a higher V_D/V_T compared to healthy aged-matched controls subjects during both submaximal and peak exercise (Clark *et al.*, 1997; J. Myers, Salleh A, Buchanan N, Smith D, Neutel J, Bowes E, Froelicher VF., 1992; M. J. Sullivan, Higginbotham MB, Cobb FR., 1988; Wasserman *et al.*, 1997). The higher measured physiological dead space in these patients is compatible with their reduced possibility for increasing cardiac output during exercise as well as a potential pulmonary interstitial oedema, both of which alter the ventilation: perfusion ratio. However, despite their higher dead space, CHF patient typically maintain PaO_2 and SaO_2 within normal range up during exercise including peak work intensity because of their ability to compensate by an exaggeration in ventilation (M. J. Sullivan, Higginbotham MB, Cobb FR., 1988). $PaCO_2$ typically remains the same or declines modestly from rest to peak exercise in moderate to severe CHF patients, likely driven down by a hyperventilatory drive, which could also contribute to the elevation of the V_E/VCO_2 slope (M. J. Sullivan, Higginbotham MB, Cobb FR., 1988; Wasserman et al., 1997). The V_E/VCO_2 ratio is often considered an index of ventilatory efficiency. In healthy individuals, normal V_E/VCO_2 ratio is 33 L/min or less at peak exercise, while in CHF patients, values as high as 71 have previously been reported (Fink et al., 1986). Whether the hyperventilatory response in CHF results from the increased V_D alone is presently a question of debate. The debate results from evidence obtained using animal studies suggesting that there may also be dysregulation of the baroreflexes well as the chemoreflexes (Ponikowski & Banasiak, 2001).

3.4. ROLE OF CIRCULATORY FACTORS IN THE EXERCISE INTOLERANCE IN COPD AND CHF

As dictated by the Fick principle for oxygen transport, the increase in exercise-induced increase in VO_2 is met through an increase in cardiac output (Qc) and oxygen extraction by the peripheral working skeletal muscles. Measurements of exercise VO_2 and Qc allow to examine the central and peripheral exercise responses of the oxygen transport system: Qc ($L \cdot min^{-1}$) = VO_2 ($L \cdot min^{-1}$) / a-vO_2 difference (ml per L blood)

Thus, the Fick equation provides the opportunity to identify a potential central or peripheral source of limitation in the oxygen transport system

3.4.1. Normal central circulatory response to acute dynamic exercise

The Qc response during exercise is affected by age, gender, and conditioning status. In healthy persons, the Qc, which is the product of heart rate (HR) and stroke volume (Qs) increases in a quasi-linear fashion during incremental exercise with maximal upright exercise values being typically four to six fold resting values. In general, in healthy young and older adults, Qc can be estimated as Qc ($L \cdot min^{-1}$) = 5.5 [VO2 ($l \cdot min^{-1}$)] + [0.06 · body mass (kg)] with a 95% confidence interval of ± 2 $L \cdot min^{-1}$ (P. O. Astrand *et al.*, 1964; Jones, 1997; Sun *et al.*, 2001).

The increase in HR is closely adjusted to O_2 consumption and power output through stimulation of the sinus node by sympathetic nerve activation. Regulation of the HR is partially controlled through retro action from central command as well as peripheral mechanical receptors, chemical receptors and baroreceptors. Heart rate increases linearly during incremental exercise up to a plateau, which is the maximal heart rate and can be estimated using the following formula: HR = 208 – (0.7 · age) ±10 beats/min (Tanaka *et al.*, 2001).

The increase in stroke volume results from a combined increase and decrease in left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) respectively. It is well known that the Frank-Starling law of the heart and the myocardial contractility contribute to the kinetics of changes in LVEDV and LVESV. During light exercise intensities, the increase in ventricular filling increases mainly through the contribution of the Frank-Starling mechanism. Thus the increase in EDV depends mainly on ventricular filling as a result of venous return due to the enhanced contributions of muscle pump and respiratory pump. During incremental exercise there is a continued decrease in ESV, which may be related to an increase in ventricular contractility as measured by ventricular ejection fraction (Cohen-Solal *et al.*, 1999). Hence, the exercise induced-increase in stroke volume is achieved through the contribution of both the Starling law of the heart and an increase in myocardial contractility mediated by sympathetic stimulation to the ventricular myocardium. The increase in stroke volume is however also affected by the extent of ventricular afterload. While, a decrease in total peripheral resistance and thus a decrease in ventricular afterload is generally observed during dynamic exercise, an exaggerated ventricular afterload due to valvular disease or hypertension can compromise the extent of stroke volume increase.

It has traditionally been accepted that in healthy individuals, Qs increases in a curvi-linear fashion in function of power output to reach a maximal value corresponding to 1.5 times resting values. Maximal stoke volume is usually reached at a power output corresponding to 30 to 50% of VO_{2peak}, such that a plateau is reached despite the continuing increase in power output. However, recent data obtained in endurance trained male and female subjects showed that Qs did not reach a true plateau in response to incremental cycling exercise to maximum (Ferguson *et al.*, 2001; Gledhill *et al.*, 1994; Zhou *et al.*, 2001). Despite the reduction in filling time due to progressive acceleration in heart rate, these athletes showed an accelerated diastolic relaxation time, which allowed greater ventricular filling and in turn result in an increased ejection fraction. Weather this

phenomenon is the result of a chronic adaptation to exercise training or is a result of a natural selection factor contributing to the success of these high performance athletes remains unclear.

3.4.2. Central circulatory response to acute dynamic exercise in COPD and CHF

The reduced aerobic capacity common to both patients with COPD and CHF is attributable to inadequate O_2 supply to skeletal muscles secondary to impaired cardiac output or impaired gas exchange. In both chronic conditions there exist some measurements of circulatory response to exercise either during peak incremental exercise or submaximal steady state cycling. Considering the importance of the circulatory factor in exercise capacity, there is surprisingly a limited number of data on exercise cardiac output measurements or its determinants during exercise, especially in COPD patients.

3.4.2.1. Central circulatory response to acute dynamic exercise in COPD

In COPD, it has long been suggested that exaggerated respiratory flow requirements or pulmonary pressures could influence exercise ventricular filling and limit the exercise cardiac output. It is well documented in physiological studies that the respiratory cycle has an impact on cardiac function (De Cort *et al.*, 1993; Guz, 1987; Harms *et al.*, 1998; Kim *et al.*, 1987; Peters *et al.*, 1989; Pinsky *et al.*, 1986; Robotham *et al.*, 1978), in which right ventricular filling as well as left ventricular preload and afterload are consistently modified during the respiratory cycle, notably when the breathing pattern or the respiratory constraints are experimentally changed. However, it is difficult to extrapolate those data to the patients for whom the situation is much more complex. It has been suggested that the dynamic hyperinflation commonly seen in some patients with COPD during exercise may compromise the normal increase in stroke volume on account of an impairment in end-diastolic ventricular filling (O'Donnell, 2001; Sietsema, 2001). Although alterations to ventricular diastolic and systolic functions clearly

contribute to the limitation in patients with cardiac failure, the repercussions of a chronic obstructive lung disease on the central circulatory adaptations to dynamic exercise remain incompletely documented. Results obtained under resting conditions suggest that a diastolic impairment could exist in patients with COPD, which could contribute to an abnormal exercise response. The possibility of a concomitant systolic dysfunction has however not been excluded (Boussuges *et al.*, 2000; Scharf *et al.*, 2002).

To date, there is only a limited number of studies that measured Qc during incremental and submaximal exercise in patients with COPD. Most of these studies measure Qc at peak cycling in COPD patients. The cardiac output was measured using either the direct Fick method (Charloux *et al.*, 2000; Ježek *et al.*, 1973; Light *et al.*, 1984; Mahler *et al.*, 1985; Minh *et al.*, 1981; Minh *et al.*, 1979; Oelberg et al., 1998a; Stewart & Lewis, 1986b), thermodilution (Raffestin *et al.*, 1982), radionuclide ventriculography (Morrison *et al.*, 1987; Oelberg *et al.*, 1998b) or CO_2-rebreathing (Bogaard *et al.*, 1997). No studies reported measurements of Qc done at multiple exercise intensities. Peak cardiac output values obtained in COPD are lower compared to aged matched controls (Oelberg et al., 1998a; Oelberg et al., 1998b). However, it must be noted that the lower absolute values of cardiac output are in line with the lower peak oxygen uptake. A better index of the normality of the cardiac output exercise response lies in the kinetics of increase of Qc in relation to oxygen uptake, which has never been examined.

End-diastolic and end-systolic ventricular volume changes from rest to dynamic exercise in patients with COPD have never been reported. However, Qs at peak exercise has been reported in a limited number of studies. In these studies, the fold-increase in Qs in COPD patients from rest to peak exercise were reported to be within the normal range (Bogaard et al., 1997; Light et al., 1984; Minh et al., 1979; Morrison et al., 1987). Several studies however have measured stroke volume during exercise in patients with cystic fibrosis. These patients exhibit

reduction in pulmonary function comparable to those of COPD subjects. It has been shown that the increase in stroke volume during exercise is impaired in the majority of these patients, despite having a normal or slightly decreased cardiac output response (Benson *et al.*, 1984; Perrault *et al.*, 1992; Pianosi & Pelech, 1996). These patients have also been shown to exhibit dynamic hyperinflation during incremental arm and cycling exercise, especially moderately severe patients who have an expiratory flow limitation (J. Alison *et al.*, 1998a). It is thus possible that stroke volume could also be reduced in patients with COPD. On the other hand, the resting heart rate of patients with COPD has consistently been reported to be elevated as compared to age-matched healthy controls (Bartels *et al.*, 2003). This could be attributed at least in part to the effects of $beta_2$-agonists used in the treatment of COPD, which are known for their cardio-accelerating effect (Matthay, 1987).

Results from the few studies to date that measured central circulatory factors during exercise in COPD may be taken to suggest that the central circulation may not be a major limiting factor in the exercise response of COPD, although it may be a contributing factor. On the other hand, the extent to which dynamic hyperinflation may in some cases compromise the cardiac output response to moderate or more intense exercise, remains to be examined.

3.4.2.2. Central circulatory response to acute dynamic exercise in CHF

Over the last decade, a limited number of studies only have examined exercise cardiac output in CHF. Most of these studies measured Qc at peak cycling in CHF patients measured using either the direct Fick method (Gordon *et al.*, 1999; Maurer *et al.*, 2003; Tanabe *et al.*, 2002; Tanabe *et al.*, 2000; Yamabe *et al.*, 1997), dye-dilution (Matsumoto *et al.*, 2000), thermodilution (P. Agostoni et al., 2005; Butler *et al.*, 1999; Wilson *et al.*, 1996), or CO_2-rebreathing (P. Agostoni et al., 2005; P. G. Agostoni *et al.*, 2000; S. G. Williams *et al.*, 2001). Only three studies reported measurements of Qc done at multiple exercise

intensities (P. Agostoni et al., 2005; P. G. Agostoni et al., 2000; Yamabe et al., 1997). CHF patients may have less than 50% of the maximal cardiac output of a healthy person at peak exercise. When CHF patients are compared to healthy control subjects at the same level of VO_2 the cardiac output is lower (Wilson & Ferraro, 1983). On the other hand, the slope of the relationship between Qc and VO_2 has been shown to remains normal in moderate to severe CHF patients (D. Mancini *et al.*, 1996; Wilson *et al.*, 1995).

In general, the inability to increase cardiac output is related mainly to a lower maximal heart rate achieved at a lower workload and the minimal increase in stroke volume (M. J. Sullivan & Cobb, 1992). The abnormal Qs kinetics to exercise in CHF patients results from a reduction in the ability to modify its determinants, ESV and EDV. End-systolic volume does not decrease and in fact, it generally increases in the most severe CHF patients during incremental exercise as a result of the combined effects of reduced myocardial contractile properties of the left ventricule and increased afterload (Shen *et al.*, 1985). As ESV increases during incremental exercise CHF in patients, the only way to increase or maintain Qs is to increase EDV. However, it has been shown CHF patients have a reduced increase in EDV during incremental exercise compared to age-matched controls as a result of impaired filling as a result of a less accelerated left ventricular relaxation than in normal subjects (Cohen-Solal et al., 1999). This is why during incremental exercise, Qs increase less, or in the most severe CHF patients, tends to fall.

3.4.3. Peripheral blood flow distribution during acute dynamic exercise

In healthy individuals, as much as 85 percent of the cardiac output is redistributed to the working skeletal muscle during high-level exercise. Recently, there has been much interest is examining the limitation in blood flow supply to working muscle in individuals with chronic disease. A thorough review of limitation in blood flow distribution is beyond the scope of this thesis but is

provided in several recent review papers (Cohen-Solal et al., 1999; Harms & Dempsey, 1999; Richardson *et al.*, 2000)

In COPD for example, it has been proposed that an exaggerated proportion of the central blood flow might be diverted to the respiratory muscles on account of the elevated breathing requirements (Aliverti & Macklem, 2001; Sietsema, 2001). The concept of respiratory steal is not new but its contribution to exercise limitation in health or disease has not been thoroughly investigated. In healthy young individuals, Harms et al. (Harms *et al.*, 1998) showed a reduction in femoral artery blood flow during maximal cycling when blood flow requirements to the respiratory muscles were increased on account of breathing with added resistance. This phenomenon was however not found when the experiment was repeated during submaximal exercise (Wetter, 1999).

Considering the exaggerated ventilatory requirements of both patients with COPD and CHF during exercise, the question currently examined is whether a respiratory steal phenomenon could contribute to the exercise limitation of these patients and to what extent redistribution to respiratory blood flow at the expense of working muscle exists in patients with marked pulmonary hyperinflation. Data thus far shows evidence of inadequate blood flow to skeletal muscles secondary to impaired cardiac output and impaired peripheral vasodilatory capacity is present in patients with CHF (M. J. Sullivan *et al.*, 1989). For example, it has been shown in moderate to severe CHF patients, that leg blood flow was reduced during peak two-legged exercise compared with one-leg exercise, which suggest that leg blood flow may also be limited during exercise requiring a large muscle mass involvement (Magnusson *et al.*, 1997). It has also been shown that vascular resistance in the muscle fails to decrease normally during exercise in CHF patients (M. J. Sullivan et al., 1989). Data thus far suggests that leg blood flow may also be limited in a number of COPD patients during exercise requiring a large muscle mass involvement (F. Maltais *et al.*, 2001a). For instance, a plateau in leg blood flow measures using thermodilution has been observed despite increasing cycling workrates in six out 14 moderate to severe COPD patients, suggesting impaired redistribution of blood flow in these patients (Simon, 2001).

Similarly, when exercise ventilation was decreased in these patients by the administration of supplemental oxygen, the mean femoral oxygen delivery, calculated from the arterial oxygen content and the femoral blood flow, was increased (F Maltais *et al.*, 2001b). Whether this phenomenon follows from a redistribution of cardiac output to the respiratory muscles, or is the result of a reduced skeletal muscle capillarization in these patients remains to be determined.

4. POSITION OF THE PROBLEM

As may be seen from this brief overview of the literature, reduced maximal exercise capacity is the hallmark of patients with both COPD and CHF. Recent data showed that patients with CHF may have a restrictive ventilatory defect and reduced lung diffusion capacity. The extent to which pulmonary limitation in CHF also contributes to the impaired exercise oxygen delivery and exercise intolerance needs to be further examined. Similarly, the role of circulatory factors in the exercise intolerance of patients with COPD has not been closely studied. Inasmuch as lung hyperinflation may affect the intrathoracic pressure and thus could impair venous return and ventricular filling, lung hyperinflation possibly could impact on the exercise cardiac output in COPD. However, the extent to which dynamic hyperinflation influences cardiac output response to exercise has not been examined. While measurements of exercise Qc have mainly been obtained at peak incremental exercise in patients with COPD, the kinetics of Qc response in relation to the metabolic demands has not been examined across several submaximal exercise intensities. Thus, it remains unknown whether patients exhibit a normal adaptive stroke volume response to increasing metabolic demands. In addition, since inspiratory capacity was not measured in these previous studies, the extent to which dynamic hyperinflation affects the exercise stroke volume, has not been examined. On the other hand, little is know about ventilatory patterns on exertion in CHF patients. The interaction between lung mechanics and cardiac output on exertion need to be further assessed in patients with COPD and CHF. More information are needed to

improve our understanding of heart and lung interdependence and the way by which lung mechanics can affect cardiac output. The purpose of the present study was thus to examine the influence of dynamic hyperinflation on central circulation and to compare the kinetic of increase in stroke volume across three steady-state submaximal cycling loads in COPD and CHF patients with moderately severe disease to that of age-matched healthy control subjects.

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PART II: EXPERIMENTAL ARTICLE

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) share common elements with respect to their physiological response to exercise. Maximal exercise capacity is reduced to the same extent in both groups, and both present great resemblance in histological and biochemical skeletal muscle characteristics. In addition, both COPD and CHF patients exhibit exaggerated ventilatory responses for any given oxygen consumption. While an impaired cardiac output in CHF and inadequate gas exchange in COPD are the predominant explanations for their exercise intolerance, the contribution of circulatory factors in COPD, and respiratory factors in CHF remain incompletely documented.

It is well established that a large proportion of patients with COPD identify leg fatigue and not dyspnea as being their main exercise limiting factor (Killian et al., 1992). Little attention has however been devoted to the possibility of a circulatory steal from respiratory muscles at the expense of exercising muscles occurring in these patients. Similarly, the variations in right ventricular filling, left ventricular preload and afterload resulting from changes in breathing pattern or imposition of respiratory constraints are well established (De Cort *et al.*, 1993; Guz, 1987; Harms *et al.*, 1998; Kim *et al.*, 1987; Peters *et al.*, 1989; Pinsky *et al.*, 1986; Robotham *et al.*, 1978). Yet, the possibility that exercise cardiac output itself may be limited in these patients on account of dynamic hyperinflation and the resulting increase in intrathoracic pressure (Stark-Leyva *et al.*, 2004) has not been clearly established. Results from several studies of COPD patients indicate low peak exercise cardiac output, yet the normality of the response is difficult to establish since a control group is often not included and measurements were not obtained for several submaximal loads allowing to examine the adequacy of the circulatory response in light of the metabolic demands (Bogaard *et al.*, 1997; Light *et al.*, 1984; Minh *et al.*, 1981; Minh *et al.*, 1979; Morrison *et al.*, 1987; Oelberg *et al.*, 1998a; Oelberg *et al.*, 1998b; Raffestin *et al.*, 1982). In addition, while dynamic hyperinflation is frequently

observed in exercising COPD patients (Belman *et al.*, 1996; Murciano *et al.*, 2000; Denis E. O'Donnell *et al.*, 2001; Pecchiari *et al.*, 2004; Vogiatzis *et al.*, 2004), its determination in conjunction with measurements of cardiac output has not been achieved in previous investigations of exercise circulatory responses in COPD.

Similarly, the exercise response of patients with CHF is characterized by exaggerated ventilation. Exercise-induced lung hyperinflation has previously been reported during submaximal steady-state cycling in CHF patients (D. E. O'Donnell *et al.*, 1999). It has been theorized from previous studies that exercise-induced increases in stroke volume and cardiac output may be hindered by increased intrathoracic pressure resulting from lung hyperinflation and greater expiratory loads (Stark-Leyva et al., 2004). However, the extent to which the exaggerated ventilation and possibly dynamic lung hyperinflation also contribute to the impaired exercise oxygen delivery of CHF has not been examined.

The purpose of this study was thus to examine the exercise cardiac output response to various submaximal intensities of cycling in moderately severe COPD and CHF patients compared to healthy age-matched control subjects while assessing the extent of dynamic hyperinflation. In order to exclude the interference of circulatory co-morbidity in COPD patients and respiratory co-morbidity in CHF patients, all subjects underwent a complete resting echocardiographic evaluation as well as pulmonary function assessment.

MATERIALS AND METHODS

Subjects

The study was approved by the ethics review board of the Montreal Chest Institute. Thirty-seven male subjects aged between 40 and 75 years were included in the study after having provided written informed consent. Participants

were 17 patients with clinical diagnosis of COPD according to the guidelines of the American Thoracic Society of FEV_1/FVC ratio of 70% or less; FEV_1 between 25 and 60% of the predicted normal values, ten patients with clinical diagnosis of CHF according to the guidelines of the New York Heart class II and III and ten healthy age-matched control subjects (CTRL) with no known heart or lung disease as assessed by their medical history and clinical examination. CHF patients were excluded if they had a pacemaker, any known history of lung disease while COPD patients were excluded if there was any known history of heart disease. COPD patients were taking inhahed short and/or long acting adrenergic bronchodilator and all CHF patients, except one was taking beta-blocking medication.

Study Design

Baseline resting measurements included: a resting 12-lead electrocardiogram in supine position (Hewlett Packard® Pagewriter XLi); echocardiographic screening examination, performed in a left lateral decubitus position to screen for left or right heart disease and to further characterize the COPD population; a venous blood sample analyzed for hemoglobin, hematocrit, platelets, coagulation factors and electrolytes; a full pulmonary function assessment conducted in accordance with the standards set by the American Thoracic Society (Clausen, 1997). In addition, all participants were screened by a study physician to deem their readiness for exercise and suitability for participation in the study. Within one week of the initial laboratory visit, subjects performed a maximal cycling exercise test followed by a one-hour rest period. They then performed three bouts of steady-state submaximal cycling exercise while gas exchange, ventilatory and circulatory measurements were taken.

Baseline Measurements

Blood cell counts, electrolytes, haemoglobin and serum creatinine concentration as well as coagulation factors were normal in all three groups. Subjects' morphometric characteristics and pulmonary function parameters are shown in table 1. No differences were found in age or height between the control and patients groups but body weight, body mass index and body surface area were significantly lower in COPD. As expected, COPD patients had significantly lower FEV_1, FEV_1/FVC, D_LCO and D_LCO/V_A, and significantly greater values of FRC, RV and RV/TLC than those of age-matched controls. Although there is a statistically significant difference between CHF and control subjects, this is not clinically meaningful as the threshold for abnormal expiratory flow is < 80% (Pawels *et al.*, 2001). Patients with CHF exhibited a lower lung diffusion capacity than predicted for age but the mean values of DLCO (% predicted) or DLCO/VA did not reach statistical significance (p =0.07).

TABLE 1: Subjects' characteristics.

	CTRL (n=10)	COPD (n=17)	CHF (n=10)
Age (years)	62 ± 5.3	64 ± 7.6	57± 9.5
Height (m)	173.6 ± 4.5	170.2 ± 3.6	173 ± 6.6
Weight (kg)	86.5 ± 12.3	72.7 ± 12 * †	93.6 ± 14
FEV_1 (L)	4.75 ± 0.80	1.23 ± 0.51	4.00 ± 0.85
FEV_1 (% predicted)	114 ± 21	41 ± 15 *†	93 ± 13 *
FEV_1/FVC	74.9 ± 5.9	37.0 ± 10.6 *†	73.8 ± 5.6
RV (% predicted)	92 ± 22	207 ± 62 *†	115 ± 33
RV/TLC	0.3 ± 0.1	0.6 ± 0.1 *†	0.4 ± 0.1
D_LCO/V_A	4.2 ± 0.8	2.3 ± 0.6 *†	3.8 ± 0.8
D_LCO (% predicted)	100 ± 24	50 ± 14 *†	79 ± 18

* $p \leq 0.05$ *vs* controls, † $p \leq 0.05$, COPD *vs* CHF;

Prediction are from ECSS (Quanjer *et al.*, 1993)

Table 2 shows results from the echocardiographic evaluation.

TABLE 2. Supine resting echocardiographic evaluation. Values are means ± sd.

	CTRL (n=10)	COPD (n=16)	CHF (n=10)
HR (beats/min.)	70 ± 9	86 ± 17 *†	64 ± 12
LVED d (mm)	51.1 ± 4.8	47.3 ± 4.3	63.3 ± 6.2 * †
LVES d (mm)	31.4 ± 3.7	29.2 ± 4.5	47.4 ± 8.1 * †
LV mass (g/m^2)	83 ± 18	96 ± 33	154 ± 49 * †
PW t (cm)	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.3
IVS t (cm)	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.3
Aod (mm)	31.6 ± 3.3	32.9 ± 4.3	32.2 ± 3.8
LAd (mm)	37.9 ± 5.3	34.6 ± 2.8	46.8 ± 4.8 * †
LVOT d (cm)	2.1 ± 0.2	2.2 ± 0.2	6.4 ± 6.7 * †
TVI Ao (cm)	29.4 ± 5.6	22.0 ± 4.7 *†	32.8 ± 9.2
LVI LVOT (cm)	23.5 ± 3.9	23.2 ± 22.3	23.6 ± 9.4
FS (%)	36 ± 9	35 ± 5	26 ± 8 * †
EF (%)	62 ± 6	62 ± 9	41 ± 10 * †
Vel_{max} Ao (cm/s)	130.3 ± 17.6	121.4 ± 21.2	148.8 ± 38.3 †
Vel_{max}LVOT (cm/s)	115.2 ± 27.2	92.3 ± 24.6 *	100.8 ± 10.5
$PulmVeinSyst_{peak}$(cm/s)	54.2 ± 15.7	46.3 ± 13.9	54.4 ± 15.5
$PulmVeinDiast_{peak}$(cm/s)	47.8 ± 10.4	52.5 ± 9.2	46.3 ± 12.0
DT (ms)	259.1 ± 84.7	284.9 ± 80.3	249.3 ± 68.9
E/A ratio	0.9 ± 0.2	0.9 ± 0.2	1.1 ± 0.4

* $p \leq 0.05$ *vs* controls, † $p \leq 0.05$, COPD *vs* CHF

LVEDd = Left ventricular end-diastolic diameter; LVESd = Left ventricular end-systolic diameter; LVmass = left ventricular mass; PW t = Posterior wall thickness; IVS t = interventricular septal thickness; Aod = Aortic diameter; LAd = Left atrial diameter; LVOT d = left ventricular outflow track diameter; TVI Ao = time-velocity integral across the aortic valve; LVI LVOT = Left ventricular inflow at the LVOT; FS = fraction shortening; EF =ejection fraction; Vel_{max} Ao = maximal velocity at the Aortic valve; Vel_{max}LVOT = maximal velocity at the left ventricular outflow track; DT = deceleration time; E/A = early to late filling peak velocity ratio

Results show as expected, significantly lower left ventricular fractional shortening and estimated ejection fraction in CHF compared to CTRL. There were also evidences of significantly larger left ventricular dimensions as well as estimated left ventricular mass, left atrial and left ventricular outflow tract dimensions in CHF compared to healthy controls. Cardiac output estimated from aortic flow and diameter was significantly lower in the CHF group (4.6 ± 0.7) compared to both COPD patients and CTRL (5.8 ± 1.5 and 5.8 ± 1.1 respectively).

The severity of valvular regurgitation was classified as trivial, mild, moderate or severe by using color flow Doppler according to accepted definitions (Gardin *et al.*, 2002). Trivial or mild mitral and tricupid regurgitation has been found to be present in almost equal proportions in the three groups of patients, while mild aortic regurgitation was found to be present two of the control patients and two of the CHF patients. Pulmonary artery pressure was measured in only 5 patients of each group. Data shows that pulmonary artery pressure above 30 mmHg was present in three COPD patients, one control subject and none of the CHF patient.

Several indices of diastolic function have also been examined. The mean early to late peak filling velocity ratio (E/A ratio) and deceleration time (DT) were not statistically different between groups. The maximum velocity of the left ventricular outflow tract (LVOT) and the time-velocity integral across the aortic valve (TVI Ao) were found to be significantly reduced in COPD compared to the two other groups. Measurements of the mitral valve early peak filling velocity (E), the late peak filling velocity (A), the E to A ratio and the deceleration time of E-wave (DT) yielded different individual pattern. E/A ratio < 0.8 was found in seven out of 15 COPD patients, two out of 10 control patients and one out of 10 CHF patients which could indicate an "impaired relaxation" pattern (E/A ratio $<$ 1). No subjects showed a "restrictive" pattern where the E/A ratio is typically > 2, or between 1 and 2 with an E-wave deceleration time (DT) ≤ 130 ms. On the

other hand, 3 CHF patients and 1 control subject had a E/A ratio > 1.3 and normal DT and could possibly indicate "pseudonormal" or "normalized" pattern which are typically seen when the E/A ratio is between 1 and 2 and DT > 130 ms.

Exercise protocol

The maximal power output for each subject was evaluated by an incremental maximum exercise test on an electromagnetically braked cycle ergometer (Ergoline®). A metabolic cart (Medisoft®) was used to measure oxygen uptake (VO_2) and carbon dioxide production (VCO_2) throughout the exercise. Subjects were asked to maintain a pedal rate between 50 and 70 pedal revolutions per minute for as long as they could while the resistance was increased automatically every minute by 10 Watts for the COPD and CHF subjects and 20 Watts for control subjects. The test was terminated when the subjects could no longer maintain the pedaling rate, or when they voluntarily stopped exercising. Heart rate was continually monitored with a 12-lead ECG. Oxygen saturation was also monitored continually with a finger oximeter (Radical® signal extraction pulse oximeter). Arterial blood pressure was taken manually prior to the beginning of the test, every 2-3 minutes during the test, at peak work rate and during recovery.

Following a one-hour rest period, arterial blood gases, arterial blood pressure, and baseline respiratory gas exchange measurements were obtained and inspiratory capacity and cardiac output were determined. Participants performed three 8 to 10-minute bouts of steady-state submaximal exercise, at 20, 40 and 65% of their pre-determined peak power. They were given a period of 10-15 minutes rest or return to baseline heart rate, breathing pattern and dyspnea score between each steady-state exercise bout. Inspiratory capacity (IC) was measured between the third and fifth minutes of exercise at each steady-state work rate. Care was taken to ensure that the subjects had at least ten regular breaths between each IC manoeuvre, and that tidal volume (V_T) values returned to those observed

prior to the previous manoeuvre. Subjects performed as many manoeuvres as required to obtain two reproducible measurements (within 10%). The higher of these two closest measurements was reported and used for the calculation of operating lung volumes. Arterial blood pressure and an arterial blood gas sample were taken after the IC measurements.

Cardiac output measurements

Cardiac output was measured by the CO_2-rebreathing indirect Fick method between the fifth and eighth minutes of exercise. A rebreathing bag was filled to approximately 1.5 times the tidal volume with a mixture of 9-12% CO_2 and O_2. Subjects were instructed to inhale and exhale through a two-way valve into this bag for 10-12 seconds or until PCO_2 equilibrium was obtained, as first described by Collier and Clarence (Auchincloss *et al.*, 1980; Collier, 1956). The subjects were asked to breathe slightly deeper and more rapidly than tidal breathing in order to facilitate gas mixing between the bag and the lung. The measurement was performed three times for each submaximal exercise stage, with the breathing of room air between each measurement for a sufficient time in order for the expiratory gases to return to the pre-measurement value. For each subject, the mean cardiac output measurements reported at each stage is the average of a minimum of two of three rebreathing maneuvers where a satisfactory PCO_2 equilibrium was obtained. A value differing from the 2 measurements by more than 15% was excluded for averaging. The mixed venous CO_2 content (c_VCO_2) was calculated from the equilibrium PCO_2 after it was corrected for the "downstream difference" (Jones, 1997), according to the formula:

$$PvCO_2 = 0.76 \times PeqCO_2 + 11$$

The arterial CO_2 content (C_aCO_2) was calculated from the measured $PaCO_2$ during steady metabolic state prior to the rebreathing manoeuvre. In patients, $PaCO_2$ was obtained from a radial artery catheter blood gas, while in control subjects in order to comply with recommendation from the ethics review

board, an arterialised capillary blood sample was obtained from the earlobe after application of a vasodilatory cream (Finalgon®). Both arterial and capillary blood gas samples were analysed using the Bayer® 840 blood gas analyser.

Statistical analysis

Results are presented as means ± standard deviations. Group mean comparisons for baseline characteristics and peak exercise data were achieved using a one-way analysis of variance (ANOVA) with post-hoc Bonferroni post-hoc analyses. Mean comparisons for submaximal exercise-related dependent variables on circulatory and respiratory responses were achieved through a (3 × 3) two-way ANOVA for group and exercise intensity factors for repeated measures on the last factor. The slope of the Qc/VO_2 relationship was also assessed; individual slopes were calculated from the Qc values of each subjects and comparison of individual slope means for each group of subjects was assessed using a one-way analysis of variance (ANOVA) with post-hoc Bonferroni post-hoc analyses. Confidence interval of the slopes was obtained by regression analysis. Statistical significance was considered as $p \leq 0.05$. Statistical computations were carried using Statistica for Windows version 5.0 statistical software package.

RESULTS

Results from the peak incremental cycling test are shown in Table 3.

TABLE 3. Peak cycling data

	Controls (n = 10)	COPD (n = 17)	CHF (n=10)
Power (Watts)	179 ± 35	75 ± 25 * †	122 ± 23 *
HR (beats•min^{-1})	159 ± 15	127 ± 14 *	119 ± 19 *
VO_2 (L•min^{-1})	2.25 ± 0.46	1.09 ± 0.28 * †	1.73 ± 0.39 *
VO_2 (ml•kg•min^{-1})	26.2 ± 4.8	15.4 ± 5.16 *	17.7 ± 3.8 *
VE/VO_2	41.7 ± 4.5	44.3 ± 7.8	41.5 ± 4.4
VE/VCO_2	35.8 ± 3.6	45.5 ± 6.4 * †	39.9 ± 6.1
RR (breaths•min^{-1})	35 ± 7	35 ± 6	36 ± 7
V_T (L)	2.72 ± 0.44	1.38 ± 0.28 * †	2.00 ± 0.34 *
SaO_2 (%)	97 ± 2	91 ± 4 * †	96 ± 2

* $p \leq 0.05$ *vs* control subjects, † $p \leq 0.05$, COPD *vs* CHF

As expected, the peak power and VO_{2peak}, peak heart rate and peak V_T were lower in both patient groups compared to controls. Peak VE/VCO_2 ratio was significantly elevated in the COPD group compared to both controls and CHF. Peak cycling power was lower in COPD patients compared to the CHF patients although HR_{peak} was not higher in CHF likely as a result of their use of beta-blocking drugs. Peak VCO_2, VO_2, ventilation (V_E) and tidal volume (V_T) was reduced in the COPD group compared to both controls and CHF while the VE/VO_2 ratio and peak respiratory rate (RR) were not different between groups. Only COPD subjects showed a significant fall in oxygen saturation at peak exercise. The breathing reserve (not shown), which is calculated as the difference between the estimated maximal voluntary ventilation (MVV) and the VE_{peak}, was not different between the CHF patients and the CTRL, while COPD patient exhausted their BR. Similarly, the dyspnea index calculated as VE/MVV in %

was significantly higher in the COPD group compared to the control and CHF subject groups.

Submaximal exercise pulmonary ventilation and gas exchange

Table 4 shows the arterial blood gases at rest and during the submaximal cycling exercise. As expected in the COPD, resting PaO_2 was lower compared to both CHF and CTRL. Exercise did not cause significant changes from baseline in any group. No difference between groups or as a result of exercise was found for $PaCO_2$.

TABLE 4. Arterial blood gas at rest and during steady-state submaximal exercise at 20%, 40% and 65% of peak power in COPD, CHF and control subjects (CTRL).

	Subj.	Rest	20%	40%	65%
PaO_2 (mmHg)	CTRL[§]	108.4 ± 5.4	103.2 ± 3.5	104.9 ± 3.9	108.7 ± 4.3
	COPD	76.9 ± 10.1 *	78.4 ± 9.3 *	75.1 ± 9.7 *	74.8 ± 12.7 *
	CHF	90.3 ± 11.0 *	96.8 ± 7.4	99.5 ± 5.9	102.4 ± 8.8
$PaCO_2$ (mmHg)	CTRL[§]	33.7 ± 3.7	37.8 ± 2.5	39.2 ± 3.0	37.5 ± 2.6
	COPD	38.6 ± 3.6	40.4 ± 4.8	39.6± 3.7	39.3 ± 4.6
	CHF	34.5 ± 5.6	38.0 ± 2.4	37.1 ± 2.9	34.8 ± 2.2

* $p \leq 0.05$ *vs* control subjects; † $p \leq 0.05$ *vs* rest;

§ In control subjects PaO_2 and $PaCO_2$ are derived from $P_{ET}O_2$ and $P_{ET}CO_2$.

The operating lung volumes calculated from the resting and exercise inspiratory capacity in COPD, CHF and CTRL are shown in figure 1(a). Results from the ANOVA on operating lung volumes indicate for EILV a significant main effect of group and of exercise condition. Thus, patients with COPD exhibit a significant upward shift in both operating lung volumes. Exercise resulted in a significant rise in EILV in controls but not COPD and CHF patients. However, when EILV is expressed as EILV (% TLC the change from baseline at 65% peak

power in CHF and controls was significantly more important compared to COPD (42 and 47 versus 18% respectively). Alternately, EELV did not rise from baseline at 65% peak power in any group. Altought, it did not reach statistical significance, COPD and CHF patients showed a similar increase in EELV of approximately 400 ml.

Analysis of the tidal volume exercise response shown in figure 1 d indicate the V_T to increase to a lesser extent during intensifying exercise in both COPD and CHF than in controls, with the ΔV_T from baseline at 65% peak power, being 113% in COPD and 132% in CHF compared to 229% in controls subjects.

Figure 1 b and c shows markers of dynamic hyperinflation. The mean inspiratory reserve volume expressed relative to total lung capacity is shown in figure b. As expected, exercise resulted in a significant decrease in IRV with values at 20, 40 and 65% peak power being significantly lower than baseline values. A significant downward shift in values may be seen for COPD patients compared to those of controls and CHF, with values corresponding to almost half that of controls both at rest and for each submaximal exercise load. Similarly, the resting mean inspiratory capacity expressed relative to TLC was significantly lower in COPD compared to both controls and CHF. As can be seen in figure (c), there was a significant 10 ± 12% which however did not reach significance in inspiratory capacity 65% peak power compared to baseline in CHF patients. A decrease of a similar magnitude (13 ± 20%) was also found for the COPD group, which also reach did not reach statistical significance (p=0.13). As expected, inspiratory capacity was maintained in the control group.

FIGURE 1. (*a*) **End Inspiratory (EILV) and end-expiratory (EELV) lung volumes** (*b*) **Inspiratory reserve volume relative to total lung capacity (IRV/TLC %),** (*c*) **inspiratory capacity relative to total lung capacity (IC/TLC %) and** (*d*) **change in tidal volume from baseline (ΔVT %), at rest, 20, 40 and 65% of peak power in COPD** (*triangles*) **CHF** (*squares*) **and control subjects** (*circles*)**. Values are mean ± SD.**

* indicates $p \leq 0.05$ *vs* control and CHF subjects; § indicates $p \leq 0.05$ *vs* rest.

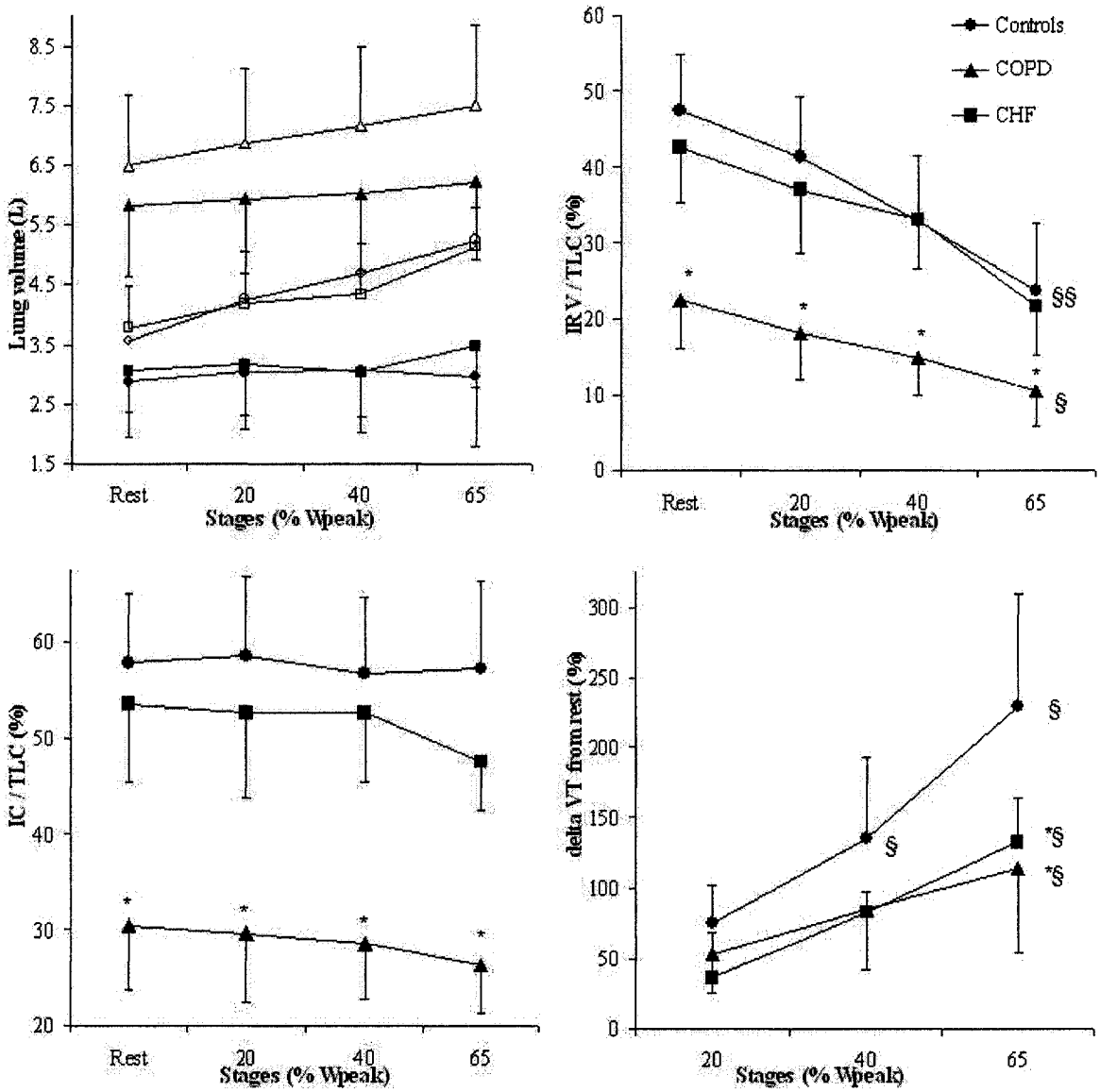


Figure 2 shows the scatter plot of individual data points against oxygen uptake in CHF, COPD and controls at the three steady state submaximal exercise intensities for cardiac output (a), stroke volue (b), heart rate (c) and calculated arteriovenous oxygen difference (d). A line of best fit is drawn for each data point series, COPD, CHF and controls. At 95% level of confidence, the line of best fit for figure 2(a) confidence interval for the slope are 4.43, 10.40 in COPD; 5.25, 8.39 in healthy; 3.06, 6.94 in CHF and shows a statistically significant linear relationship since it does not include 0. Similarly, figure 2 (c) and (d) shows a statistically significant linear relationship for all 3 groups.

Mean absolute values of Qc obtained at 65% steady state cycling were statistically lower in COPD and CHF patients compared to controls, which is in line with the lower absolute work rate exhibited by patients at each exercise load. Similarly, oxygen delivery, calculated from the product of CaO_2 and cardiac output, was also significantly lower in COPD and CHF compared to controls at 65% steady state submaximal cycling exercise.

The slope of the Qc-VO_2 regression line found in the control subject group was 6.8 which is in agreement with the value of 5.5-7.0 generally reported in healthy subjects (W. B. Jones *et al.*, 1970; T. Taivassalo *et al.*, 2003b). In COPD the average slope is found to be 7.4 while a slope of 5.0 is found in the CHF patients.

As seen in Figure 2(c), HR rose linearly with increasing oxygen uptake in both patients and age-matched controls. The slope of the line of best fit between the HR and VO_2 in the COPD group was higher compared to both CHF and CTRL. In the CHF patients the slope was similar to that of control patients, however a downward shift was observed.

Results for the steady-state Qs measurements are shown in Figure 2(b). The line-of-best fit describes the expected curvilinear relationship between stroke volume and VO_2 in both patients groups and controls. Data points from the CHF show an upward shift in Qs values for any given oxygen uptake which is also

compatible with their downward shift in the HR-VO2 relationship such that a longer filling time may account for a higher stroke volume. Similarly, as can be seen in figure 2(d), individual CHF values show an exaggerated slope of the A-vO_2 difference *vs* VO_2 compared to controls suggesting higher O_2 extraction.

FIGURE 2: Scatter plot of cardiac output (*a*) , stroke volume (*b*), heart rate (*c*) and A-vO_2 difference (*d*) versus steady-state submaximal oxygen consumption at 20%, 40% and 65% of peak work rate in patients with CHF (*squares and black solid regression line*) **COPD** (*triangles and gray regression line*) **and in healthy controls** (*circles and dashed regression line*).

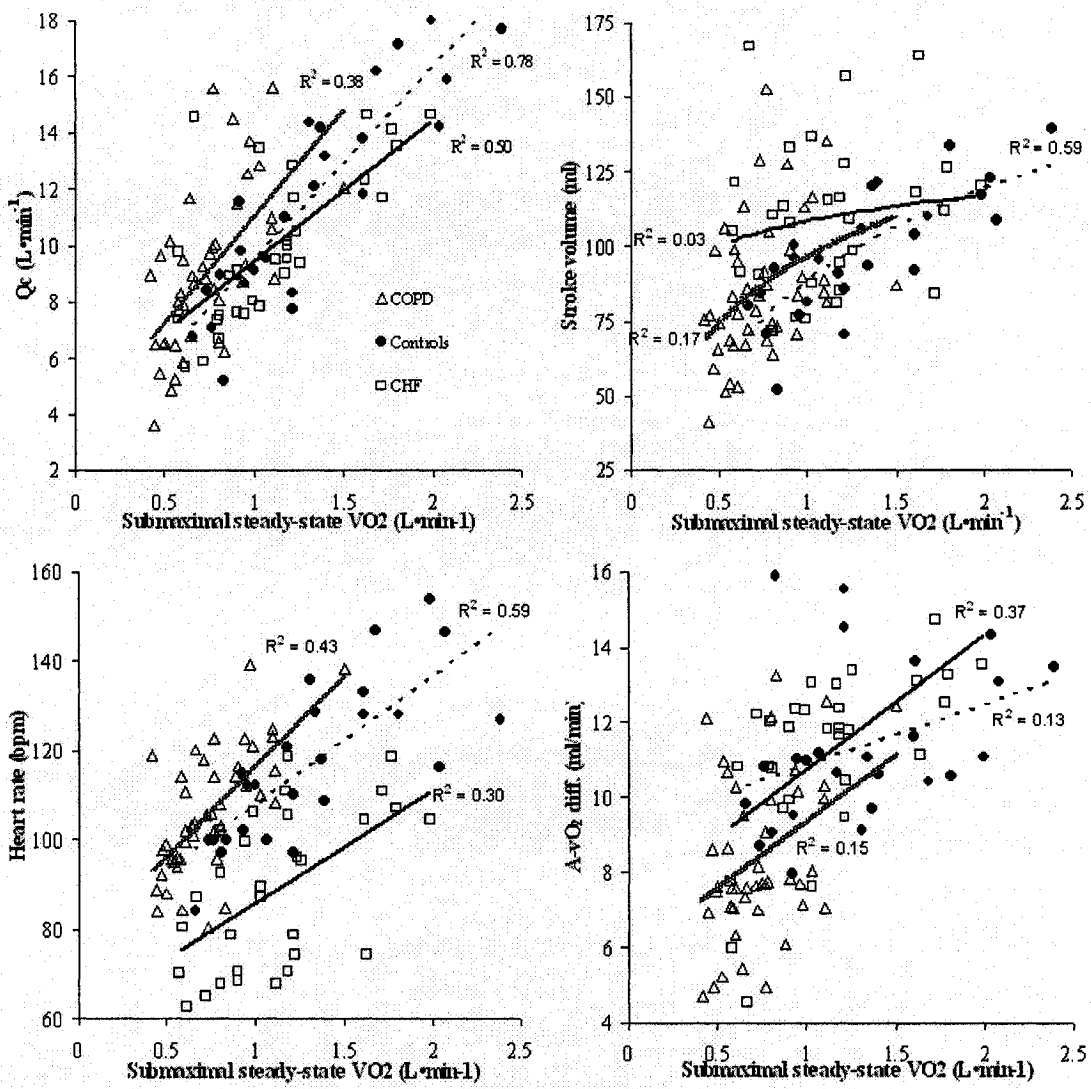


Table 4 shows circulatory data during steady-state submaximal exercise at 20%, 40% and 65% of peak power. Results show that cardiac output was lower compared to controls at 65% in both COPD and CHF. Furthermore, the Qc was not significantly different between COPD and CHF despite a significant difference between the two for power output. Stroke volume in patients did not significantly differ from the control subjects. On the other hand, the mean HR in the CHF patients group was significantly lower compared to the controls during all submaximal level of exercise.

TABLE 4. Circulatory data during steady-state submaximal exercise at 20%, 40% and 65% of peak power in control subjects (CTRL), COPD and CHF patients.

	Subj.	20%	40%	65%
Work rate (Watts)	CTRL	37 ± 6	71 ± 14 †	113 ± 25 †‡
	COPD	15 ± 5 *	31 ± 11 *§†	50 ± 17 *§†‡
	CHF	24 ± 5	49 ± 9†	79 ± 15 †‡
Qc ($L \cdot min^{-1}$)	CTRL	7.9 ± 1.5	11.4 ± 2.3 †	15.6 ± 2.2 †‡
	COPD	7.2 ± 2.0	9.2 ± 2.3	11.3 ± 2.4 *†
	CHF	7.8 ± 1.6	9.9 ± 2.3	12.4 ± 2.1 *†
Qs ($ml \cdot min^{-1}$)	CTRL	79.9 ± 13.8	99.7 ± 18.4	113.9 ± 15.8 †
	COPD	75.5 ± 23.4	87.7 ± 23.2	95.9 ± 20.1 §
	CHF	95.9 ± 21.0	111.6 ± 30.3	119.8 ± 22.0
HR ($Breaths \cdot min^{-1}$)	CTRL	99 ± 8	114 ± 8	137 ± 10 †‡
	COPD	96 ± 11	105 ± 9	118 ± 12 *†‡
	CHF	83± 16*	91 ± 18 *§	105 ± 19 *

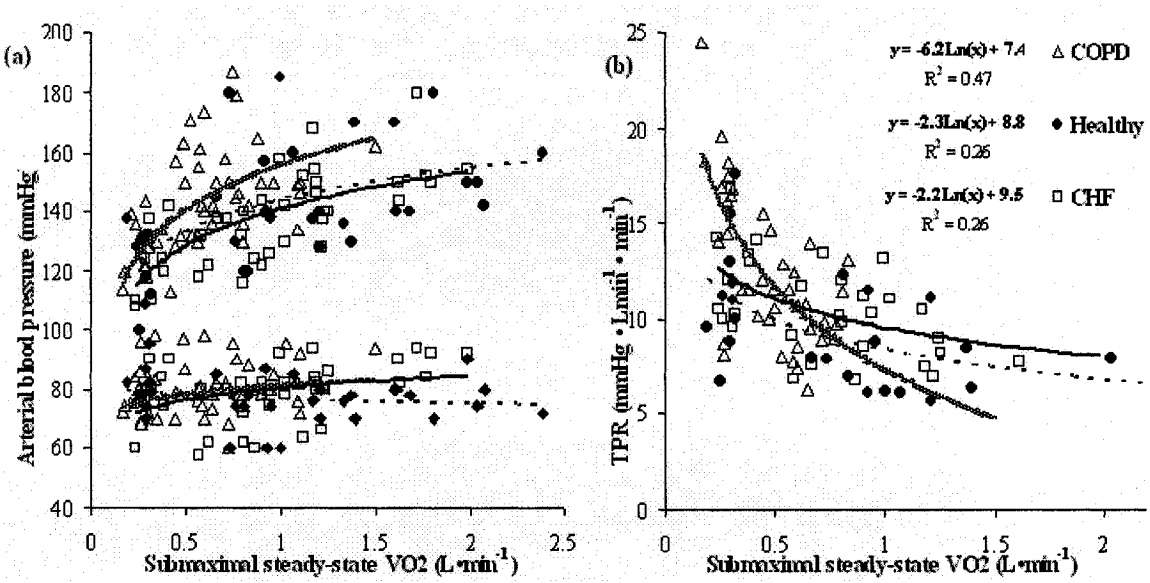
* $p \leq 0.05$ *vs* control subjects; § $p \leq 0.05$ COPD *vs* CHF

† $p \leq 0.05$ *vs* 20% of peak power; ‡ $p \leq 0.05$ *vs* 40% of peak power

Qc = cardiac output; Qs = stroke volume; HR = heart rate

Figure 3 shows the scatter plot of systolic and diastolic blood pressure measurements (a) as well as total peripheral resistance estimated from cardiac output and mean arterial pressure computations, at rest as well as at each submaximal cycling intensity. The trend line through all COPD patients' systolic blood pressure points indicates an upward shift for any given VO_2 compared to both controls and CHF. Diastolic blood pressure adaptation to exercise appears similar in all three groups. In agreement with the literature (Gielen *et al.*, 2002), the trend line through all points of total peripheral resistance in CHF patients suggests a blunted decrease in total peripheral resistance with increasing exercise intensity.

FIGURE 3. Arterial blood pressure (*a*) and total peripheral resistance (*a*) plotted against submaximal steady-state VO_2 ($L \cdot min^{-1}$) in COPD *(triangles and gray regression line)*, **CHF** *(squares and black solid regression line)* **and controls** *(circles and dotted regression line)*.



Figures 4 shows relative changes from baseline in VO2 (a), Qc (b, Qs (c), HR (d), mean arterial pressure (MAP) (e) and Total peripheral resistance (TPR) at 20, 40 and 65% peak power output in COPD, CHF and controls. As expected from their reduced peak oxygen uptake, COPD and CHF showed lesser changes in VO_2 from baseline than controls (a). Figure 4(b) shows no significant difference in the extent of change in Qc from rest in COPD compared to the control group. However, CHF patients showed a lesser increase in Qc than both COPD and controls at 65% peak power. Similarly, CHF patients showed significantly lesser increases in both HR and Qs (4c and d) than controls. Despite a significantly greater change in VO_2 CHF compared to COPD, the change and HR, Qs and Qc was not significantly difference between these two groups. The magnitude of changes in mean arterial pressure from rest was not significantly different between groups. Although both COPD and CHF patients showed lesser mean decreases in TPR compared to controls, a significant difference in the mean change was only found for CHF compared to controls at 65% peak power.

FIGURE 4. Relative changes from steady state cycling at 20% to 65% of peak power output in COPD, CHF and controls.

* indicates $p \leq 0.05$ *vs* control; § indicates $p \leq 0.05$ *vs* CHF subjects.

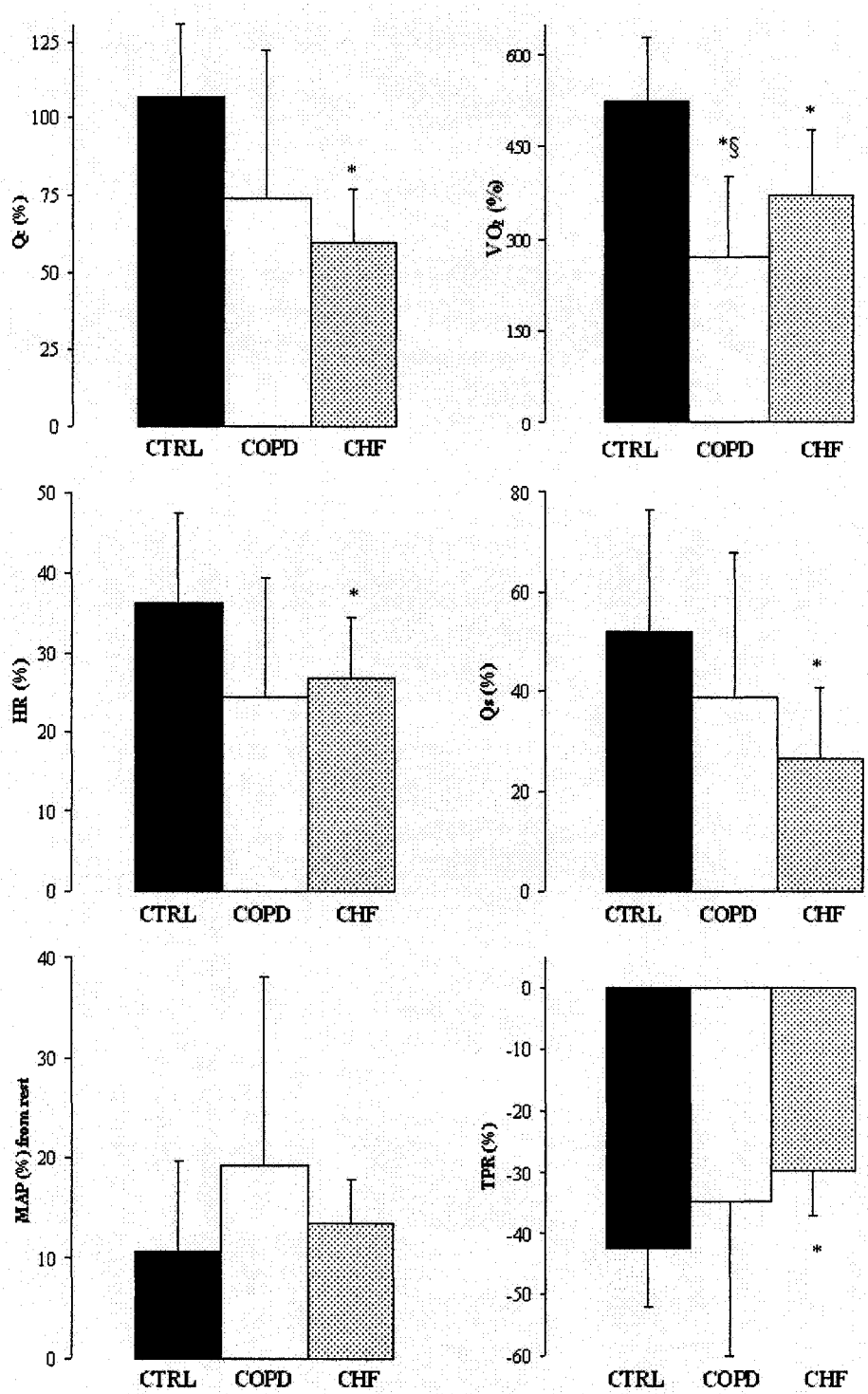
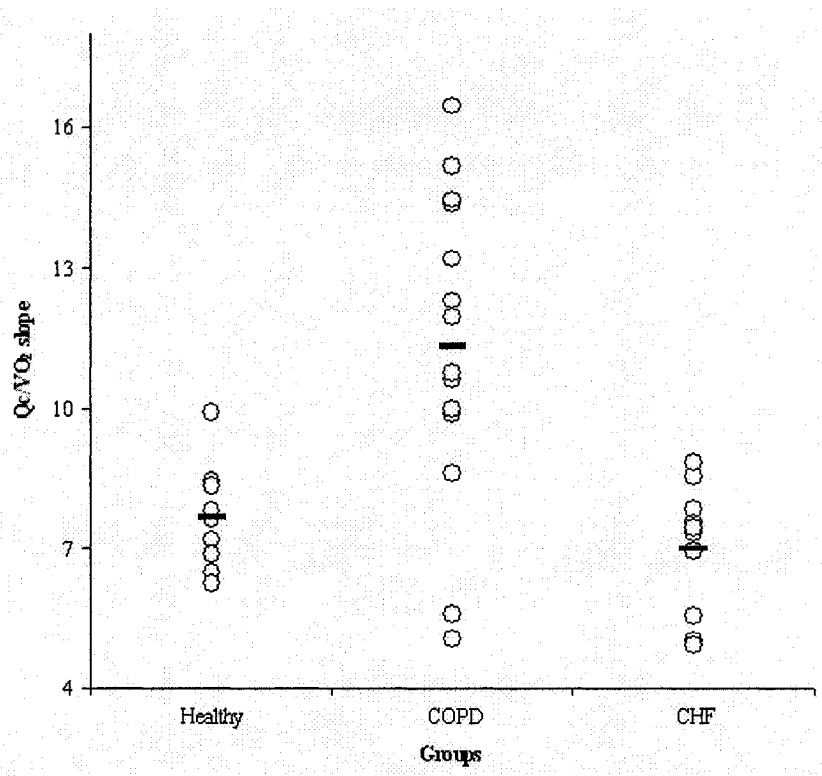


Figure 5 shows the individual Qc *vs* VO_2 slopes obtained across the three submaximal exercise loads in controls, CHF and COPD. As can be seen, the slopes observed for the control subjects ranged between 6.3 and 9.9. Slopes found in CHF patients also ranged between 4.9 and 8.9. On the other hand, values in COPD patients may be seen to range between 5.1 and 16.5, with the majority of patients showing a slope much greater than 7.0.

FIGURE 5. Individual slopes and mean slopes of cardiac output against VO_2 in COPD, CHF and controls.



DISCUSSION

The main findings from this study indicate that although patients with COPD and CHF share a similar degree of impairment in relative peak oxygen uptake, they present distinct adaptive responses to submaximal exercise. Contrary to the proposed hypothesis, patients with COPD did not exhibit an impairment in their cardiac output adaptive response to submaximal exercise, despite a marked static lung hyperinflation and additional exercise-induced hyperinflation. Moreover, several patients with COPD exhibit an exaggerated slope of the Qc *vs* VO_2 relationship, accounted for by an exaggerated HR *vs* VO_2 response and an upward shift in the Qs *vs* VO_2 responses. A significant dynamic hyperinflation was not found in patients with CHF and could therefore not account for their lower relative hemodynamic changes at 65% peak power.

Exercise cardiac output in CHF

An impaired circulatory response naturally accounts for the impaired oxygen delivery and limited exercise tolerance of patients with CHF. Surprisingly however there are a limited number of studies quantifying extent of impairment in cardiac output associated with CHF (Cotter *et al.*, 2003; Drexler, 1991; Maurer *et al.*, 2003; Myers & Froelicher, 1991).

Over the last 10 years, three studies have examined the kinetics of the Qc response to exercise in patients with moderate to severe CHF disease (P. Agostoni *et al.*, 2005; P. G. Agostoni *et al.*, 2000; Yamabe *et al.*, 1997).Results obtained using direct Fick at peak exercise capacity showed patients to exhibit "low" peak cardiac output also associated with a abnormally low peak VO_2 (Gordon *et al.*, 1999; Maurer et al., 2003; Tanabe *et al.*, 2002; Tanabe *et al.*, 2000).

The determining factor in the oxygen transport capacity of patients with CHF cannot be ascribed to gas exchange disturbances which generally remain

normal in most patients with CHF (Guazzi, 2003) nor is it related to an impaired peripheral extraction since patients with CHF calculations generally show a compensatory increase in arterio-venous oxygen difference for any given level of VO_2 (Cohen-Solal *et al.*, 1999).

Results from studies of the exercise Qc kinetics have shown the slope of the relationship between Qc and VO_2 to remain within the normal range in moderate to severe CHF patients (Mancini *et al.*, 1996; Wilson *et al.*, 1995). However, when CHF patients are compared to healthy subjects at the same level of VO_2, the Qc is significantly lower (Wilson & Ferraro, 1983).

Results from the present study show the mean Qc-VO_2 slope of patients with CHF not to be statistically lower than that found in the age-matched control group. Yet, patients exhibited a greater dispersion with several individual slopes being at the lower end of normality. In agreement with previous observations, at 65% peak cycling power, CHF patients exhibited smaller relative changes in Qc than both controls and COPD on account of smaller changes in both heart rate and stroke volume. As previously reported (Cohen-Solal *et al.*, 1999), the present results also show CHF to exhibit a greater total peripheral resistance and greater estimated oxygen peripheral extraction.

Exercise cardiac output in COPD.

Experimental evidence of abnormal cardiovascular responses to exercise in COPD such as increases in pulmonary artery pressure and vascular resistance and or failure of right ventricular ejection fraction to increase (Morrisson; see others...in Aliverti & Macklem review 2001) have been reported presumably on account of right ventricular failure or a reduced space for ventricular expansion within the pericardium and/or within the limited thoracic volume.

Over the last twenty-five years, some twelve studies have specifically examined the cardiac output adaptation to exercise in COPD. In most cases, cardiac output was obtained only upon reaching peak exercise using a direct Fick procedure. Authors generally reported cardiac output to be lower than the normally predicted value leading them to conclude to a circulatory abnormality may be responsible for the equally low peak oxygen uptake (Bogaard et al., 1997; Charloux *et al.*, 2000; Ježek *et al.*, 1973; Light et al., 1984; Mahler *et al.*, 1985; Minh et al., 1981; Minh et al., 1979; Morrison et al., 1987; Oelberg et al., 1998a; Oelberg et al., 1998b; Raffestin et al., 1982; Stewart & Lewis, 1986)

Considering a strong relationship between maximal oxygen uptake and right ventricular ejection fraction, stroke volume and cardiac output, Morrisson et al. (Morrison et al., 1987) suggested that a right ventricular dysfunction may contribute to the exercise intolerance of patients with COPD. A similar link was also proposed by Montes de Oca (Montes de Oca et al., 1996) on grounds of correlational observations that oxygen pulse (VO_2/HR) was the best predictor of peak VO_2 while the best predictor of O_2 pulse was the amplitude of the exercise pleural pressure swing. Moreover in addition to finding a lower than predicted exercise cardiac output, Oelberg et al. (Oelberg et al., 1998a) also observed that while breathing He-O_2 increased maximal ventilation by 30% and maximal VO_2 by 15%, cardiac output did not increase. This observation may be taken to suggest that unloading of the ventilatory muscles and thus presumably also reducing expiratory flow limitation, allowed enhanced blood flow redistribution to the exercising muscles without affecting the magnitude of central blood flow.
Thus results on peak exercise cardiac output remain controversial and reported values show a wide dispersion of values making it difficult to establish the physiological and clinical significance of findings. This is especially true if one considers that dyspnea is a major limiting factor in the exercise performance of COPD, and that peak exercise is often terminated before the full heart rate reserve is solicited, it remains to be determined whether the reportedly "low" peak cardiac output of patients is the cause or the consequence of a reduced peak exercise

capacity. The adequacy of the cardiac output response to exercise need thus be examined under conditions where the ability to exercise will not compromise the measured response i.e. under submaximal exercise.

In the present study, cardiac output was determined at three submaximal power output of mild moderate and more exhaustive intensity without compromising the ability of the patient to complete the constant load exercise bout. To date, only two studies have measured cardiac output during submaximal exercise in COPD. Using both the direct Fick and the CO_2-rebreathing methods in moderate and severe patients, Mahler et al. (1985) assessed cardiac output during cycling at 50% peak VO_2 while Stewart & Lewis (1986) used a direct Fick technique to measured Qc during treadmill exercise at 60-70% peak VO_2. Neither of these studies included a healthy control group. Results obtained by Mahler et al. and Stewart & Lewis show increases in Qc from rest of the same magnitude as those observed in the present study for work rates equivalent to 40 or 65% peak power. However, because a single measurement was obtained in those studies, it was not possible to assess the normality of the Qc *vs* VO_2 response.

It has previously been established from evidence in young healthy control subjects that exercise cardiac output can be predicted from VO_2 such that it increases with a slope of approximately 6 L/min for every litre increase in VO_2, with 95% confidence limits of ± 2 L/min (N. L. Jones, 1997).

Results from the present study show COPD patients to exhibit a mean slope of the Qc *vs* VO_2 relationship markedly higher than that of the age-matched control group with more than half of patients showing a Qc *vs* VO2 slope, well in excess of the 2 standard deviations from the predicted value of 6.0. The enhanced cardiac output response can be accounted for by exaggerated adaptations in both heart rate and stroke volume as may be seen from the exaggerated HR *vs* VO_2 and the upward shift in the Qs *vs* VO_2 relationship.

Use of CO_2-rebreathing to measure exercise cardiac output in COPD.

The observation of an exaggerated Qc *vs* VO_2 relationship in the COPD patients is in agreement with the exaggerated HR *vs* VO_2 slope previously found between rest and peak exercise in COPD (Light et al., 1984) and the use of beta-agonist medications. Yet, the validity of the measurement technique may also be questioned.

Validation studies to examine the adequacy of CO_2-rebreathing against the direct Fick method for use during submaximal exercise in healthy humans have resulted in correlation coefficients of 0.80 (Warburton et al., 1999). In a validation study in patients with COPD, Mahler et al (Mahler et al., 1985) found a correlation coefficient similar to that reported in healthy humans and found no consistent error in exercise measurement as long as arterial PCO_2 was measured directly, rather than estimated from end-tidal CO_2. In the present study, the CO2-rebreathing technique was used as validated by Mahler et al (Mahler et al., 1985) with $PaCO_2$ of COPD and CHF being obtained from a direct arterial blood sample to dismiss an effect of inadequate gas exchange. Measurements of $PaCO_2$ indeed show no significant differences between COPD and CHF suggesting that any bias in the observed exaggerated Qc of COPD related to the measurement of $PaCO_2$ would be equally applicable to the CHF population. Second, the present study used the equilibrium CO_2 method for establishing $PvCO_2$. This technique is superior to the extrapolation method since equilibrium is either achieved and the manoeuvre is considered adequate, or it is not achieved and the manoeuvre is rejected by the automated system. Thirdly, for each constant load exercise, the CO_2-rebreathing manoeuvre was repeated three times to ensure that a reproducible measurement was obtained. Finally, while end-tidal CO_2 is generally found acceptable in the use of CO_2-rebreathing in a healthy population, to optimize the arterial PCO_2 measurement, control subjects from the present study were submitted to an earlobe puncture to obtain an arterialized capillary blood PCO_2 which have been shown to be highly correlated with direct arterial PCO_2,

both at rest and during exercise (Sauty et al., 1996; Fajac et al., 1998). Given these precautions, we are confident that the exaggerated Qc *vs* VO_2 slope observed in the majority of COPD patients is not the result of measurement artifact.

The influence of lung hyperinflation.

The influence of the respiratory cycle on cardiac function such respiratory sinus arrhythmia (Eckberg, 2003) or changes in ventricular preload and afterload throughout the execution of a Valsalva maneuver or when respiratory constraints are applied have long been established (De Cort et al., 1993; Guz, 1987; Harms et al., 1998; Kim et al., 1987; Peters et al., 1989; Pinsky et al., 1986; Robotham et al., 1978),

More than 30 years ago, Potter et al reported high expiratory pressures during exhaustive exercise in COPD (Potter *et al.*, 1971) and suggested that the resulting slowing of expiratory muscle would maintain an elevated intrathoracic pressure during expiration which could have adverse circulatory effects. More recently, experimental evidence has been provided that in healthy exercising subjects the application of an expiratory resistance caused a substantial blood shift from the trunk to the extremities (Iandelli *et al.*, 2002) and reduced cardiac output (Aliverti *et al.*, 2005; Stark-Leyva et al., 2004).

It has been suggested that the hyperinflation commonly seen in patients with COPD may compromise the normal increase in stroke volume on account of an impairment in end-diastolic ventricular filling (D.E. O'Donnell, 2001; Sietsema, 2001).

In the present study COPD patients exhibited marked lung hyperinflation at rest compared to CHF and controls subjects and developed a significant exercise dynamic hyperinflation. The magnitude of the observed dynamic

hyperinflation is similar to that generally reported for submaximal intensities of 50 to 75%.

Despite the presence of lung hyperinflation, the cardiac output response of COPD patients was not impaired. Therefore, results from the present study do not support that lung hyperinflation compromises the normal exercise-induced increase in stroke volume and cardiac output.

The effects of lung hyperinflation on the central circulation have not been clearly examined in CHF. On exertion, an expiratory flow limitation has been shown in these patients with an increased expiratory pleural pressure and a flow volume loop exceeding resting maximal flow volume loop (Johnson BD, 2000; Johnson *et al.*, 1999; D. E. O'Donnell et al., 1999). In patients with severe CHF (EF < 35%) a slight (0.26 ± 0.06L) but significant dynamic hyperinflation as defined by an increase in EELV from baseline has been reported for constant load cycling at 75% peak power (D. E. O'Donnell et al., 1999). This observation was however in contrast with a previous observation by B.D. Johnson and al. (Johnson BD, 2000) who found no hyperinflation during cycling at 50 and 70 % peak power despite an increase from baseline in the IC/FVC ratio. Results from the present study only show a slight increase in the end-expiratory lung volume at 65% peak power in patients with CHF, which however did not reach statistical significance. This observation contrasts with that previously reported by O'Donnell (1999). Yet, patients from our study were not as severely impaired as those in the latter study (EF (%) = 41 *vs* < 35) and were submitted to a greater relative exercise intensity (75% peak power) than in the present study. Whether or not the occurrence of marked dynamic hyperinflation in selected CHF patients but not others affected ventricular filling and further contributed to reducing the cardiac output response to exercise cannot be ascertained from this small sample of CHF patients.

On the other hand, an exaggerated VE/V_{CO_2} is a hallmark of ventilatory exercise response in patients with moderate-severe CHF (Metra & Dei Cas, 1996). In the present study, the VE/V_{CO_2} measured in CHF at peak exercise was not significantly higher than that of age-matched control subjects. It is thus possible that exercise dynamic hyperinflation in CHF becomes apparent only in patients with more advanced disease severity or for near-maximal exercise.

It has recently been shown using optoplethysmography that some patients with COPD may exhibit only a "late hyperinflation" response to exercise i.e. for exhaustive near-maximal exercise as opposed to those who experience exercise-induced hyperinflation for mild and moderate exercise intensities (Vogiatzis *et al.*, 2005). In the present study, the highest work rate was equivalent to 65% peak power. It can therefore not be excluded that more marked exercise-induced hyperinflation might have been seen in COPD and perhaps also in CHF patients for higher exercise intensities.

Significance of a hyperdynamic circulation in COPD.

Abnormally high ΔQc/ΔVO2 slopes ranging from three times normal up to 73 have been reported in patients with mitochondrial myopathies (T Taivassalo *et al.*, 2003a) and McArdle's disease or myophosphorylase deficiency (Lewis *et al.*, 1984). It is believed that this hyperdynamic circulatory response results from an abnormal peripheral muscle bioenergetic signalling secondary to the mitochondrial dysfunction or a related impairment in peripheral oxygen utilisation to induce a compensatory adaptive response (Haller & Bertocci, 1994; T Taivassalo & Haller, 2004).

In the last decade, an increasing number of publications have been produced to corroborate the multisystemic nature of COPD and CHF disease (Agusti et al., 2003; Conraads et al., 2002; Wouters, 2002). In both diseases, evidence of peripheral muscle atrophy, decrease in type I muscle fibres, reduction

in capillary to fibre ratio, as well as a decrease in oxidative enzymes have all been reported in patients with COPD (Allaire et al., 2004; Franssen et al., 2002; Gosker et al., 2000).

While peripheral skeletal muscle biopsies were not obtained in the present study to verify this phenomenon, it is possible that there exists in some COPD patients a disturbance in the peripheral muscle bioenergetic that results in an enhanced exercise cardiovascular drive,seen both in their chronotropic and inotropic responses.

Considering that similar peripheral muscle changes and a reduced oxygen delivery capabilities are also reported in moderate to severe CHF patient (Conraads et al., 2002; Filippatos et al., 2005), one would also expect to find in these patients, a bioenergetic deficit signalling for a compensatory cardiovascular mechanism.

An exaggerated Qc *vs* VO2 slope is not found in the CHF population. This however does not preclude the existence of a peripheral bioenergetic signalling as would be expected from their altered peripheral muscle histological characteristics. The overactivity of arterial chemoreceptors and the muscle ergoreflexes during exercise have long been recognized in CHF (Ponikowski & Banasiak, 2001) and have been called upon to explain the exaggerated ventilation observed in CHF patients (Coats et al., 1994). Administration of carvedilol (a beta-blocking medication) has however been found to in to decrease the exaggerated exercise ventilatory response presumably throught a blunting of the hyperventilatory drive. The possibility can therefore not be excluded that a similar exercise bioenergetic deficit signalling exist in CHF patients which however cannot trigger the compensatory cardiovascular response on account of beta-blocking medication in addition to their pre-existing inotropic limitation. In the present CHF population, nine of the ten CHF patients were taking beta-blocking

medication. The observation of a downward shift in the HR *vs* VO2 regression line is indeed in agreement with a negative chronotropic response.

Limitation of the study.

Further studies of the Qc *vs* VO_2 response in a larger group of COPD patients with concurrent measurements of intrathoracic pressure kinetics over a wider range of exercise intensities including more exhaustive exercise are needed to confirm the absence of relationship between ventilatory mechanics and ventricular output. Similarly, the occurrence of a hyperdynamic circulation in COPD patients needs to be confirmed with a concurrent assessment of potential markers of a peripheral bioenergetic deficit. The study should be repeated in patients with varying degrees of CHF and over a wide range of exercise intensities to better understand factors leading to dynamic hyperinflation in patients with CHF.

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APPENDIX

Centre universitaire de santé McGill
McGill University Health Centre

February 14, 2006

Jean Bourbeau, MD
Room K1.32
Montreal Chest Institute

Re:	"Respiratory Constraints and Cardiac Output on Exertion in Patients with Chronic Obstructive Pulmonary Disease (COPD) and Chronic Heart Failure (CHF)".
MCI Identifier:	03-10
Approved:	February 27, 2003 / February 27, 2004 February 27, 2005
Closed:	February 14, 2006

Dear Dr. Bourbeau,

This letter is to confirm your notification of closure for the study entitled: "Respiratory Constraints and Cardiac Output on Exertion in Patients with Chronic Obstructive Pulmonary Disease (COPD) and Chronic Heart Failure (CHF)".

This protocol has been terminated by the Biomedical-C Research Ethics Board of the McGill University Health Centre. The dossier on this protocol is now officially closed.

Sincerely,

Sharyn Mannix, MD
Chair, Biomedical-C
Research Ethics Board of the MUHC.

cc: Carmen Darauay
Project Manager