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CARDIAC FUNCTION AND
PULMONARY HEMODYNAMICS
DURING EXERCISE IN COPD

Cardiac function and pulmonary hemodynamics during exercise in COPD

The research presented in this thesis is part of the research program of the Institute for Cardiovascular Research (ICar-VU). The studies were carried out at the Department of Pulmonary Diseases, VU University medical center, Amsterdam, The Netherlands

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VRIJE UNIVERSITEIT

Cardiac function and pulmonary hemodynamics during exercise in COPD

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
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door Sebastiaan Holverda
geboren te Apeldoorn

promotor prof.dr. P.E. Postmus

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CHAPTER ONE

General introduction

Sebastiaan Holverda and Anton Vonk-Noordegraaf

Definition

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world, and is predicted to become one of the major global causes of disability and death in the next decade. COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases [1]. The expiratory flow limitation arises because of the combined effects of reduced elastic lung recoil and increased airway resistance. Note, that the term COPD does not describe one homogeneous disease process, but rather a heterogeneous group of disease subtypes that share airway obstruction as a prominent feature.

COPD and pulmonary hypertension

Pulmonary hypertension (PH) developing in COPD was formerly described as secondary PH, but has been differentiated from the other causes of PH. Since research revealed that hypoxemia plays a pivotal role in the development of COPD related PH, this type of PH is now classified in group 3 of the WHO, i.e. PH associated with disorders of the respiratory system and/or hypoxemia, according to the classification adopted in 2003 at the World Symposium on Pulmonary Hypertension [2]. COPD represents by far the most common cause of pulmonary hypertension in this group, with a reported prevalence of 20 to 90 % [3-7] in patients with GOLD stages III-IV [1]. The patients that were included in the different series were of various functional severity which may cause the large range in prevalence. With time, pulmonary hypertension may lead to the development of right ventricular hypertrophy, cor pulmonale, and may result in right ventricular failure [8;9]. Pulmonary hypertension complicating chronic respiratory disease is generally defined by the presence of a resting mean pulmonary artery pressure (mPpa) above 25 mmHg [10]. In general, the degree of PH in COPD is mild to moderate, with resting mPpa in a stable state of the disease ranging between 20 and 35 mmHg [11]. This is clearly illustrated in Figure 1. It shows the frequency distributions of mPpa in 215 advanced COPD patients who underwent right heart catheterization and were screened for either lung transplantation or lung volume reduction surgery [7]. Pulmonary hypertension was present in 50.2% of the patients, and was considered as mild (mPpa, 26 to 35 mmHg) in 36.7%, moderate (mPpa, 36 to 45 mmHg) in 9.8% and severe (mPpa, > 45 mmHg) in 3.7%.

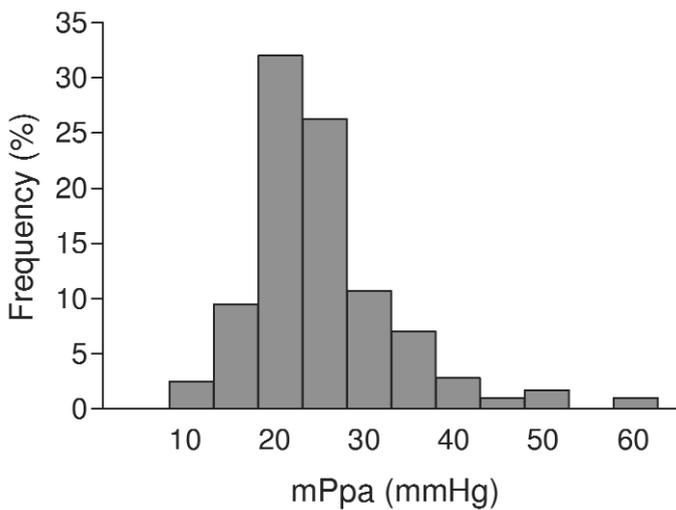


FIGURE 1. Frequency distribution of mean pulmonary artery pressure (mPpa) in 215 advanced COPD patients. Pulmonary hypertension was present in 50% and was considered severe (mPpa > 45 mmHg) in 3.7% of the patients. Adapted from reference 7.

In the natural history of COPD, pulmonary hypertension is often preceded by an abnormal large increase in mPpa during exercise [12;13], defined by a pressure above 30 mmHg for a mild level of steady-state exercise. In COPD patients, the rate of progression of pulmonary hypertension is slow [4]. The latter study, in which 93 COPD patients were followed for 5-12 years, demonstrated that the changes of mPpa were rather small: + 0.5 mmHg/year for the group as a whole. Interestingly, the evolution of mPpa was identical in patients with and without initial pulmonary hypertension.

The pathological picture of the pulmonary vasculature shows that although all layers of the vessel appear to be involved in pulmonary vascular remodeling in COPD, the most typical finding is media hypertrophy and intima degradation, figure 2. Long-lasting hypoxic vasoconstriction is believed to be the predominant factor leading to pulmonary artery remodeling [14]. Acute hypoxia causes pulmonary vasoconstriction whereas chronic longstanding hypoxia induces structural changes in the pulmonary vascular bed. Mechanical stress or inflammatory reaction due to repeated stretching of hyperinflated lungs, and very important, the toxic effects of cigarette smoke may also be involved in the pathobiology of pulmonary artery remodeling [15].

Pulmonary hypertension is associated with increased morbidity [11;16], and survival of COPD patients were found to be inversely related to their pulmonary vascular resistance (PVR) index or pulmonary artery pressure [3;11;16]. Despite the fact that all of these studies showed that Ppa is one of the most important

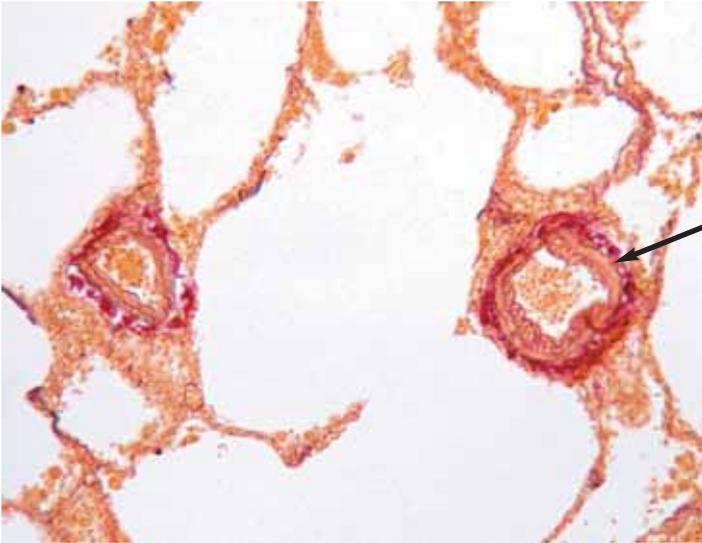


FIGURE 2. Optic-microscopic view of a pulmonary artery from a patient with pulmonary hypertension secondary to COPD. All three vessel wall layers are remodeled, with prominent intimal thickening (arrow).

prognostic factors in COPD, this complication of the disease received little attention in comparison to other pathophysiological factors involved in this disease, such as airflow limitation. In addition, in 2003 it was ignored as a topic on the National Heart, Lung, and Blood Institute (NHLBI) workshop, during which important questions in the field of COPD research were determined [17].

The right ventricle in COPD

Pulmonary hypertension will increase right ventricular afterload and affect right ventricular pump function. Although these effects on right ventricular function can be absent at rest [18], less is known about the adverse effects of a sudden increase in afterload during exercise, that might hamper stroke volume response and thus oxygen delivery to the tissues. To understand these effects, insight in the normal right ventricular function is obligatory. Bordered by the concave free wall and the convex intraventricular septum, the normal right ventricle is a crescent-shaped chamber with a thin lateral free wall and greater volume and surface area than the left ventricle. The function of right ventricular contraction is to generate sufficient stroke volume to maintain an adequate cardiac output rather than generating pressure. Hence, the right ventricle operates as a “volume” rather than a “pressure” pump [19]. The thin-walled right ventricle, contracting against the low-pressure pulmonary circulation, is more compliant than the thicker walled left ventricle. The geometric configuration of the right ventricle is therefore more suited to ejecting large volumes of blood with minimal myocardial shortening. In

physiological terms, the right ventricle is more able to adapt to changes in preload than to acute increases in afterload [19].

Pulmonary artery pressures in most COPD patients are not markedly elevated [20], and the rate of progression of pulmonary hypertension is slow [4]. Therefore, the right ventricle has time to adapt to the modest increase in pressure load in COPD. The presence of pulmonary hypertension alters right ventricular structure and function [21], so-called cor pulmonale. Cor pulmonale is defined as an alteration of right ventricular function, with right ventricular dilatation and hypertrophy, in response to increased pulmonary artery pressures caused by a pulmonary disease [8;9]. This remodelling implies the transformation of the right ventricle from a “volume” pump to a “pressure” pump.

Patients with mild COPD have normal or low cardiac output, normal right atrial and right ventricular end-diastolic pressures. Once pulmonary hypertension is established, the right ventricle dilates with an increase in both end-diastolic, or preload, and end-systolic volumes, and a maintained stroke volume [22]. The increase in preload, in response to increased afterload, is enhanced by an increase in systemic venous return due to activation of sympathetic nervous and renin-angiotensin-aldosterone systems, and associated hypervolemia caused by renal salt and water retention [22].

In COPD, the assessment of right ventricular function is difficult, due to marked increase in intrathoracic gas, expansion of the thoracic cage, and alterations in the position of the heart, making it difficult to visualize the ventricle by means of echocardiography. In addition, right ventricular ejection fraction (RVEF) is difficult to assess by means of standard techniques. Earlier radionuclide angiographic techniques showed that RVEF is depressed to less than 50% in about half of unselected but advanced COPD patients [23;24]. A reduced RVEF is associated with increased pulmonary artery pressures [25]. Nonetheless, a decrease in RVEF does not mean that there is true ventricular dysfunction [26] since RVEF, in contrast to left ventricular ejection fraction, is not a sole parameter of contractility but is also largely dependent on preload, afterload and heart rate. A better approach to measure right ventricular function is the assessment of end-systolic pressure volume relationships. Using this approach, that requires simultaneous pressure and volume measurements in the right ventricle, it has been shown that, irrespective of the Ppa, the contractility of the right ventricle in COPD patients lies within normal limits [27]. In addition, correlations between Ppa and RVEF vary widely in the literature [25;27;28]. The latter may in part be accounted for by differences in the technique used to measure RVEF. Thus, RVEF probably reflects the consequences of an increased afterload rather than the presence of a decreased right ventricular performance in COPD patients.

Left ventricle

In most patients with advanced COPD there is no intrinsic left ventricular dysfunction in the absence of coexisting coronary artery or hypertensive heart disease [29]. However, left ventricular diastolic function could be impaired. The right and left ventricle both share the interventricular septum and both are enclosed in the pericardium. As a consequence, an overloaded right ventricle may cause a geometric distortion, thereby impeding left ventricular diastolic filling [30].

Increased ventilation during exercise, in the presence of airflow obstruction results in significant intrathoracic pressure swings. These changes in pressure may reduce cardiac output by altering systemic venous return or by increasing left ventricular afterload [31].

Hemodynamics during exercise

The primary hemodynamic abnormality in severe COPD is an increase in pulmonary vascular resistance (PVR). During steady-state exercise, an abnormal increase in mPpa has been demonstrated, especially in COPD patients with resting pulmonary hypertension [3;32]. Patients that appear more prone to the development of pulmonary hypertension may show an abnormal rise in afterload during exercise years before pulmonary hypertension is apparent at rest [12]. This

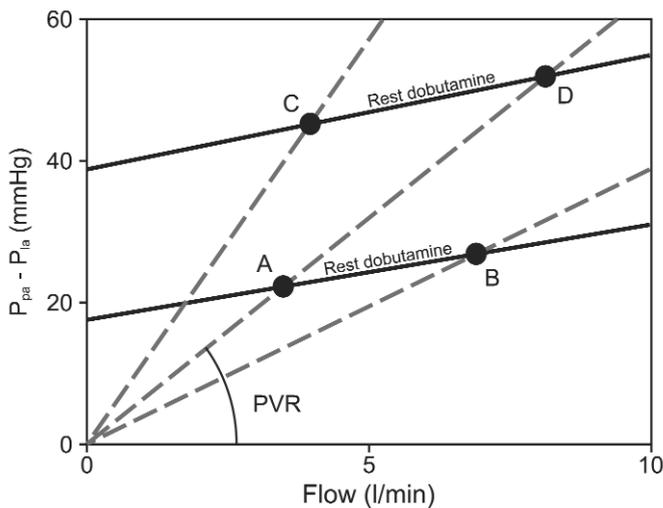


FIGURE 3. Relation between pulmonary artery pressure (P_{pa}) minus left atrial pressure (P_{la}) and pulmonary blood flow in a representative patient with COPD at rest (A) and during exercise (C). Pulmonary vascular resistance (PVR) is the slope of the $(P_{pa} - P_{la})/\text{flow}$ relationship (dotted lines). Dobutamine is supposed to induce a passive increase in flow. Passive increases in flow (A to B and C to D) increase pressure less than predicted by the PVR equation. Exercise (A to C and B to D) increases pressure more than predicted by the PVR equation. Figure adapted from reference (33).

abnormal rise in mPpa is explained by the fact that, in contrast to healthy subjects, recruitment of underperfused vessels does not occur during exercise. In addition, the augmentation of mPpa is greater than predicted by the PVR equation (Figure 3) [33], indicating enhanced pulmonary vasoconstriction on exertion [34]. The latter may be due to enhancement of hypoxic pulmonary vasoconstriction by decreased mixed venous PO_2 , increased tone of the sympathetic nervous system or decreased arterial PO_2 [33]. Another explanation is that augmented expiratory pressures during exercise as a result of dynamic airway collapse might further elevate pulmonary artery pressure [31].

It remains unclear whether this steep increase in Ppa during exercise affects right ventricular pump function. The results of maximal cardiopulmonary exercise tests and its parameters that provide information on both ventilatory as well as cardiac function have not been shown to elucidate this question. The fact that patients with COPD show a reduced maximum exercise capacity than normal controls, but no difference in slope of the oxygen consumption versus cardiac output relationship, has been taken as an indication that exercise limitation in COPD is not of cardiovascular origin. This, however, might not be true for several reasons. First, regardless the origin of the limitation in exercise capacity, it has been demonstrated that oxygen consumption and cardiac output remain linearly related up to maximum oxygen consumption [35]. Second, although the cardiac output response to exercise is normal in patients with COPD, the heart rate is higher and, consequently, stroke volume is smaller than in normal subjects at the same VO_2 [36;37]. The oxygen uptake per heart beat or oxygen pulse, a measure of stroke volume, is characteristically low and may be a major factor limiting exercise capacity in these patients. Finally, oxygen uptake is not only the product of cardiac output but also peripheral oxygen extraction. Hence, an increased peripheral oxygen extraction might falsely mimic a normal stroke volume response during exercise.

Radionuclide studies have shown that patients with advanced COPD frequently fail to increase, or even decrease their right ventricular ejection fraction, which is in favor of a cardiac limitation to exercise capacity [38]. Accordingly, Bogaard and co-workers found a lower stroke volume index (i.e. stroke volume divided by body surface area) and higher heart rate in patients than in controls during submaximal exercise measured non invasively using electrical impedance cardiography [39]. They suggest that in mild COPD predominantly ventilatory factors determine exercise tolerance, whereas in more severe COPD, hemodynamic factors may contribute.

Pulmonary vasodilation in COPD

As mentioned previously, PH in COPD patients is generally mild to moderate. This raises the question whether it is necessary to treat PH in this patient group.

The best argument in favour of treatment is that PH, even when modest at rest, may worsen, particularly during acute exacerbations and exercise. These acute increases in right ventricular afterload can contribute to the development of right heart failure. In addition, the presence of PH in COPD reduces survival.

Chronic hypoxemia plays an important role in the development of pulmonary hypertension, and therefore, correction of alveolar hypoxia with supplemental oxygen seems appropriate for treatment of PH in COPD. Patients receiving long-term oxygen therapy showed a progressive decrease of pulmonary artery pressure of -2.2 mmHg/year, whereas pulmonary artery pressure increased by $+1.5$ mmHg/year before initiating oxygen therapy. Despite this improvement normalisation of pulmonary artery pressure was rarely observed [40]. When oxygen is administered during exercise it improves pulmonary hemodynamics [3] and has either no effect or slightly increases right ventricular ejection fraction [41;42]. However, the fall in RVEF that occurs in most COPD patients during exercise can be prevented by oxygen [41]. After 6 months of continuous oxygen therapy, stroke volume index during exercise was significantly increased in 48 COPD patients. Note, that pulmonary hypertension is still a good predictor of mortality in COPD patients treated with supplemental oxygen. In a series of 84 patients with advanced COPD treated with long-term oxygen, the five-year survival rate was 62% in patients without pulmonary hypertension and only 36% in patients with a mPpa higher than 25 mmHg [16].

Pulmonary vasodilators, by decreasing right ventricular afterload and allowing cardiac output to increase, should improve oxygen transport, tissue oxygenation and exercise tolerance. There are very few selective pulmonary vasodilators. Numerous studies of pulmonary vasodilators, (including β_2 -agonists, nitrates, calcium channel blockers, angiotensin converting enzyme inhibitors, theophylline, α_1 -receptor antagonists), have been undertaken in COPD patients. Although most studies have shown a modest fall in Ppa accompanied by a rise in cardiac output, they have in addition shown a deleterious effect on gas exchange [43-46]. The latter is a consequence of vasodilation of unventilated areas in the lungs and hence worsening venous admixture and a fall in arterial PO_2 occurs. Inhaled nitric oxide (NO), a selective pulmonary vasodilator, [47] can reduce pulmonary artery pressure, and has been shown to improve gas exchange during exercise. In contrast to these findings, it has been shown that in patients with COPD inhaled NO can worsen gas exchange because of impaired hypoxic regulation of ventilation to perfusion matching [48].

Administration of sildenafil, a phosphodiesterase 5 inhibitor, is a well-recognized alternative to stimulate NO-mediated vasodilatation, by degradation of cyclic GMP, as demonstrated in Figure 4. Recent evidence showed that this medication is effective in the treatment of pulmonary arterial hypertension [49]. Although evidence is lacking that this medication is effective in COPD related PH, it has been shown that sildenafil can reduced Ppa at high altitude in hypoxic

human volunteers [50;51], and in patients with severe lung fibrosis [52]. The potential for this agent in COPD is currently being tested.

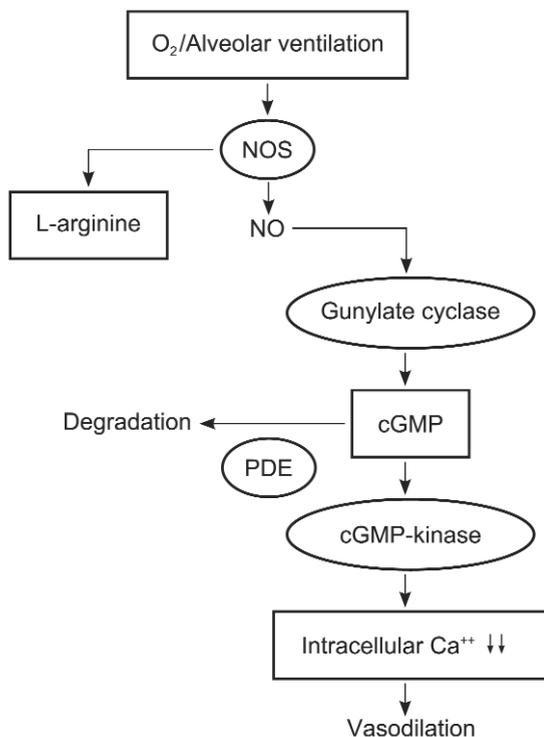


FIGURE 4. Endothelium-derived or exogenous (inhaled) NO activates soluble guanylate cyclase, thereby stimulating the production of cyclic guanosine monophosphate (cGMP) in pulmonary artery smooth muscle cells. cGMP relaxes the smooth muscle cells through several mechanisms, including enhanced opening of large-conductance, calcium-sensitive K⁺ channels. This causes a reduction in intracellular Ca⁺⁺, that leads to vasodilation. By selectively inhibiting phosphodiesterase type 5 (PDE), sildenafil promotes the accumulation of intracellular cGMP and thereby enhances nitric-oxide (NO) mediated vasodilation.

Aims and outline of this thesis

In order to elucidate the influence of a cardiovascular component to limitation in exercise tolerance in COPD patients, it is necessary to study both cardiac function and pulmonary hemodynamics at rest and during exercise. The results of these studies are presented in this thesis. For the study of cardiac function we used Magnetic Resonance Imaging (MRI). MRI is now considered as the gold standard

for measuring right ventricular volume and function. It relies solely on magnetic fields and is harmless to the human body. Furthermore, MRI does not require any assumptions to be made on anatomy of function of the heart, offers high quality images, and is reproducible. In addition, this thesis describes the possible role of vasodilatory therapy on alleviating cardiac function, especially during exercise, and whether this results in an improved stroke volume response to exercise and, consequently, an improved exercise tolerance in patients with COPD.

The question whether adaptation of the right ventricle occurs in COPD patients without clinical signs of pulmonary hypertension is dealt with in **Chapter 2**. To gain insight in the effect of an increased afterload on right and left ventricular function during exercise, we studied cardiac function during exercise in patients with a pulmonary vascular exercise limitation (idiopathic pulmonary hypertension patients). The results are described in **Chapter 3**. In **Chapter 4**, it was investigated whether the exercise-induced rise in Ppa in COPD patients alters right ventricular pump function. In addition, exercise-induced changes in cardiac structure and function were related to changes in pulmonary artery pressure to exercise. The next step was to determine whether acute vasodilation, by means of oral intake of a phosphodiesterase 5 inhibitor, sildenafil, can reduce Ppa during exercise, **Chapter 5**. Furthermore, **Chapter 5** describes whether a possible reduction in right ventricular afterload during exercise translates into an improved stroke volume response and maximal exercise capacity. In **Chapter 6** we sought to assess differences in physiological response to a maximal cardiopulmonary exercise test in COPD patients with and without the presence of pulmonary hypertension. In **Chapter 7**, the results from the preceding chapters are summarized, conclusions are made and some directions for future research are indicated.

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CHAPTER TWO

Early changes of cardiac structure and function in COPD patients with mild hypoxemia

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ABSTRACT

Background COPD is often associated with changes of the structure and the function of the heart. Although functional abnormalities of the right ventricle have been well described in COPD patients with severe hypoxemia, little is known about these changes in patients with normal to mild hypoxemia.

Study objectives To assess the structural and functional cardiac changes in COPD patients with normal partial pressure of arterial oxygen and without signs of right ventricular failure.

Methods In 25 clinically stable COPD patients (FEV_1 : 1.23 ± 0.51 l/s, PaO_2 : 82 ± 10 mm Hg) and 26 age-matched control subjects, the right and left ventricular structure and function were measured by MRI. Pulmonary artery pressure was estimated from right pulmonary artery distensibility.

Results Right ventricular mass divided by right ventricular end-diastolic volume as a measure of right ventricular adaptation was 0.72 ± 0.18 g/ml in the COPD group and 0.41 ± 0.09 g/ml in the control group ($p < 0.01$). Left and right ventricular ejection fraction were $62 \pm 14\%$ and $53 \pm 12\%$ in the COPD patients, and $68 \pm 11\%$ and $53 \pm 7\%$ in the controls. Pulmonary artery pressure (Ppa) estimated from right pulmonary artery distensibility was not elevated in the COPD group.

Conclusion From these results we conclude that concentric right ventricular hypertrophy is the earliest sign of right ventricular pressure overload in COPD. This structural adaptation of the heart does not alter right and left ventricular systolic function.

INTRODUCTION

The classic view of the development of right ventricular hypertrophy in chronic obstructive pulmonary disease (COPD) is that a reduction of the pulmonary vascular bed and hypoxia induced pulmonary vasoconstriction increase pulmonary vascular resistance, leading to pulmonary hypertension. Clinical studies have shown that hypoxemia is one of the major determinants of pulmonary hypertension [1;2]. Different patterns of hemodynamic abnormalities have been described in COPD. Patients with a severe obstructive ventilatory impairment but with relatively normal arterial blood gas values do not usually demonstrate pulmonary hypertension during rest. Patients with hypoxemia typically demonstrate pulmonary hypertension at rest accompanied by clinical and ECG evidence of right ventricular hypertrophy [1;3]. Post-mortem findings provide further evidence of the relation between hypoxemia and the development of right ventricular hypertrophy [4]. Given these findings, it can be hypothesized that the adaptational mechanism of the right ventricle is different in COPD patients without hypoxemia compared to patients with hypoxemia. Recent studies in large groups of patients with COPD and hypoxemia demonstrated increased right ventricular volumes, decreased right ventricular function, and impaired left ventricular diastolic function [5;6].

Advances in MRI have made it possible to accurately measure early changes of the complex geometry of the right ventricular wall and chamber volume [7]. In most MRI studies in COPD, however, patients with severe hypoxemia were included [8-11]. Therefore, no strong conclusions can be drawn from the early adaptational mechanisms of the right ventricle in patients with normoxemia or mild hypoxemia and the consequences of any structural changes on right and left ventricular function.

The objective of this study was to assess the early right ventricular changes and the effect of these changes on both right and left ventricular function in a group of COPD patients with normoxemia compared to an aged-matched control group of normal subjects.

METHODS

Subjects

Twenty-five patients (19 men and 6 women) with a mean age of 68 ± 7 (mean \pm sd) years participated in the study. All patients had been diagnosed as having COPD according to the criteria of the American Thoracic Society and had an arterial oxygen pressure (PaO_2) above 60 mm Hg measured at rest [12]. The subject

group was compared to a control group consisting of 26 age-matched healthy non-smoking subjects with a mean age of 56 ± 8 years.

All patients were investigated during a stable period of their disease. Patients with a history of systemic hypertension, ischemic or valvular heart disease or episodes of right and/or left-sided cardiac failure were excluded from the study. The protocol was approved by the Medical Ethical Committee of the VU University medical center. All patients were informed about the aim of the study and gave their informed consent.

Lung function

Lung function measurements were performed within 2 months of the MRI measurements. Dynamic and static lung volumes and single-breath carbon monoxide diffusing capacity (Vmax 229 and 6200, SensorMedics, Yorba Linda, USA) were determined according to the ERS guidelines and compared to the ERS reference values [13]. Arterial blood gases were measured at rest with the patient breathing room air.

TABLE 1. Pulmonary function and arterial blood gas data of the COPD patients

FEV ₁ , l	1.23 ± 0.51
FEV ₁ , % predicted	41 ± 15
FEV ₁ /VC, %	34 ± 8
VC, l (% predicted)	3.64 ± 1.22 (90 ± 20)
TLC, l (% predicted)	8.1 ± 1.4 (121 ± 19)
RV/TLC, %	52 ± 11
DLCO, % predicted	41 ± 16
PaO ₂ , mmHg	82 ± 10

Values are mean ± SD. Abbreviations: FEV₁ = forced expiratory volume in one second, VC = vital capacity, TLC = total lung capacity, RV = residual volume, DLCO = diffusing capacity of the lungs for carbon monoxide

Magnetic resonance imaging protocol

The patients and controls were scanned using a 1.5 T Siemens Vision whole body system and a phased-array body coil (Siemens Medical Systems, Erlangen, Germany). All image acquisition was gated of the R-wave of the electrocardiogram. During all image acquisitions (thus also during scout imaging for localization of the heart) the subject was instructed to hold breath after moderate inspiration.

Short-axis ventricular imaging

The horizontal long-axis view was determined in a late diastolic frame [14]. By using the end-diastolic cine frame of this long-axis view, a series of parallel short-

axis (SA) image planes was defined starting at the base of the left ventricle (LV) and right ventricle (RV), and encompassing the entire LV and RV from base to apex. The most basal image plane was positioned close to the transition of the myocardium to the mitral and tricuspid valve leaflets (at a distance of half the slice thickness). This ensured that the most basal part of the LV and RV were also covered. At every short axis plane, a breath-hold cine acquisition was performed. For the cine-imaging, a gradient-echo pulse sequence was applied with segmented k-space, $7k_y$ lines per heart beat, and a temporal resolution of 80 ms. Echo-sharing yielded a temporal frame at every 40 ms. The excitation angle was 25 deg; the field of view was 280x320 mm; matrix size was 126x256. Slice thickness was 6 mm and gap 4 mm, resulting in a slice distance of 10 mm. Heart rate was monitored during the acquisition of the SA images.

Image analysis

The images were processed on a Sun Sparc station using the 'MASS' software package (Dept. of Radiology, Leiden University Medical Center, Leiden, The Netherlands). All MRI data were processed by a blinded observer. End-diastole was defined as the first temporal frame directly after the R-wave of the ECG. End-systole was defined as the temporal frame at which the image showed the smallest right and left ventricular cavity area, usually 240-320 ms after the R-wave. Epi- and endocardial contours were manually traced. The papillary muscles were excluded from the RV and LV volume and included in the determination of RV and LV mass. Because of RV and LV shortening, at least one extra slice at the RV and LV base was needed at end-diastole to encompass the complete RV and LV. If the most basal image at end systole was difficult to interpret (due to partial volume effects), this most basal plane was projected on to the end-systole frame of the long-axis cine images. The resulting projection line on this long-axis view was used to decide whether or not to include the end-systolic short axis image as a part of the LV or RV. The LV end-diastolic mass was obtained from the volume of the LV muscle tissue including the interventricular septum. The RV end-diastolic mass was obtained in a similar way, but excluding the septum. In the mass calculation, the specific weight of muscle tissue was 1.05 g/cm^3 based on an earlier study in dogs [15]. The distensibility of the right pulmonary artery defined as maximal systolic cross-sectional area minus end-diastolic cross-sectional area divided by the end-diastolic cross-sectional area was derived from cine images acquired in a plane orthogonal to the right pulmonary artery [8]. The distensibility of the right pulmonary artery was regarded as an indicator of pulmonary artery pressure [16;17].

Statistical analysis

The results were reported as mean \pm S.D. Differences between patients and controls were tested using the Student-t Test for two independent groups. For analy-

sis of factors associated with right ventricular hypertrophy, univariate regression analysis was performed. Data were analysed using SigmaStat 2.03 (SPSS Inc., Chicago, IL). A p-value less than 0.05 was considered significant.

RESULTS

Mean pulmonary function data and the arterial blood gases of the 25 COPD patients are presented in Table 1. Most of the patients had considerable bronchial obstruction, as reflected by a mean FEV₁ of 1.23 l and a mean FEV₁/VC of 34%. None of the patients had an increased PaCO₂ level. Nineteen patients had a PaO₂ above 80 mmHg, and only three patients had a PaO₂ between 60 and 70 mm Hg.

Diagnostic MRI measurements were performed in all patients included in the study. The average time required for the total MRI protocol was about 30 minutes. Figure 1 shows the short and long axis of the heart of a COPD patient and a healthy control subject during end-diastole. The short axis image corresponds to the short axis view of the heart at the mid-level between base and apex. The position of the heart of the COPD patient is altered to a more vertical position in the thoracic cavity due to hyperinflation of the lungs, increasing the retrosternal space. The patient's short and long axis images showed right ventricular hypertrophy and an altered morphology of the right and left ventricle.

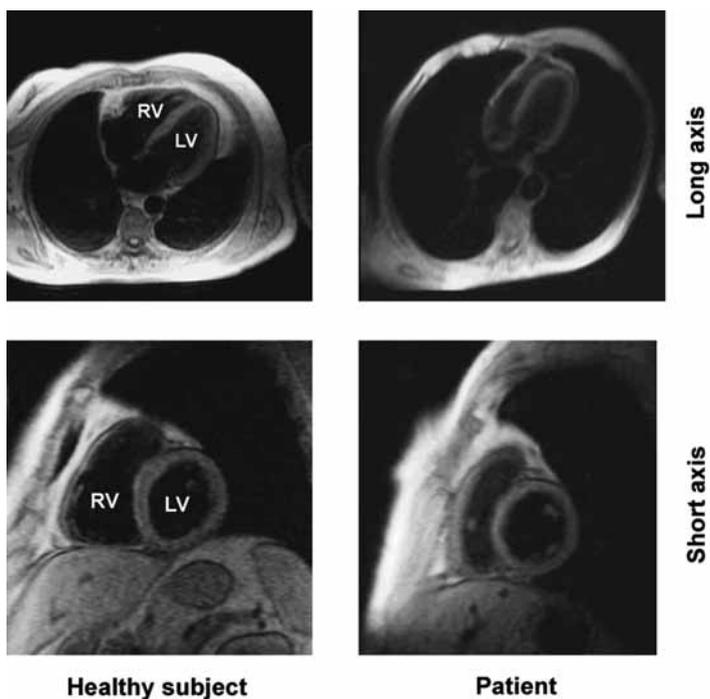


FIGURE 1. Short and long axis MR images of the heart in a healthy subject and a COPD patient. Abbreviations: RV = right ventricle, LV = left ventricle.

Table 2 compares the cardiac parameters between subjects and control groups. Stroke volume was significantly lower in the COPD group. Since the heart rate in the COPD group was higher than the controls, cardiac output was similar between both groups. RV wall mass was significantly higher in the patient group, whereas LV wall mass did not differ significantly between both groups. Both right ventricular end-diastolic volume and end-systolic volume were significantly lower compared to the controls. While left ventricular end-diastolic volume was lower compared to the controls, left ventricular end-systolic volume was within a normal range. Right and left ventricular ejection fractions were similar in the COPD group compared to the control group.

TABLE 2. Structural and functional cardiac parameters

	Controls (n = 26)	COPD (n = 25)	P value
LVEDV, ml	117 ± 21	92 ± 25	<0.01
RVEDV, ml	145 ± 35	100 ± 23	<0.01
LVESV, ml	41 ± 13	39 ± 17	NS
RVESV, ml	68 ± 22	48 ± 19	<0.01
LVEF, %	68 ± 11	62 ± 14	NS
RVEF, %	53 ± 7	53 ± 12	NS
CO, l/min	4.6 ± 1.4	4.1 ± 1.0	NS
CI, l/min/m ²	2.3 ± 0.7	2.2 ± 0.5	NS
SV, ml	77 ± 18	53 ± 14	<0.01
HR, bpm	60 ± 12	78 ± 12	<0.01
RVEDM, g	59 ± 14	68 ± 12	<0.01
LVEDM, g	134 ± 23	111 ± 26	<0.01
LVEDM/LVEDV, g/ml	1.18 ± 0.15	1.30 ± 0.44	NS
RVEDM/RVEDV, g/ml	0.41 ± 0.09	0.72 ± 0.18	<0.01
RVEDM/LVEDM	0.44 ± 0.04	0.63 ± 0.09	<0.01

Values are mean ± SD. Abbreviations: LVEDV, RVEDV = left and right ventricular end-diastolic volume, LVESV, RVESV = left and right ventricular end-systolic volume, LVEDM, RVEDM = left and right ventricular wall mass, LVEF, RVEF = left and right ventricular ejection fraction, SV = stroke volume, CO = cardiac output, CI = cardiac index, HR = heart rate.

Right ventricular systolic dysfunction defined as a right ventricular ejection fraction lower than 45 % was present in 20 % of the patients, and a left ventricular systolic dysfunction, defined according to the same criteria, was present in 16 % of the patients.

The right pulmonary artery distensibility was not significantly different in the patient group (37±18%) compared to the control subjects (39±17%). This suggests that pulmonary hypertension was not present in the COPD patients during resting conditions.

Table 3 presents the results of the univariate regression analysis comparing right ventricular mass and the pulmonary function outcomes in the patient group. No significant relationship was found.

TABLE 3. Univariate regression analysis between right ventricular mass and pulmonary function parameters of the patient group

	Coefficient	Adjusted R ²	P value
FEV ₁ , % predicted	0.14	0.16	0.42
FEV ₁ /VC	-0.56	0.38	-0.18
DLCO, % predicted	-0.001	0.16	0.94

Abbreviations: FEV₁ = forced expiratory volume in 1 s, VC = vital capacity, DLCO = diffusing capacity of the lungs for carbon monoxide

DISCUSSION

This study is the first documentation of right ventricular hypertrophy as an early sign of adaptation of the right ventricle to pressure overload in COPD. It shows that even in patients with normoxia ($\text{PaO}_2 > 80$ mmHg) or mild hypoxemia ($\text{PaO}_2 > 60$ mmHg) this adaptation is present. No data relative to sleep-related hypoxemia were obtained from these patients. Since the patients had no history of systemic hypertension, ischemic or valvular heart disease, the changes in structure and function of the right and left ventricle were considered to be adaptive responses to COPD. The outcomes of the cardiac parameters of the control group were within the same range as two earlier MRI studies providing reference data for the right and left ventricle [14;15].

Although we did not measure pulmonary artery pressure in our patients it can be safely assumed that pulmonary hypertension was not present during resting conditions because: 1) All our patients had a PaO_2 above 60 mm Hg and Oswald Mammoser et al. showed that pulmonary hypertension is rarely present at rest in COPD patients with a PaO_2 of > 60 mm Hg [2]. 2) The distensibility of the right pulmonary artery, an indirect measure of the pulmonary artery pressure, did not show a significant difference between the COPD patients and controls. The altered structure of the right ventricle can thus be attributed to the intermittent increases in pulmonary artery pressure that most likely occur during exercise and sleep in COPD [1;2;18].

Our results showed that marked right ventricular hypertrophy accompanies decreased right ventricular end diastolic volume. The hypertrophy is classified as concentric hypertrophy and is consistent with the well-known radiological characteristics of emphysema patients with a narrow vertical heart. Right ventricular systolic function was similar in COPD and control groups. This finding is in agree-

ment with those of earlier studies that show well-preserved right ventricular systolic function in most patients with COPD [19-21]. Thus, although our patients exhibited concentric hypertrophy as an early sign of intermittent pressure overload this hypertrophy was not accompanied by a loss of systolic function. This finding is in agreement with earlier studies on cardiac hypertrophy, which showed that concentric hypertrophy occurs in case of intermittent pressure-overload [22]. A pressure-overload causes an increase in right ventricular wall stress. By thickening the wall, the ventricle tends to normalize wall stress. This adaptation to intermittent pressure-overload does not depress systolic function. In the above-mentioned studies [19-21], it has also been shown that dilatation of the ventricle occurs when the hypertrophy is not able to keep pace with increased systolic pressure and/or volume overload. This latter mechanism might explain the findings of a previous echocardiographic study by Boussuges et al., who demonstrated a right ventricular dilatation in patients with severe COPD with pronounced hypoxemia (Mean PaO₂ = 54 mmHg) [6]. Thus, it can be postulated that in patients with COPD concentric right ventricular hypertrophy precedes dilating right ventricular hypertrophy. We did not find a significant relation between right ventricular mass and pulmonary function parameters. This may be explained by the small range of pulmonary function parameters in our patients due to our selection criteria. Thus, although our data did not show a relationship between the pulmonary function parameters and right ventricular mass, it does not exclude such a relationship in a more heterogenous patient group.

Left ventricular mass was not increased in our COPD group. In contrast, an earlier post-mortem study showed that the left ventricle wall is thickened in patients with chronic cor pulmonale without a history of hypertension who died of respiratory failure due to end-stage chronic pulmonary disease [4]. These findings indicate that left ventricular hypertrophy occurs in patients with severe COPD but is absent in patients with moderate COPD without clinical signs of cor pulmonale. Animal studies have shown that the magnitude of left ventricular hypertrophy is well correlated with the duration of right ventricular pressure overload [23;24].

Structural changes of the right ventricle might also alter left ventricular structure and filling due to the phenomenon of ventricular interdependency. This might explain lowered left ventricular end diastolic volumes found in COPD patients [6;25]. Left ventricular ejection fraction, as a global measure of left ventricular systolic function, was relatively normal in the patient group. Only 16 % of the patients had left ventricular systolic dysfunction, corresponding to findings in earlier studies [26]. Since the development of cor pulmonale is not accompanied by a decrease in left ventricular ejection fraction [27], the left ventricular systolic dysfunction found in some COPD patients is probably attributable to coincidental diseases affecting the left ventricle.

In conclusion, the data obtained in this study indicate that concentric right ventricular hypertrophy is already present in COPD patients with normoxemia or

mild hypoxemia, probably due to intermittent increases in pulmonary arterial pressures that occur during exercise and/or sleep. Concentric right ventricular hypertrophy does not impair right and left ventricular systolic function.

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CHAPTER THREE

Impaired stroke volume response to exercise in pulmonary arterial hypertension

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ABSTRACT

Introduction: In idiopathic pulmonary arterial hypertension (iPAH), right ventricular (RV) afterload is increased at rest and may increase further during exercise. Little is known about the effects of increased pressure overload during exercise on cardiac function and stroke volume response in these patients.

Aim: To investigate exercise-induced changes in cardiac function in patients with iPAH.

Methods: In 10 iPAH patients (NYHA 3, mean pulmonary artery pressure (mPpa) = 51 ± 18 mmHg) and 10 controls MRI measurements were performed during rest and sub maximal exercise. The exercise protocol consisted of 3 minutes of cycling in supine position at 40% of maximal workload. SV, RVEDV, LVEDV were assessed on short-axis cine heart images.

Results: In controls SV increased during exercise from 86 ± 25 to 109 ± 34 ml ($p < 0.01$). In iPAH, SV did not change during exercise (61 ± 27 vs. 60 ± 31 ml). Though not significantly, RVEDV was higher in iPAH and did not change during exercise. LVEDV was lower in iPAH (128 ± 32 vs. 88 ± 24 ml, $p < 0.05$) and decreased further during exercise (88 ± 24 vs. 76 ± 29 ml, $p < 0.05$).

Conclusion: We conclude that in patients with iPAH an exercise-induced rise in Ppa results in further impairment of RV function and underfilling of the LV, both leading to a failing SV response to exercise.

INTRODUCTION

Idiopathic pulmonary arterial hypertension (iPAH) is a rare, but fatal disease characterized by an increased right ventricular (RV) afterload, due to remodelling of the pulmonary arteriolar vessels [1]. Most patients with iPAH have severe exercise limitation, which can be explained by the inefficient lung gas exchange and the inability of the heart to adequately increase pulmonary blood flow during exercise. The latter may be due to an exercise-induced increase in pulmonary artery pressure [2;3]. It is unclear however to what extent exercise impairs right ventricular function in iPAH and whether LV function is also affected by a sudden increase in pulmonary artery pressure. Arguments that left ventricular (LV) function might also be impeded during exercise in iPAH are provided by recent research showing that leftward septal bowing is pressure dependent and impairs left ventricular filling [4;5]. An exercise-induced increase in pulmonary artery pressure might thus further worsen the leftward ventricular septal bowing and subsequently diastolic filling of the left ventricle.

The hypothesis of this study is that in iPAH exercise-induced increase in pulmonary vascular resistance and pulmonary artery pressure prevents appropriate cardiac output augmentation by an impaired increase in stroke volume. We, therefore, aimed to evaluate the effects of submaximal exercise on stroke volume and right and left ventricular function.

METHODS

Study population

The study group consisted of 10 iPAH patients (age 38 ± 16 , 5 female) all in NYHA class 3 and 10 healthy non-smoking control subjects (age 41 ± 13 , 6 female) without a history of cardiopulmonary disease. The iPAH patients were stable on daily treatment at the time of examination, which consisted of epoprostenol in 4 patients and bosentan in 6 patients. The Institutional Review Board on Research Involving Human Subjects of the VU University Medical Center approved the protocol and written informed consent was obtained from all subjects.

TABLE 1. Summary of demographics and resting hemodynamics in iPAH

Gender f/m	5/5
Age (yr)	38 ± 16
BSA (m ²)	1.94 ± 0.15
Medication	
Tracleer (Bosentan ^R)	6
Epoprostenol (flolan ^R)	4
Hemodynamics	
RAP (mmHg)	8 ± 5
mPpa (mmHg)	51 ± 18
sPpa (mmHg)	77 ± 25
PVR (dynes·s ⁻¹ ·cm ⁻⁵)	720 ± 428

Values are expressed as mean ± SD. Abbreviations: iPAH = idiopathic pulmonary arterial hypertension; BSA = body surface area, RAP = right atrial pressure, mPpa = mean pulmonary artery pressure, sPpa = systolic pulmonary artery pressure, PVR = pulmonary vascular resistance

Cardiac catheterization

All patients underwent right heart catheterization with a 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp; Irvine, CA), within two days of MRI.

Exercise testing

A maximal exercise test was performed within 4 days of catheterization and MRI measurements. Both patients and controls performed a physician-supervised, standard, progressively increasing work rate cardiopulmonary exercise test to maximum tolerance on an electromagnetically braked cycle ergometer. Pulse oximetry, heart rate and gas exchange were recorded and monitored (Vmax 229, SensorMedics, Yorba Linda, USA) during 3 minutes of rest, 3 minutes of unloaded cycling at 60 rpm followed by progressively increasing work rate to maximum tolerance, and 3 minutes of recovery [6].

MRI measurements

The MR images and flow measurements were acquired with a 1.5 Tesla Siemens Sonata whole body system (Siemens Medical Solutions, Erlangen, Germany) equipped with a circularly polarized phased-array body coil, as previously described [7]. The same MRI protocol was used for the resting and exercise measurements. The ECG was recorded with MRI compatible leads, to enable prospective ECG-R wave triggering. In contrast to the previously described method (7), no breathholds were used and temporal resolution was increased to 56 ms and 35 ms, respectively, for cine imaging and flow quantification. For short-axis cine imaging a Steady State Free Precession pulse sequence was applied. This cine

imaging was ECG triggered and realtime, which means that per temporal phase of 56 ms a complete image was acquired. From the stack of parallel short-axis cine images at end-diastole and systole, quantitative analysis of right ventricular volumes and geometry was performed by manual detection of endocardial and epicardial borders on each slice, using the MR Analytical Software System (Medis, Leiden, The Netherlands).

LVSV and RVSV were determined by assessing the flow in the aorta and main pulmonary artery, respectively. The pulse sequence was the same for both the aorta and the main pulmonary artery. Only the velocity sensitivity was set to 120 cm/s for the pulmonary artery, because of lower peak velocities. For the exercise measurements, the number of time phases in the cardiac cycle, and the velocity sensitivity were adjusted to the increased heart rate. By determining the flow in the main pulmonary artery it is possible to calculate effective forward stroke volume to the pulmonary circulation, not confounded by tricuspid regurgitation. The MRI exercise protocol consisted of a 3-minute period of cycling in supine position on a recumbent bicycle (Lode, Groningen, The Netherlands). Work rate was increased in the first minute to 40% of maximal workload as previously determined during maximal exercise testing. Between exercise measurements was a 5-minute resting period. Occurrence of exercise induced right- to-left shunting was measured by comparing flow in the aorta and main pulmonary artery.

Data analysis

The Mann Whitney test was used for between group analyses. To test for significance within groups between resting and exercise conditions the Wilcoxon signed rank test was used. A p-value < 0.05 was considered statistically significant for all tests.

RESULTS

Patient characteristics

Ten patients with iPAH were included in the study. Demographic and hemodynamic characteristics of the patient group are summarized in Table 1. Ten age-matched healthy controls underwent cardiac MRI at rest and during submaximal exercise. Mean age (41 ± 13 years) and body surface area (1.89 ± 0.16 m²) in the healthy controls (6 female) were not significantly different from the patients with iPAH.

TABLE 2. Resting and exercise cardiac function parameters by MRI.

	Controls		PAH	
	Rest	Exercise	Rest	Exercise
HR (beats / min)	66 ± 10	100 ± 14 ^Ø	80 ± 12 [*]	105 ± 12 ^Ø
<i>Right ventricle</i>				
SV (ml / beat)	86 ± 25	109 ± 34 ^Ø	61 ± 27	60 ± 31 [*]
CO (l / min)	5.5 ± 1.3	10.6 ± 2.6 ^Ø	4.7 ± 1.7	6.0 ± 2.7 [*] Ø
EDV (ml)	134 ± 40	138 ± 32	162 ± 49	172 ± 55
ESV (ml)	48 ± 19	29 ± 11 ^Ø	101 ± 62 [*] Ø ‡	111 ± 62 [*] Ø ‡
EF (%)	65 ± 7	78 ± 10 ^Ø	42 ± 23 [*]	38 ± 20 [*] Ø
<i>Left ventricle</i>				
SV (ml / beat)	82 ± 22	102 ± 30 ^Ø	57 ± 21 [*]	57 ± 23 [*]
CO (l / min)	5.2 ± 1.0	10.0 ± 2.4 ^Ø	4.4 ± 1.4	5.8 ± 2.1 [*] Ø
EDV (ml)	128 ± 32	131 ± 31	88 ± 24 [*] ‡	76 ± 29 [*] Ø ‡
ESV (ml)	47 ± 13	29 ± 9 ^Ø	31 ± 17 [*] ‡ Ø	19 ± 10 [*] Ø ‡
EF (%)	64 ± 7	77 ± 9 ^Ø	64 ± 15 [‡]	74 ± 11 ^Ø ‡

Values are mean ± SD. Abbreviations: HR = heart rate, SV = stroke volume, CO = cardiac output, RVEDV = right ventricular end-diastolic volume, LVEDV = left ventricular end-diastolic volume, RVEF = right ventricular ejection fraction, LVEF = left ventricular ejection fraction. * p < 0.05, iPAH versus healthy controls; Ø p < 0.05, rest versus exercise within groups, ‡ p < 0.05, right ventricle versus left ventricle within groups

Cardiac function at rest

Resting and exercise cardiac function parameters as measured by MRI are presented in Table 2. Heart rate (HR) was higher in the patient group. SV was larger in controls, though did not reach significance (p = 0.06) for the RV. Cardiac output (CO), product of HR and SV, yielded a comparable result in both groups. Though not significantly, RV end-diastolic volume (RVEDV) was higher, whereas LV end-diastolic volume (LVEDV) was significantly lower in iPAH. RV ejection fraction (RVEF) showed a lower value in iPAH in comparison with healthy controls.

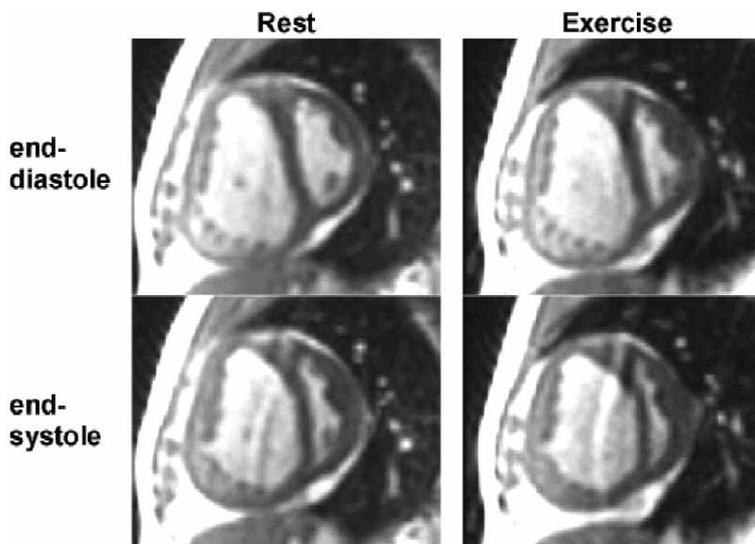


FIGURE 1. Example of a mid ventricular short axis MR cine image of a patient with iPAH at rest (left panels) and during exercise (right panels), during end-diastole (top panels) and during end-systole (bottom panels). Resting images were acquired at 40 and 289 ms after the R wave of the ECG when heart rate was 85 beats per minute. Exercise images were acquired at 40 and 237 ms when heart rate was 115 beats per minute. Note that left ventricular cavity size is smaller in the exercise conditions, and that leftward ventricular septal bowing is apparent in both conditions during end-systole and during exercise at end-diastole.

Cardiac function during exercise

An example of a mid-ventricular short axis MR cine image of a patient with iPAH at rest and during exercise is presented in Figure 1. It shows images of both conditions during end-diastole and end-systole. Note, that end-diastolic LV cavity size is small and becomes even smaller during exercise. RV dilatation is apparent, and both end-systolic and early diastolic frames show LV septal bowing at rest and during exercise.

All patients and healthy subjects were able to perform the MRI exercise test at 40 % of their maximal workload. Since the maximal work load, as determined by cardiopulmonary exercise testing, was lower for the iPAH group in comparison to the controls (105 ± 53 vs. 250 ± 93 W), the MRI measurements were therefore performed on different exercise levels in the iPAH group (42 ± 21 W) than in the controls (100 ± 37 W). Except for RVEDV and LVEDV, all cardiac parameters significantly increased to exercise in healthy controls (Table 2). In contrast to controls, iPAH patients were not able to significantly increase SV from rest to exercise

(Figure 2). Only one out of ten patients showed a clear increase in SV, and in most patients CO was therefore augmented by an increase in heart rate only. CO was higher in the control group, and was augmented significantly from rest to exercise in both groups.

RVEDV showed a not significant increase during exercise whereas LVEDV decreased. Although the absolute changes to exercise in LVEDV and RVEDV were almost similar (-12 ± 14 and 10 ± 18 mL, respectively), no correlation was found between the increase in RVEDV and the decrease in LVEDV. As a consequence of the changes in ventricular volumes and no changes in stroke volume from rest to exercise, RVEF worsened and LV ejection fraction (LVEF) increased in the patient group.

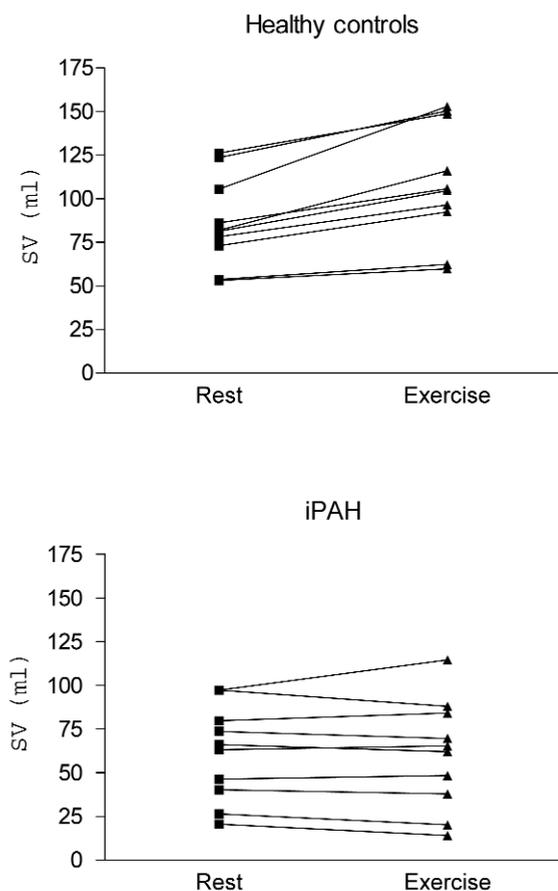


FIGURE 2. Stroke volume (SV) at rest and during exercise in healthy controls and patients with iPAH. SV in the patient group was lower at rest ($p = 0.06$), and did not change during exercise. In contrast to the patient group, SV was significantly increased to exercise ($p < 0.05$) in healthy controls. Mean values are presented in Table 2.

DISCUSSION

To our knowledge, this is the first MRI study to investigate the effects of submaximal exercise on cardiac function in patients with iPAH. SV was not increased during exercise; hence CO solely depended on an increase in HR in this group. An exercise-induced decrease in LVEDV, showed that exercise not only affects RV function but also impairs LV filling.

The finding that stroke volume is not increased in iPAH is in agreement with an earlier imaging study in 16 patients with pulmonary hypertension in which a decrease in SV to near maximal exercise was observed [8]. Although our study did not show a decrease in SV in most of the patients, the difference between both studies might be explained by differences in exercise protocols: near maximum versus submaximal exercise level. In healthy subjects, it is known that maximal SV is reached around 40 % of maximal oxygen uptake [9] (our protocol), and that SV can decrease in untrained subjects at near maximum exercise levels [10]. Another finding that provides strong evidence that SV progression during exercise is impaired in iPAH is given by a recent study showing that those patients have a reduced peak O₂ pulse during cardiopulmonary exercise testing, reflecting a reduction in peak SV [11].

During dynamic exercise venous return is augmented as well as myocardial contractility in healthy subjects. Earlier studies have revealed that an increase in left ventricular stroke volume during exercise in supine position is caused by either an increase in left ventricular end-diastolic volume and thus preload [12-14] or a reduction of end-systolic volume without changing end-diastolic volume due to an increase in myocardial contraction [15]. In the present study RVEDV and LVEDV remained stable during exercise whereas end-systolic volume decreased in our age-matched control group, showing that the augmentation of SV in this group was due to increased myocardial contractility during exercise. In contrast, the iPAH patients were not able to augment SV to exercise, in spite of a small increase in RVEDV, and a decrease in LVEDV. The decrease in LVEDV can be explained by the following mechanisms:

First, our findings showed that LVEDV was decreased in the patient group, together with a small but not significant increase in RVEDV. Total cardiac end-diastolic blood volume did not change from rest to exercise (250 ± 57 and 248 ± 60 mL, respectively). Since the right and the left ventricle are enclosed in a relatively nondistensible pericardium and separated by the interventricular septum, changes in one ventricular volume will directly influence the other [16]. Therefore, exercise-induced changes in RV volume and pressure-mediated septal curvature will occur at the expense of the LV volume. This is in agreement with a study in an animal model, which showed that a sudden increase in RV end-diastolic pressure occurs at the expense of the left ventricular end-diastolic volume [17].

Second, our results showed a slight reduction of the RVEF during exercise in the patients in contrast to an increase in RVEF in controls providing evidence that right ventricle failure becomes more manifest during exercise. Forward failure of the right ventricle will also hamper an adequate filling of the left ventricle. Since it can be assumed that the left ventricle is brought in a state of increased inotropic activity during exercise, inadequate filling of the left ventricle will lead to a reduction of LVEDV.

Study limitations

Since we did not measure pulmonary artery pressure during exercise, we were not able to relate stroke volume response to exercise-induced Ppa. In addition, without knowledge of direct invasive measurements of Ppa and pulmonary capillary wedge pressure leaves it unclear as to the relative contribution of impaired RV contractile function and impaired LV diastolic function to failure to augment stroke volume during exercise. Furthermore, this study only provides insight in exercise performed in supine position, whereas it is well known that cardiac adaptation to exercise can be different when performed in the upright position, as explained in the above.

Conclusion

We conclude that in patients with iPAH an exercise-induced rise in Ppa results in underfilling of the LV. The latter was more pronounced in patients with a high RV afterload at rest. An increased RV afterload and LV underfilling may both lead to a failing SV response to exercise.

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CHAPTER FOUR

Stroke volume increase to exercise in COPD is limited by pulmonary artery pressure

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submitted

ABSTRACT

Aim: This study was designed to investigate the mechanism by which the right ventricle is able to increase stroke volume during exercise in COPD patients with and without pulmonary hypertension. A second aim was to determine whether resting pulmonary artery pressure (Ppa) is predictive for exercise SV.

Methods: 16 COPD patients (GOLD stages II-IV) underwent right heart catheterization at rest and during exercise. In this group and 8 age-matched controls resting and exercise right ventricular SV, end-diastolic volume (RVEDV) and end-systolic volume (RVESV) were assessed by MRI. The exercise protocol during both measurements consisted of 3 minutes of cycling in supine position at 40% of maximal workload.

Results: In all patients mPpa increased significantly in response to exercise (21 ± 8 versus 33 ± 11 mmHg, $p < 0.01$), whereas pulmonary vascular resistance did not change. In the patient group, RVEDV (129 ± 42 versus 135 ± 42 mL, $p < 0.05$) and SV (63 ± 13 versus 69 ± 14 mL, $p < 0.05$) increased significantly from rest to exercise, but RVESV and RV ejection fraction remained unaltered. In contrast, in healthy controls SV is augmented (81 ± 22 versus 101 ± 28 mL, $p < 0.05$) by both increased RVEDV (123 ± 33 versus 134 ± 134 mL, $p < 0.05$) and reduced RVESV (37 ± 9 versus 27 ± 10 mL, $p < 0.05$). Resting mPpa was related to SV during exercise ($r = -0.59$, $p < 0.02$).

Conclusion: As a consequence of unaltered pulmonary vascular resistance to exercise in COPD patients, SV increase is limited and results from an increased preload only. Ppa at rest is related to exercise SV.

INTRODUCTION

Advanced chronic obstructive pulmonary disease (COPD) is associated with changes in cardiac structure and function due to increased pulmonary artery pressures [1]. Before elevated pulmonary artery pressure (Ppa) is apparent at rest, patients with COPD may develop pulmonary hypertension (PH) during physical activity [2;3]. This abnormal rise in Ppa is explained by the fact that pulmonary vascular resistance (PVR) does not decrease or might even increase during exercise in COPD patients. As a consequence, cardiac output augmentation during exercise is limited and will lead to an increase in Ppa. In contrast to this, in healthy subjects pulmonary vasodilatation, through recruitment and distention of the pulmonary vascular bed, occurs during exercise and pulmonary blood flow increases. Hence, PVR is reduced and the Ppa increase is limited [4].

Studies on the effects of exercise and the subsequent rise in Ppa on cardiac function have shown that right ventricular end-diastolic volume (RVEDV) increases [5;6] and right ventricular ejection fraction (RVEF) fails to augment to exercise in most COPD patients [7-10]. Right ventricular dilatation and a consequent unaltered RVEF, however, does not necessarily reflect an impaired stroke volume response [11]. For this reason there is still ongoing dispute whether these findings of right ventricular dysfunction reflect impaired pump function or should be interpreted as physiological adaptation of the right ventricle to the increased afterload.

Therefore, the first objective of this study is to investigate the exercise-induced changes of right ventricular structure and function in relation to stroke volume response to exercise in COPD patients in comparison with healthy controls. Second, it is studied whether resting pulmonary arterial pressure is predictive of an abnormal stroke volume response to exercise in this patient group.

METHODS

Subjects

This study is part of a larger research project on the development of exercise-induced increases in pulmonary artery pressure in COPD that requires right heart catheterization and exercise testing in all patients. The VU University medical ethics committee approved the study, and informed consent was obtained from all subjects. Sixteen patients with moderate to severe COPD and increasingly symptomatic during daily activities despite stable pulmonary function participated in the study. All patients had COPD according to ATS/ERS criteria [12]. All patients were studied during a stable period of their disease. Patients with a history of cardiovascular disease, in the presence of an abnormal left ventricular

function on echocardiography were excluded. A mean Ppa > 25 mmHg with a wedge pressure below 15 mmHg at rest or a mean Ppa > 30 mm Hg during exercise confirmed the diagnosis of PH secondary to COPD [13].

Study design

The following 3 measurements, which are described in more detail below, were performed in all COPD patients within one week on consecutive days; patients underwent 1) a cardiac MRI scan, which was performed both at rest and during submaximal exercise, 2) a right heart catheterization both at rest and during submaximal exercise 3) extensive lung function testing followed by a maximal cardiopulmonary exercise test. The MRI scan and the right heart catheterisation were performed within 24 hrs, and both exercise tests were performed on the same recumbent ergometer (Lode, Groningen, The Netherlands) at identical workload levels. As a control group, 8 gender and age matched healthy controls underwent pulmonary function testing and cardiac MRI both at rest and during submaximal exercise. The healthy controls did not undergo right heart catheterization.

MRI measurements

The MR images and flow measurements were acquired with a 1.5 Tesla Siemens Sonata whole body system (Siemens Medical Solutions, Erlangen, Germany), equipped with a circularly polarized phased-array body coil. The ECG was recorded with MRI compatible leads, to enable prospective ECG-R wave triggering. The same MRI protocol was used for the resting and exercise measurements, as previously described [14;15]. The MRI exercise protocol consisted of a 3-minute period of cycling in supine position on a recumbent bicycle (Lode, Groningen, The Netherlands). For the patient group, work rate was increased in the first minute to 40% of maximal workload as previously determined during maximal exercise testing. The exercise level for healthy controls was set at 40% of the predicted maximal workload for gender, age, weight and length. Between exercise measurements was a 5-minute resting period.

For the measurements of the RV and LV volumes at end-diastole and systole, a stack of short-axis image planes covering the LV and RV from base to apex was acquired. From the stack of parallel short-axis cine images, quantitative analysis of right ventricular volumes and geometry was performed by manual detection of endocardial and epicardial borders on each slice, using the MR Analytical Software System (Medis, Leiden, The Netherlands). Stroke volume (SV) was measured using MR phase-contrast flow quantification [14].

Right heart catheterisation

The tests were performed at the ICU with patient in stable condition breathing room air under continuous monitoring of ECG and systemic blood pressures. The right heart catheterization was performed with a balloon tipped, flow direct-

ed 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp; Irvine, CA). Pulmonary artery pressures were taken at the end of expiration. Cardiac output was determined with the direct Fick method. Pulmonary vascular resistance was calculated as the ratio of mean pressure to cardiac output. Hemodynamic measurements were obtained at baseline and while cycling. The exercise protocol consisted of a 3-minute period of cycling in supine position using the same recumbent bicycle as during MR measurements with the Swan-Ganz catheter in situ. Work rate was increased in the first minute to 40% of maximal workload as previously determined during maximal exercise testing (as described below) and was identical to exercise MRI measurements.

TABLE 1. Patient demographics and pulmonary function.

	Healthy controls (n = 8)	COPD (n = 16)
Male / female	5/3	10/6
Age, yr	66 ± 3	67 ± 9
BSA, m ²	1.95 ± 0.16	1.87 ± 0.16
VC, % predicted	118 ± 22	100 ± 20
FEV ₁ , % predicted	109 ± 16	51 ± 24 [*]
FEV ₁ /VC, %	72 ± 6	40 ± 17 [*]
TLC, % predicted	103 ± 9	125 ± 16 [*]
DLCO, % predicted	94 ± 12	44 ± 17 [*]

Values are mean ± SD. Abbreviations: BMI = body mass index, VC = vital capacity, FEV₁ = forced expiratory volume in 1 s, TLC = total lung capacity, DLCO = carbon monoxide transfer capacity. ^{*}p < 0.01, versus healthy controls.

Lung function and exercise testing

Pulmonary function was evaluated by standard spirometry, determination of carbon monoxide transfer capacity (DLCO), and measurement of functional residual capacity (FRC) and total lung capacity (TLC) following ERS/ATS guidelines [16-18]. General characteristics and pulmonary function data are shown in Table 1.

Maximal exercise tolerance and peak oxygen uptake (VO₂) were assessed by a standard, incremental, maximal exercise test on an electronically braked cycle ergometer (Lode, Groningen, The Netherlands). Measurements of VO₂ and carbon dioxide output were made breath-by-breath (Vmax229, SensorMedics, Yorba Linda, California, USA). The exercise protocol consisted of 3 minutes of rest, 3 minutes of unloaded cycling at 60 rpm followed by a progressively increasing work rate to maximum tolerance, and 3 minutes of recovery [19].

TABLE 2. Right heart catheterization results in COPD patients

	Rest	Exercise
sPpa, mmHg	35 ± 15	55 ± 18*
dPpa, mmHg	12 ± 7	19 ± 11*
mPpa, mmHg	21 ± 8	33 ± 11*
PVR, dynes·s ⁻¹ ·cm ⁻⁵	276 ± 170	280 ± 171
SaO ₂ , %	92 ± 4	88 ± 6*
SvO ₂ , %	67 ± 7	51 ± 8*

Values are mean ± SD. Abbreviations: sPpa = systolic pulmonary artery pressure, dPpa = diastolic pulmonary artery pressure, mPpa = mean pulmonary artery pressure, PVR = pulmonary vascular resistance, SaO₂ = arterial oxygen saturation, SvO₂ = mixed venous oxygen saturation. * p < 0.01, versus rest.

Statistics

Data are presented as mean ± SD. SPSS 12.0 software package was used for statistical analyses and a value of p < 0.05 was considered significant. A Wilcoxon signed rank test was used to compare between resting and exercise conditions. The Mann Whitney U test was applied to compare cardiac function between healthy controls and COPD patients. Spearman correlation analyses were calculated to determine the correlations between hemodynamic and cardiac function data.

RESULTS

General characteristics

The results of the right heart catheterization of the COPD patients both at rest and during submaximal exercise are presented in Table 2. Nine out of 16 patients were diagnosed with PH: 4 patients showed PH at rest, in 5 patients exercise induced an increase in mPpa above 30 mm Hg. In all patients Ppa increased significantly in response to exercise, whereas pulmonary vascular resistance did not change. As shown in Figure 1, resting mPpa is related to mPpa during exercise in COPD patients.

All patients and healthy subjects were able to perform the MRI exercise test at 40 % of their maximal workload. Right and left ventricular characteristics at rest and during exercise of both groups are presented in Table 3. Both heart rate and stroke volume were significantly augmented in exercise. However, the changes were significantly larger in the control group, and consequently cardiac output increased much more in the control group.

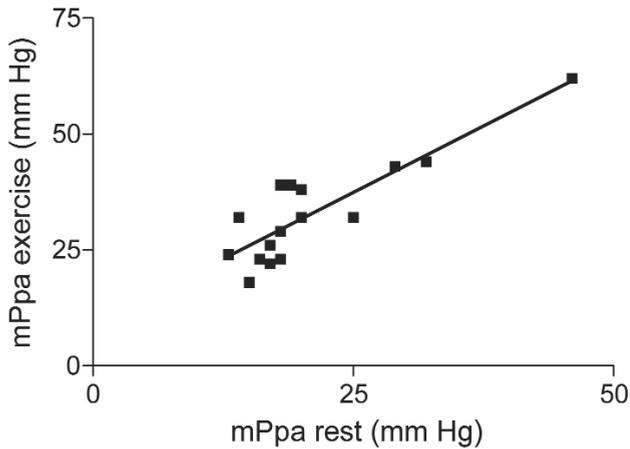


FIGURE 1. Correlation of resting mean pulmonary artery pressure (mPpa) with exercising mPpa in 16 COPD patients ($r = 0.87$, $p < 0.001$).

TABLE 3. Cardiac structure and function at rest and during exercise in healthy controls and COPD patients

	Healthy controls		COPD patients	
	Rest	Exercise	Rest	Exercise
HR, beats/min	71 ± 8	96 ± 12*	81 ± 11†	96 ± 14**
SV, ml	81 ± 22	101 ± 28*	63 ± 13†	69 ± 14* ‡
CO, l/min	5.7 ± 1.5	9.6 ± 2.6*	5.1 ± 1.2	6.7 ± 1.9** †
<i>Right ventricle</i>				
EDV, ml	127 ± 35	136 ± 35*	129 ± 42	135 ± 42*
ESV, ml	46 ± 17	35 ± 15*	65 ± 46	65 ± 48†
EF, %	64 ± 6	74 ± 8*	52 ± 13‡	54 ± 14‡
<i>Left ventricle</i>				
EDV, ml	121 ± 35	129 ± 36*	94 ± 16	98 ± 17†
ESV, ml	40 ± 15	28 ± 14*	31 ± 12	29 ± 12
EF, %	68 ± 6	79 ± 8*	67 ± 11	71 ± 11*

Values are mean ± SD. Abbreviations: CO = cardiac output, EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, HR = heart rate, SV = stroke volume.

* $p < 0.05$, ** $p < 0.01$, rest versus exercise measurements, † $p < 0.05$, versus healthy controls, ‡ $p < 0.01$ versus healthy controls.

Figure 2 demonstrates the differences in right ventricular response to submaximal exercise between healthy controls and COPD patients. In the patient group, right ventricular end-diastolic volume (RVEDV) and SV increased significantly from rest to exercise, but RV end-systolic volume and RVEF did not. While in the COPD group SV is solely increased due to an increased RVEDV, SV in healthy controls is raised by both an increased RVEDV and a reduced RVESV. Stroke volume at rest and during exercise was significantly smaller in the patient group in comparison with healthy controls. The individual responses from all COPD patients in SV from rest to exercise are presented in Figure 3. This figure shows that although SV increased significantly during exercise, this change is modest. Note that three out of 4 COPD patients with PH at rest did not show an increased SV to exercise. In contrast to healthy controls, exercise did not alter LV end-diastolic and LV end-systolic volume in COPD patients.

Relation pulmonary artery pressure and cardiac function

To investigate the predictive value of mPpa at rest on right ventricular structure and function during exercise, we assessed the relation between resting mPpa and SV, RVEDV and RVEF during exercise. As shown in Figure 4, resting mPpa was inversely related to SV during exercise ($r = -0.59$, $p < 0.02$). In addition, both mPpa at rest and during exercise showed an inverse correlation with the percentage change in SV from rest to exercise ($r = -0.54$, $p < 0.05$ and $r = -0.53$, $p < 0.05$, respectively). Furthermore, mPpa at rest showed a correlation with both RVEDV and RVEF during exercise ($r = 0.75$, $p < 0.001$ and $r = -0.80$, $p < 0.001$, respectively).

DISCUSSION

This is the first cardiovascular MR study to investigate the mechanism by which right ventricular stroke volume is augmented during exercise in COPD patients. The results show a limited increase in stroke volume during submaximal exercise. In healthy controls, stroke volume augmentation to exercise was the result of both an increased right ventricular end-diastolic volume and a reduction in end-systolic volume, whereas in patients with COPD right ventricular stroke volume could increase by an increase in end-diastolic volume only. In addition, we found that a high resting mPpa was predictive for a low stroke volume during exercise.

In the literature, there are few data concerning the effects of exercise on right ventricular function in both healthy subjects and COPD patients. An earlier study in young healthy adults has revealed that an increase in stroke volume during submaximal exercise in upright position is mainly caused by an increased preload of both the right and left ventricle [20]. During supine maximal exercise, however, it was shown that in healthy controls SV was enhanced due to a decrease in RVESV

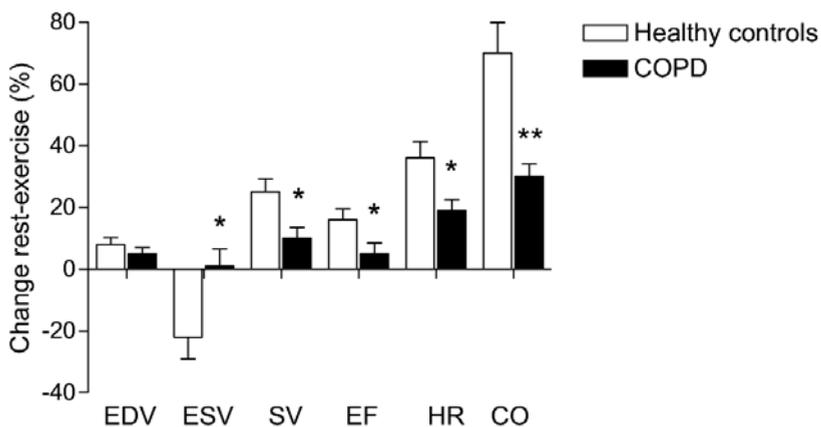


FIGURE 2. Changes in right ventricular structure and function in response to submaximal exercise in both COPD patients and healthy controls. Note, that although right ventricular end-diastolic volume (EDV) is increased in both groups, in contrast to COPD patients, the healthy controls have the ability to reduce right ventricular end-systolic volume (ESV). This results in an improved stroke volume (SV) and ejection fraction (EF). * $p < 0.05$, versus healthy controls, ** $p < 0.01$, versus healthy controls.

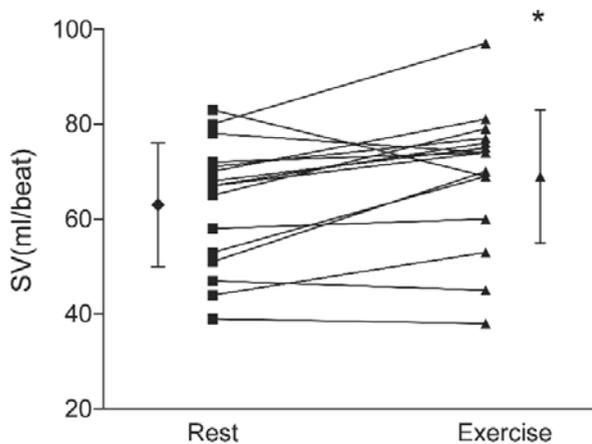


FIGURE 3. Individual values of right ventricular stroke volume (SV) response to exercise in COPD patients. Exercise induced a small but significant increase in SV to exercise, * $p < 0.05$.

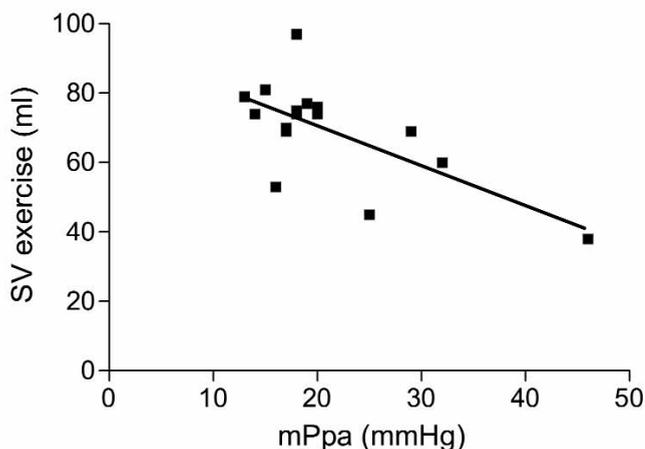


FIGURE 4. Correlation of resting mean pulmonary artery pressure (mPpa) with stroke volume (SV) during exercise ($r = -0.68$, $p < 0.004$).

[21;22]. The latter authors conclude that the enhanced right ventricular SV during progressive supine exercise seems more related to increased contractility, than to the Frank-Starling mechanism. For the left ventricle it is known that the mechanism responsible for the increase in SV is largely age dependent. In young people SV response to exercise is caused by a decrease in end-systolic volume without a change in end-diastolic volume, whereas in elderly people an opposite response occurs [23]. Whether such relations also exist for the right ventricle is unclear. The present study showed that the elderly age-matched controls increase their stroke volume during exercise in supine position by increasing right ventricular preload and reducing RVESV, suggesting an enhanced right ventricular contractility resulting in an increase in RVEF. Although a similar increase in RVEDV was observed in the COPD patients, these patients failed to reduce RVESV. Consequently, stroke volume response was augmented whereas RVEF remained unaltered during exercise in these patients.

The finding that RVEF remained unchanged in COPD patients is in agreement with previous studies using first pass quantitative radionuclide angiography [8]. These authors found that LVEF significantly increases during exercise from $62 \pm 2\%$ at rest to $71 \pm 2\%$ during exercise, which is comparable to our findings (Table 3). In a group of 25 stable COPD patients, Biernacki and co-workers [6] analysed the slope of the right ventricular end-systolic pressure-volume relationship at rest and during exercise and concluded that despite the presence of PH right ventric-

ular contractility remained relatively normal. In addition, in agreement with the present study, left ventricular function was shown to be preserved at rest [1] and during exercise [8]. Consistent with the present results, correlations with RVEF and mPpa have been found in COPD patients [24]. However, this relation has not been shown consistently; a combined hemodynamic and radionuclide approach to evaluate RV performance during upright exercise demonstrated a tendency towards a relation between mPpa and RVEF both at rest and during exercise, whereas a significant correlation was not established during simultaneous RV pressure and function measurements [6].

Whereas pulmonary artery pressures may be elevated during daily activities in COPD patients [3;25], in general pulmonary hypertension at rest is only mild to moderate [26]. Although pulmonary artery pressures are modestly increased at rest, our results, together with those of earlier studies, showed that COPD patients have a reduced SV at rest [1]. However, SV at rest was similar between controls and COPD patients when indexed for body surface area (41 ± 10 versus 34 ± 7 mL, $p = 0.14$, respectively). In addition, exercise leads to a rapid increase in pulmonary artery pressure even in patients with normal resting pressures. This increase in Ppa results from increased PVR as a consequence of hypoxic pulmonary vasoconstriction and a reduced pulmonary capillary bed [27]. High Ppa levels may furthermore be explained by increased alveolar pressures and increased intrathoracic pressure swings as a result of excessive breathing during exercise [28]. One of the major findings of our study is that an increased pulmonary artery pressure at rest is related to a low stroke volume during exercise. In patients with idiopathic PAH (iPAH) (mPpa at rest = 51 ± 18 mmHg) we have previously shown that, in spite of a small increase in RVEDV, SV was not augmented and LVEDV was decreased to exercise [15]. Although, SV increased in the COPD group, this increase was modest and absent in 3 out of 4 COPD patients with PH at rest. In contrast to patients with iPAH, increased RV preload during exercise did not affect left ventricular end-diastolic volume in the present patient group. The results suggest that cardiac performance during exercise in COPD patients can be staged between healthy controls and patients with advanced types of pulmonary arterial hypertension. A therapeutic intervention leading to a reduction in Ppa in the COPD patients with pulmonary hypertension might thus be effective to restore a normal stroke volume response during exercise.

Study limitations

Simultaneous pressure measurements and cardiac MRI could not be performed in our institute. Both measurements were therefore performed within 24 hrs. A maximal supine exercise test appeared to be difficult to perform during MRI and too uncomfortable for the patients during right heart catheterization. Therefore, a submaximal exercise level of 40% of previously determined maximal exercise

level was used to assure a maximal stroke volume response [29]. The same exercise level and bicycle ergometer was used during both tests.

Conclusion

In conclusion, in COPD patients SV increase is limited and results from an increase in end-diastolic volume only, and not by a reduced end-systolic volume. Pulmonary arterial pressure at rest predicts increase in pulmonary arterial pressure during exercise and is inversely related to stroke volume during exercise.

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CHAPTER FIVE

Acute effects of sildenafil
on exercise pulmonary
hemodynamics and capacity
in COPD

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submitted

ABSTRACT

Aim We investigated in COPD patients whether a single dose of sildenafil can attenuate the exercise-induced increase in pulmonary artery pressure, thereby allowing augmentation of stroke volume (SV), and improving peak exercise capacity.

Methods 17 COPD patients (GOLD III-IV) underwent right heart catheterisation at rest and submaximal exercise. Mean pulmonary artery pressure (mPpa) and cardiac output (CO) were assessed. Resting and exercise measurements were repeated 60 minutes after oral intake of 50mg sildenafil. Also, patients performed two maximal exercise tests (CPET)- randomly, one hour after placebo and after 50mg sildenafil.

Results 4 COPD patients had pulmonary hypertension at rest (mPpa > 25 mmHg) and 6 developed pulmonary hypertension during exercise (mPpa > 30 mmHg). In all patients mPpa increased from rest to submaximal exercise (21 ± 8 to 33 ± 11 mmHg). After sildenafil mPpa at rest was 20 ± 9 mmHg, in exercise mPpa was increased less to 28 ± 12 mmHg ($p < 0.01$). The reduced augmentation in mPpa was not accompanied by an increased SV, and CO. Maximal exercise capacity and CPET characteristics were unchanged after sildenafil.

Conclusion Sildenafil attenuates the increase in mPpa during submaximal exercise in COPD. This attenuated increase is neither accompanied by enhanced SV and CO, nor by improved maximal exercise capacity.

INTRODUCTION

A reduced exercise capacity is one of the main symptoms in chronic obstructive pulmonary disease (COPD), with important impact on quality of life and a strong relation with mortality [1;2]. Altered exercise hemodynamics, most markedly an excessive increase in pulmonary artery pressure, have been shown in COPD [3-6] and may contribute to the exercise limitation. One of the proposed mechanisms responsible for the increase in pulmonary artery pressure is a reduced production of the endothelium relaxing factor nitric oxide (NO), leading to an impaired pulmonary artery dilator response to increased flow [7]. Strategies that enhance NO signalling may therefore attenuate the exercise-induced increase in pulmonary artery pressure, thereby improving stroke volume, cardiac output and exercise capacity. For this particular purpose, phosphodiesterase 5 inhibitors seem well suited. They stimulate NO-mediated pulmonary vasodilatation by preventing the degradation of NO's second messenger cyclic guanosine monophosphate (cGMP) [8]. Cyclic GMP activates transmembrane potassium channels, which indirectly inhibits calcium entry into vascular smooth muscle cells. The result is a decrease in intracellular free calcium, smooth muscle cell relaxation and vasodilatation. Accordingly, the phosphodiesterase 5 inhibitor sildenafil reduces pulmonary artery pressure in different types of pulmonary hypertension [9-14]. A single dose of sildenafil attenuates the exercise induced rise in pulmonary artery pressure in hypoxic human volunteers [11;15] and patients with systolic heart failure [14].

The primary aim of our study was to investigate the acute effects of sildenafil on pulmonary artery pressure, stroke volume and cardiac output at rest and during exercise in COPD patients. Furthermore, we assessed whether a possible attenuation of right ventricular afterload by sildenafil translates into an increase in maximal exercise capacity.

METHODS

Patients

The committee on research involving human subjects of the VU University medical center approved this study. Written informed consent was obtained from each patient prior to the start of the study. 17 Stable COPD patients (GOLD III/IV) were included [16]. Patients with a history of systemic hypertension or left sided heart failure were excluded, as were patients with a history of pulmonary embolism or an acute exacerbation of COPD within the previous year. Prior to the study pulmonary function was evaluated by standard spirometry, determination of car-

bon monoxide transfer capacity (TL_{CO}), and measurement of residual volume (RV) and total lung capacity (TLC) following ERS/ATS guidelines in all patients [17-19]. General characteristics and pulmonary function data are shown in Table 1.

TABLE 1. General characteristics and lung function data

	COPD (n = 17)
Male / female	11/6
Age (yr)	66 ± 9
BMI (kg/m ²)	24 ± 4
VC (% predicted)	100 ± 20
fev ₁ (% predicted)	49 ± 24
FEV ₁ /VC (% predicted)	39 ± 17
TLC (% predicted)	126 ± 16
FRC (% predicted)	167 ± 30
DLCO (% predicted)	45 ± 17

Values are means ± SD. Abbreviations: COPD = chronic obstructive pulmonary disease, BMI = body mass index, VC = vital capacity, FEV₁ = forced expiratory volume in 1 s, FEV₁/VC = Tiffeneau index, TLC = total lung capacity, FRC = functional residual volume, DLCO = diffusing capacity of the lung for CO.

Study design

After screening, all subjects carried out two maximal cardiopulmonary exercise tests (CPET) on consecutive days; 60 minutes after intake of placebo and 60 minutes after intake of 50 mg sildenafil (Pfizer, Sandwich, UK), in random order. To ensure sildenafil washout, adequate recovery from exercise and a stable clinical condition, minimally 24 hours and maximally five days were allowed in between tests.

One day after the last CPET, right heart catheterisation was performed. Hemodynamic measurements were performed at rest and during submaximal exercise, and were repeated 60 minutes after oral intake of 50 mg sildenafil.

Procedures

Maximal cardiopulmonary exercise test (CPET)

All patients performed CPET with a progressively increasing work rate to maximum tolerance on an electromagnetically braked cycle ergometer (Lode, Groningen, the Netherlands). The load was increased until spontaneous interruption of exercise, while ECG, pulse oximetry and gas exchange were recorded (Vmax 229, SensorMedics, Yorba Linda, CA) [20]. Arterial blood gases were analyzed at rest and during maximal exercise. All patients performed such a test, in random order, after placebo and after sildenafil.

Right heart catheterization during submaximal exercise

Right heart catheterisation was performed in the Intensive Care Unit with continuous monitoring of ECG, while patients were breathing room air. A balloon tipped, flow directed 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp; Irvine, CA) was inserted in the internal jugular vein. The catheter was moved to the pulmonary artery under pressure wave monitoring. The external zero reference was placed on the mid-chest level. A catheter was placed into the radial artery. Pulmonary artery and systemic blood pressures were thus monitored continuously. Measurements at the end of expiration were recorded. Cardiac output was determined by the direct Fick method. Oxygen consumption (VO_2) was measured for five minutes during the catheterization. (Vmax 229, SensorMedics, Yorba Linda, CA). Arterial and mixed venous blood gases were obtained from the radial and pulmonary artery, respectively.

Hemodynamic measurements and arterial and mixed venous blood samples were obtained at supine rest. Following this, each subject was asked to cycle on a recumbent bicycle (Lode, Groningen, the Netherlands). Work rate was increased to 40% of maximal workload as previously determined during maximal exercise testing. After reaching a hemodynamic steady state, hemodynamic measurements and blood sampling were repeated. After returning to baseline values patients received 50 mg sildenafil. After sixty minutes, resting and exercise measurements, including arterial and mixed venous blood sampling were repeated.

Statistical analysis

Data are presented as mean \pm SD. SPSS 12.0 software package was used for statistical analyses and a value of $p < 0.05$ was considered significant. The *student* T-test for paired comparison was used between rest and exercise and between placebo and sildenafil.

RESULTS

Patient characteristics

17 COPD patients were included in this study. Patient characteristics and pulmonary function data are shown in Table 1. The patients had moderate to severe airflow obstruction, increased TLC and a moderate to severe reduction in TLCO . Ten patients were diagnosed with COPD-associated pulmonary hypertension (PH), which is defined as $\text{mPpa} \geq 25$ mmHg with a wedge pressure below 15 mmHg at rest, or $\text{mPpa} \geq 30$ mmHg during exercise [21]. Four out of these ten patients had PH at rest, while all 10 developed $\text{mPpa} > 30$ mmHg during submaximal exercise. Seven patients did not have PH at rest or during submaximal exercise.

TABLE 2. Hemodynamic response to submaximal exercise with and without sildenafil (n = 17)

	Rest	Rest sildenafil	Exercise	Exercise sildenafil
mPpa (mmHg)	21 ± 8	20 ± 9	33 ± 11 †	28 ± 12 † *
mPsyst (mmHg)	97 ± 14	94 ± 16	113 ± 19 †	106 ± 17 †
CO (l/min)	5.6 ± 1.0	6.2 ± 1.7 *	8.1 ± 1.6 †	8.0 ± 2.5 †
SV (ml)	72 ± 19	75 ± 24	87 ± 23 †	82 ± 27 †
PVR (dyne·s·cm ⁻⁵)	259 ± 166	248 ± 225	288 ± 174	303 ± 295
HR (beats/min)	80 ± 14	84 ± 13	96 ± 14 †	100 ± 18 †
SaO ₂ (%)	92 ± 4	91 ± 5	88 ± 6 †	87 ± 7 †
mSvO ₂ (%)	67 ± 6	67 ± 9	51 ± 8 †	49 ± 9 †

Values are means ± SD. Abbreviations: mPpa = mean pulmonary artery pressure, CO = cardiac output, mPsyst = mean systemic artery pressure, SaO₂ = arterial oxygen saturation, mSvO₂ = mixed venous oxygen saturation, SV = stroke volume, PVR = pulmonary vascular resistance, HR = heart rate. * p < 0.05 versus rest and exercise without sildenafil; † p < 0.05 versus rest (same condition).

Submaximal exercise hemodynamics

Baseline As presented in Table 2, submaximal exercise resulted in significant increases in heart rate, cardiac output and mPpa and in decreases in S_aO₂ and S_vO₂. Pulmonary vascular resistance did not change with exercise. The individual responses of mPpa's during exercise are presented in Figure 1. Exercise at 40% of maximum capacity was associated with an increase in mPpa in all patients.

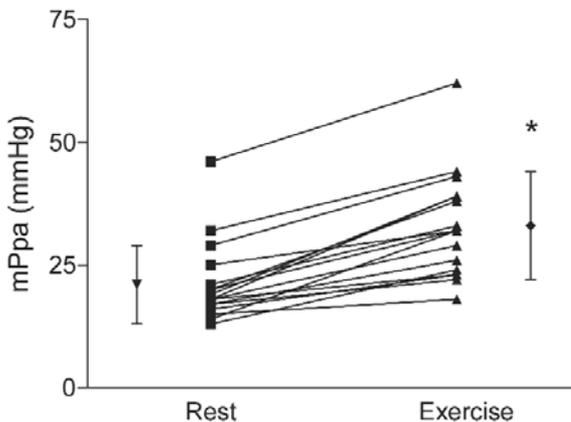


FIGURE 1. Individual values and mean ± SD of the mean pulmonary artery pressure (mPpa) at rest and during submaximal exercise of 17 COPD patients. In all patients mPpa was increased. There was a significant difference between resting and exercise mPpa, * p < 0.001.

Sildenafil Mean Ppa was significantly increased with exercise (Table 2). Sildenafil given as single dose resulted in a not significantly lower mPpa at rest (Figure 2a), whereas sildenafil significantly attenuated the exercise-induced increase in mPpa in all patients (Figure 2b). PVR was neither changed at rest nor during exercise after sildenafil, and was comparable in all 4 conditions. Although CO increased significantly in response to exercise, the absolute increase in CO from rest to exercise after sildenafil was smaller (2.5 ± 1.3 versus 1.8 ± 1.9 L/min, $p = 0.38$). CO during exercise was similar with and without sildenafil. Stroke volume and systemic blood pressure increased significantly to exercise, but this response did not change after intake of sildenafil. Sildenafil had no effect on oxygenation at rest or during exercise (Table 2). Sildenafil did not change the exercise-induced reduction in S_aO_2 and S_vO_2 .

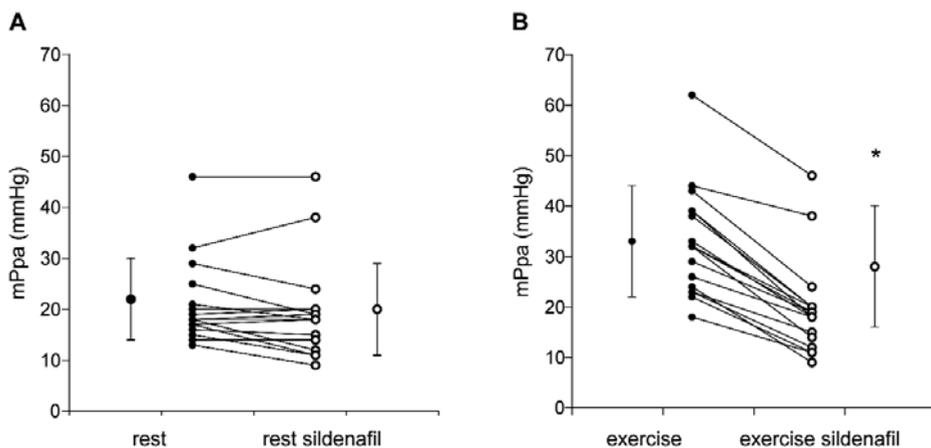


FIGURE 2. Individual values and mean \pm SD of mean pulmonary artery pressure at rest (A) and during submaximal exercise (B) in 17 COPD patients. Sildenafil decreased the mean pulmonary artery pressure significantly during exercise. * $p < 0.01$.

Maximal exercise test

As presented in Table 3, maximal workload and peak oxygen uptake were similar under the two conditions. Furthermore, peak exercise heart rate and O_2 pulse (an indicator of stroke volume) were unchanged after sildenafil. Patients at rest showed mild to moderate hypoxemia (PaO_2 9.3 ± 1.8 kPa) and no hypercapnia ($PaCO_2$ 5 ± 0.8 kPa), and sildenafil did not affect these values (Table 4). Mean PaO_2 decreased and mean $PaCO_2$ remained unaltered during maximal exercise. Sildenafil did not affect the decrease in PaO_2 and increase in $PaCO_2$. Irrespective of treatment order, both peak VO_2 and peak work rate were not different between the first and second maximal exercise test (11.2 ± 2.9 versus 11.2 ± 3.4 ml/kg/min and 48 ± 27 versus 49 ± 29 W, respectively).

TABLE 3. Maximal cardiopulmonary exercise testing in COPD patients (n = 17)

	Placebo	Sildenafil
Maximum workload, W (% predicted)	48 ± 28 (32 ± 15)	49 ± 28 (32 ± 17)
Peak VO ₂ , ml/kg/min (% predicted)	11.1 ± 3.2 (48 ± 12)	11.2 ± 1.3 (49 ± 14)
HR max, beats/min (% predicted)	117 ± 21 (77 ± 12)	120 ± 18 (79 ± 10)
Peak O ₂ -pulse, ml/beat (% predicted)	6.8 ± 2.0 (46 ± 12)	6.6 ± 1.8 (45 ± 12)
Ve max, l/min (% predicted)	40 ± 17 (61 ± 15)	40 ± 15 (63 ± 15)
Ve/VCO ₂ slope	46 ± 27	43 ± 20
ΔVO ₂ /Δ workload, ml/min/watt	7.9 ± 1.6	8.2 ± 2.0

Values are means ± SD. Abbreviations: Peak VO₂ = peak exercise O₂ uptake, HR = heart rate at peak exercise, Ve/VCO₂ = ratio of ventilation to CO₂, ΔVO₂ /Δ workload = increase in VO₂ per increase in work rate

Discussion

This is the first study to evaluate the acute effects of sildenafil on pulmonary artery pressure during exercise in COPD patients. The most relevant finding is that sildenafil attenuates the submaximal exercise-induced increase in mPpa in COPD patients (GOLD stages III and IV) with absent or mild pulmonary hypertension at rest. However, this reduction was not accompanied by an increase in stroke volume or cardiac output (Table 2). Moreover, sildenafil has no effect on maximal exercise capacity (Table 3).

TABLE 4. Blood gas values at rest and maximal exercise with and without sildenafil

	Rest placebo	Rest sildenafil	Exercise placebo	Exercise sildenafil
PaO ₂ , kPa	9.2 ± 1.8	9.2 ± 1.9	7.7 ± 2.1 †	7.7 ± 2.1 †
PaCO ₂ , kPa	5.0 ± 0.9	4.9 ± 0.7	5.2 ± 1.2	5.3 ± 1.1
SaO ₂ , %	93 ± 4	93 ± 4	87 ± 8 †	86 ± 7 †

Values are means ± SD. Abbreviations: PaO₂ = partial arterial oxygen pressure, PaCO₂ = partial arterial carbon dioxide pressure, SaO₂ = arterial oxygen saturation. † p < 0.05 versus condition at rest.

Right ventricular afterload in COPD

In the natural course of COPD, right ventricular afterload (reflected by mPpa) slowly increases, allowing the right ventricle to adapt [22]. Although this adaptation is usually sufficient at rest, an increase in mPpa during exercise might impair exercise tolerance. Several studies in COPD patients have shown resting mPpa values and exercise-induced increases in mPpa that are comparable with the results of the present study [23-26]. The increased right ventricular afterload in COPD is associated with endothelial dysfunction and impaired NO release [27]. In this regard, Roger et al. tested whether inhalation of NO could replace endoge-

nous NO and cause vasodilatation [28]. NO inhalation resulted in a reduced mPpa at rest. Although NO inhalation for acute vasoreactivity testing is feasible, it is not suitable for continuous administration. Administration of sildenafil is a well-recognized alternative to stimulate NO-mediated vasodilatation. A reduced mPpa after sildenafil intake has been reported in human volunteers exposed to high altitude-induced hypoxia [11;15] and in patients with severe lung fibrosis [9]. In a pilot study of 6 COPD patients with associated pulmonary hypertension (estimated by ultrasound), acute i.v. administration of sildenafil resulted in a reduction in mPpa measured at rest. In addition, after 3 months of oral treatment with sildenafil these patients showed improved resting pulmonary hemodynamics and exercise tolerance, as measured by the 6 minute walk test [29]. In contrast with these observations, the present study did not show a reduced mPpa at rest, which might be explained by the fact that our study group was a mixture of patients with and without COPD-associated pulmonary hypertension. The finding that sildenafil attenuates the increase in mPpa during exercise is in accordance with the observation, that administration of NO can attenuate the increase in mPpa during exercise in COPD [28]. Although, in the present study, the increase in afterload was attenuated after sildenafil, no significant increase in CO with exercise was found in comparison with baseline.

Pulmonary artery pressure is the sum of the arterial pressure drop ($PVR \times (\text{mean}) \text{ flow}$) and pulmonary capillary wedge pressure (Pcw). Since Pcw's could not be measured reliably in this study, and the focus of this study was to investigate the effects of sildenafil on Ppa at rest and during exercise, it remains speculative whether sildenafil affects either Pcw, or pulmonary vascular resistance or both.

Hemodynamic response to exercise

Due to recruitment of (previously) underperfused pulmonary vessels, PVR decreases with exercise in healthy subjects. In contrast, exercise in severe COPD is characterized by increases in PVR and mPpa [3;4]. This response has been suggested to contribute to impaired stroke volume during exercise and may thereby affect exercise limitation. However, only few investigators have compared the exercise stroke volume response of COPD patients with age-matched controls. Morrison et al. showed that in COPD patients the levels of stroke volume and cardiac output were lower than those of normal subjects at symptom-limited maximum [30]. More recently, Bogaard and co-workers showed a reduction in submaximal exercise stroke volume in COPD patients compared to healthy age-matched controls [31]. In that study, cardiac output was not different between patients and controls during submaximal exercise. In comparison with the results of a study of the cardiovascular exercise response in healthy elderly subjects (mean age 68 ± 6 years) [32], the COPD patients showed a similar SV and CO at rest, but in response to submaximal exercise the COPD patients showed a slightly reduced CO in comparison with the healthy subjects.

The attenuated increase during exercise in mPpa after sildenafil was not accompanied by an increase in exercise CO. These findings can be explained as follows: First, as outlined above, the CO response to submaximal exercise is relatively normal in our COPD patients due to a well adapted right ventricle. Weitzenblum et al. showed that pulmonary artery pressure was elevated by 0.6 mm Hg per year in a group of 93 COPD patients [22]. This slow development may provide the heart with sufficient time to adapt to an increased afterload. A recent study showed that even in normoxic COPD patients, right ventricular mass is increased, indicating that the right ventricle in patients with normal or mildly elevated pulmonary artery pressures is adapted to an increase in right ventricular afterload [33].

Second, although sildenafil significantly attenuated the increase in mPpa during exercise, this reduction may not be relevant to induce an increase in CO. In addition, in these patients CO during exercise was not related to exercise mPpa, suggesting that changes in mPpa do not necessarily result in a change in CO. Third, hemodynamic performance may be related to other factors than right ventricular afterload. Dynamic hyperinflation is known to induce increased intrathoracic pressure swings [34], which affects both right ventricular preload and afterload. Increased intrathoracic pressure and intrinsic positive end expiratory pressure (PEEP) reduce venous return thereby compromising stroke volume. The effect of a decreased venous return might be the main determinant of stroke volume in these patients, making right ventricular afterload of relatively little importance.

These arguments may also explain why sildenafil did not improve maximal exercise capacity in this patient group. Nevertheless, we cannot rule out the possibility that COPD patients with more advanced pulmonary hypertension do suffer from a circulatory exercise limitation. A recent study identified a subgroup of COPD patients characterized by an elevated pulmonary artery pressure and marked hypoxemia, contrasting with moderate airway obstruction [35]. This subgroup of patients may be more likely to benefit from vasodilator therapy than the present heterogeneous study population with mild to moderate pulmonary hypertension.

Oxygenation

Administration of vasodilators in patients with COPD could interfere with physiological hypoxic vasoconstriction and thereby increase ventilation perfusion mismatching. In our COPD patients peripheral oxygenation remained unaltered after sildenafil intake at rest and during exercise. This finding is consistent with previous studies in patients with pulmonary hypertension secondary to lung fibrosis [9] and in hypoxic human healthy volunteers [11;15] in which sildenafil reduced pulmonary artery pressure while preserving or even ameliorating gas exchange.

Study limitations

The reductions in exercise-induced afterload after vasodilatation were assessed

during submaximal exercise. Therefore, it is not clear whether these differences will sustain during maximal exercise. In addition, the present study showed the acute effects of vasodilatation on pulmonary hemodynamics and exercise capacity in moderate to severe COPD. Sildenafil may have additional intrinsic effects on vascular remodeling [36] and therefore chronic effects of sildenafil on exercise capacity, stroke volume and cardiac output may differ from the acute effects shown in the present study.

Conclusion

This study showed that sildenafil, given as a single dose, attenuates the increase in mPpa during submaximal exercise in COPD patients with moderate to severe airflow limitation regardless of mPpa at rest. This acute reduction in right heart afterload is neither accompanied by an increase in stroke volume, cardiac output, nor by an improved exercise tolerance. Future research is warranted on the chronic effects of sildenafil on cardiac function and exercise capacity in COPD patients.

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CHAPTER SIX

Cardiopulmonary exercise test characteristics in COPD patients with associated pulmonary hypertension

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Respiration, provisionally accepted

ABSTRACT

Background: Pulmonary hypertension (PH) is a well-known complication of COPD. It remains unclear whether exercise parameters can be used to discriminate between COPD patients with associated PH (COPD-PH) and COPD patients without associated PH (COPD-nonPH).

Objective: To study whether the existence of pulmonary hypertension in COPD is related to characteristic findings in gas exchange and circulatory parameters during cardiopulmonary exercise testing (CPET).

Methods: We retrospectively analysed CPET data in 25 COPD patients in whom right heart catheterization had been performed. Differences were assessed between COPD-PH and COPD-nonPH patients in peak oxygen uptake (VO_2 peak), ventilatory efficiency (VE/VCO_2), oxygen pulse (O_2 -pulse), peak ventilation and pulse oximetry (SpO_2).

Results: PH was found in 10 out of 25 patients ($\text{mPpa} = 33 \pm 7$ mmHg), in 15 patients mPpa was below 25 mmHg (18 ± 3 mmHg). CPET in COPD-PH was characterized by a higher VE/VCO_2 at nadir, a higher VE/VCO_2 slope, and a lower SpO_2 at rest and during exercise, but values in both groups were overlapping considerably. In the whole group mPpa was associated with resting PaO_2 ($r = -0.70$, $p < 0.001$), VECO_2 nadir ($r = 0.43$, $p < 0.05$), and inversely related to SpO_2 at rest and during exercise ($r = -0.58$ and $r = -0.64$, $p < 0.01$ respectively).

Conclusion: Although CPET characteristics showed a large overlap in both groups, the existence of PH in COPD is associated with a significantly reduced ventilatory efficiency during CPET. However, a low SpO_2 at rest and a further decrease during exercise similarly suggest the presence of PH in COPD.

INTRODUCTION

Pulmonary hypertension (PH) is a well-known complication of chronic obstructive pulmonary disease (COPD), with a reported prevalence of 20 to 90 % [1-5]. Recent studies indicate that the direct effects of tobacco smoke might contribute to the development of PH in COPD through effects on the intrapulmonary vessels with abnormal production of mediators that control vasoconstriction, vasodilatation, and vascular cell proliferation [6]. However, alveolar hypoxia has been identified as the main cause of PH in COPD: acute hypoxia causes pulmonary vasoconstriction and long-term hypoxia induces pulmonary vascular remodelling [7]. Scharf and colleagues demonstrated that mean pulmonary artery pressure (mPpa) correlates negatively with partial arterial oxygen pressure, but also indicated that chronic hypoxia is not the only factor contributing to the development of PH. [4;8]. Arterial oxygen saturation has been shown to inversely correlate with mPpa [1].

The degree of PH in COPD is usually mild to moderate, with resting mPpa in a stable state of the disease ranging between 20 and 35 mmHg [9]. Exercise in these patients may be associated with further marked increases in Ppa [10]. It has therefore been suggested that exercise testing may be useful in early diagnosis of PH [11;12]. Validated methods to establish the diagnosis and to grade the severity of PH are cardiac catheterization and echocardiography. While the clinical value of cardiopulmonary exercise testing (CPET) to non-invasively analyse exercise limitation in COPD is well recognized, it is not known whether the presence of PH in COPD leads to changes in gas exchange characteristics during exercise. Studies performed in idiopathic PH revealed that the most consistent and characteristic findings in these patients were: reductions in oxygen uptake (VO_2) at the anaerobic threshold and at peak exercise, a reduction in peak oxygen pulse (O_2 -pulse) and a diminished ventilatory efficiency [13]. It remains unclear whether these parameters are different between COPD patients with associated PH (COPD-PH) and COPD patients without associated PH (COPD-nonPH). The objective of the present study was to verify whether the existence of pulmonary hypertension (PH) in COPD is related to characteristic CPET findings. In addition, we investigated whether gas exchange measurements during CPET lead to a better recognition of PH in COPD than exercise pulse oximetry.

METHODS

Subjects and Pulmonary Function Testing

This study is part of a larger research project investigating the effects of treatment of pulmonary hypertension in COPD patients. This study requires right heart catheterization and exercise testing in all patients. The VU University medical ethics committee approved the study, and written informed consent was obtained from all subjects. Twenty-five patients with moderate to severe COPD and increasingly symptomatic during daily activities despite stable pulmonary function were retrospectively included in this study. Selection of patients was based on the following criteria: 1. Clinical diagnosis of COPD (GOLD criteria); 2. No clinical evidence of cardiovascular disease (including arterial hypertension and previous myocardial infarction), and a normal left ventricular function on echocardiography; 3. No pathology possibly interfering with the ability to perform exercise. Medical histories were checked and all patients underwent physical examination, and ECG. The group was divided into a COPD-nonPH and a COPD-PH subgroup. The diagnosis of PH was based on right heart catheterisation. A mPpa > 25 mmHg with a wedge pressure below 15 mmHg confirmed the diagnose of PH secondary to COPD [14]. Just before CPET studies, pulmonary function was evaluated by standard spirometry, including determination of transfer factor for carbon monoxide (DLCO), and measurement of functional residual capacity (FRC) and total lung capacity (TLC) according to ERS/ATS guidelines [15-17]. Arterial blood was obtained at rest in all patients for determination of PaO₂ and PaCO₂ and calculation of the alveolar-arterial oxygen pressure difference (D(A-a)PO₂) using the alveolar gas equation. General characteristics and pulmonary function data are shown in Table 1.

CardioPulmonary Exercise Testing

Each patient performed a standard, incremental exercise test on an electronically braked cycle ergometer (Lode, Groningen, The Netherlands). Measurements of VO₂, carbon dioxide output (VCO₂), minute ventilation (V_E) and tidal volume (V_T) were made breath-by-breath (Vmax229, Sensormedics, Yorba Linda, California, USA). Calculations were made of ventilatory equivalents for oxygen and carbon dioxide (V_E/VO₂ and V_E/VCO₂, respectively). The slope of V_E versus VCO₂ was determined and V_E/VCO₂ nadir was defined as the lowest point on the V_E/VCO₂ curve. Pulse oximetry, heart rate and gas exchange were recorded and monitored during 3 minutes of rest, 3 minutes of unloaded cycling at 60 rpm followed by a progressively increasing work rate to maximum tolerance, and 3 minutes of recovery [18]. The oxygen pulse (O₂- pulse), i.e. oxygen uptake divided by heart rate was used as an estimator of stroke volume. In the majority of the studied COPD patients the anaerobic threshold could not be identified, therefore values of exercise parameters measured at anaerobic threshold are not provided.

Right Heart Catheterization

All patients underwent diagnostic right heart catheterization at rest with a 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp; Irvine, CA) to assess Ppa within 1 week of CPET.

Statistics

Data are presented as mean \pm SD. SPSS 14.0 software package was used for statistical analyses and a value of $p < 0.05$ was considered significant. The Mann Whitney test was applied for between-group analyses. Differences between resting and exercise values within subjects were assessed by the Wilcoxon signed rank test. Pearson correlation analyses were calculated to determine the correlations between hemodynamic and CPET data.

TABLE 1. Demographics, respiratory function and hemodynamic characteristics of COPD-nonPH and COPD-PH patients

	COPD-nonPH (n = 15)	COPD-PH (n = 10)
Male / female	7 / 8	5 / 5
Age, yr	66 \pm 10 (48-78)	64 \pm 11 (46-80)
BMI, kg/m ²	25 \pm 3 (20-33)	22 \pm 4 (16-28)
VC, % predicted	101 \pm 14 (73-126)	101 \pm 26 (65-144)
FEV ₁ , % predicted	49 \pm 19 (26-80)	62 \pm 31 (21-116)
FEV ₁ /VC, %	39 \pm 15 (20-65)	47 \pm 16 (24-77)
TLC, % predicted	126 \pm 16 (101-151)	115 \pm 19 (80-146)
FRC, % predicted	169 \pm 27 (129-214)	145 \pm 37 (92-207)
DLCO, % predicted	50 \pm 13 (33-85)	37 \pm 14 (21-55)
PaO ₂ , kPa	9.9 \pm 1.4 (7.0-12.4)	7.6 \pm 2.0 (4.8-10.5)*
PaCO ₂ , kPa	5.4 \pm 0.6 (4.1-6.7)	5.0 \pm 1.3 (3.5-7.6)
mPpa, mmHg	18 \pm 3 (13-22)	33 \pm 6 (26-45)**
PVR, dyne·s·cm ⁻⁵	208 \pm 93 (51-411)	393 \pm 170 (200-713)**
SvO ₂ , %	70 \pm 6 (60-83)	68 \pm 6 (56-75)

Values are mean \pm SD (range). Abbreviations: BMI = body mass index, COPD = chronic obstructive pulmonary disease, DLCO = diffusing capacity of the lung for CO, FEV₁ = forced expiratory volume in 1 s, FEV₁/VC = Tiffeneau index, FRC = functional residual capacity, mPpa = mean pulmonary artery pressure, SvO₂ = mixed venous oxygen saturation, PVR = pulmonary vascular resistance. * $p < 0.05$, versus COPD-nonPH, ** $p < 0.01$, versus COPD-nonPH

RESULTS

Subject Characteristics

Patients were classified as having moderate (stage II) to very severe (stage IV) COPD according to GOLD criteria [19]. Patient characteristics and pulmonary function data are shown in Table 1. Although COPD-PH patients tended to have less severe airflow obstruction, reflected by a lower FEV₁ (% predicted, $p = 0.39$), and a reduced DLCO (% predicted, $p = 0.07$) compared with COPD-nonPH patients, differences in pulmonary function between COPD-nonPH and COPD-PH the patients groups were not statistically significant. PaO₂ was reduced in COPD-PH. Furthermore, COPD-PH patients showed a significantly larger D(A-a)PO₂ at rest (6.9 ± 1.9 (range: 4.0-9.4 kPa) versus 3.2 ± 2.2 (range: (0.5-7.0 kPa), $p < 0.001$).

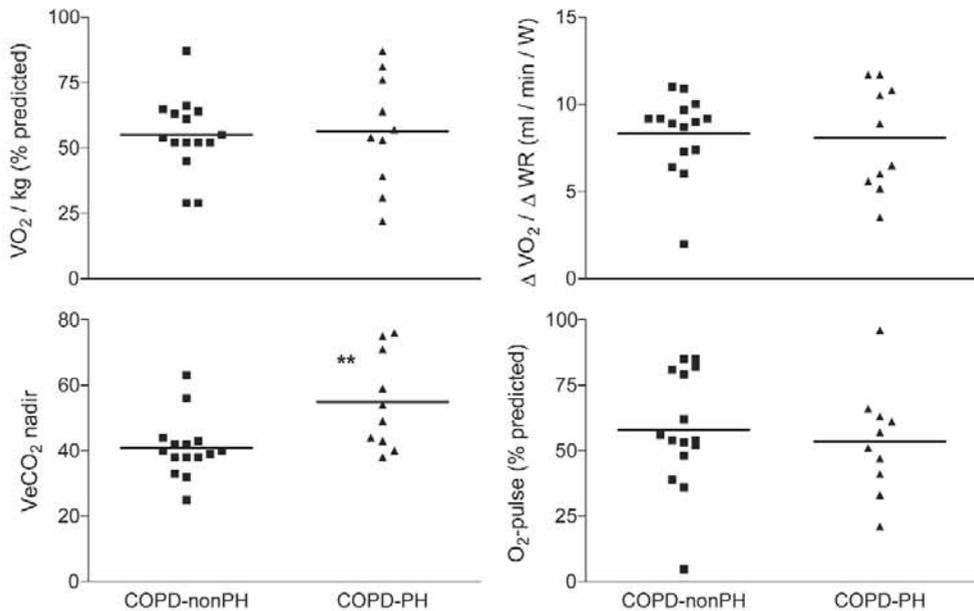


FIGURE 1. Individual values of CPET characteristics in COPD-nonPH and COPD-PH. No significant difference in peak oxygen uptake per kilogram body weight (top left), increase in oxygen uptake relative to workrate increase (top right) and maximal oxygen pulse (bottom right) was observed between both groups. The ventilatory equivalent for CO₂ (V_E/V_{CO_2}) at nadir was significantly higher in COPD-PH patients (bottom left). ** $p < 0.01$, versus COPD-nonPH.

Right Heart Catheterization

Elevated Ppa was found in 10 out of 25 COPD patients. By definition, right heart catheterization yielded a significantly higher mPpa and pulmonary vascular resistance (PVR) in COPD-PH compared with COPD-nonPH (Table1).

CardioPulmonary Exercise Testing

CPET characteristics of both groups are presented in Table 2. Peak workload and peak VO_2 as percentage of predicted were comparable in COPD-PH and COPD-nonPH patients. The individual values of peak VO_2 (% predicted), increase in oxygen uptake relative to workrate increase ($\Delta \text{VO}_2 / \Delta \text{Workload}$), $V_E/V\text{CO}_2$ nadir and maximum O_2 pulse are shown in Figure 1. COPD-nonPH patients showed more efficient ventilation during exercise, reflected by a significantly lower $V_E/V\text{CO}_2$ nadir ($p < 0.01$). Exercise capacity and VO_2 and V_E at peak exercise were not different between both groups. O_2 pulse at maximal exercise was comparable in both groups.

TABLE 2. CPET characteristics of COPD-nonPH and COPD-PH patients

	COPD-nonPH (n = 15)	COPD-PH (n = 10)
Peak workload, W	65 ± 25 (20-100)	47 ± 20 (16-77)
Peak workload, % predicted	50 ± 21 (20-96)	39 ± 23 (15-88)
Peak VO_2 , ml/kg/min	13.0 ± 3.8 (5.8-18.8)	13.2 ± 5.1 (6.8-22.7)
Peak VO_2 , % predicted	55 ± 14 (29-87)	56 ± 21 (22-87)
Peak heart rate, beats/min	119 ± 19 (84-149)	126 ± 21 (91-160)
Peak heart rate, % predicted	77 ± 11 (55-96)	81 ± 12 (65-99)
Peak O_2 -pulse, ml/beat	7.6 ± 1.6 (4.7-9.6)	6.6 ± 2.4 (2.3-9.3)
Peak O_2 -pulse, % predicted	62 ± 17 (36-85)	54 ± 21 (21-96)
Peak $P_{\text{ET}}\text{CO}_2$, kPa	4.6 ± 1.0 (2.4-6.4)	3.8 ± 1.8 (1.5-7.0)
Peak V_E , l/min	37 ± 10 (19-51)	46 ± 24 (19-86)
Peak V_E , % predicted	66 ± 16 (47-99)	68 ± 26 (43-129)
Peak $V_E/V\text{O}_2$	39 ± 7 (29-54)	56 ± 16 (27-80)**
Slope $V_E/V\text{CO}_2$	36 ± 11 (20-65)	51 ± 23 (24-103)*
$V_E/V\text{CO}_2$ nadir	41 ± 9 (25-63)	55 ± 15 (38-76)**
$\Delta\text{VO}_2 / \Delta\text{Workload}$	8.3 ± 2.3 (2.0-11.0)	8.0 ± 3.0 (3.5-11.7)
Desaturation, %	-4 ± 3 (-11-0)	-8 ± 5 (-16-(-1))*

Values are mean ± SD (range). Abbreviations: COPD = chronic obstructive pulmonary disease, O_2 -pulse = oxygen pulse, $P_{\text{ET}}\text{CO}_2$ = end-tidal CO_2 pressure, V_E = minute ventilation, $V_E/V\text{CO}_2$ = ventilatory equivalent for CO_2 , $V_E/V\text{O}_2$ = ventilatory equivalent for O_2 , VO_2 = oxygen uptake. * $p < 0.05$, versus COPD-nonPH, ** $p < 0.01$, versus COPD-nonPH.

Figure 2 shows that arterial oxygen saturation (SpO_2) was lower in COPD-PH both at rest (96 ± 3 (range: 88-99 %) versus 91 ± 4 (range: 85-99 %), $p < 0.01$) and at peak exercise (92 ± 5 (range: 84-99 %) versus 83 ± 7 (range: 72-98 %), $p < 0.01$). The extent of desaturation from rest to exercise was larger in COPD-PH patients (Table 2).

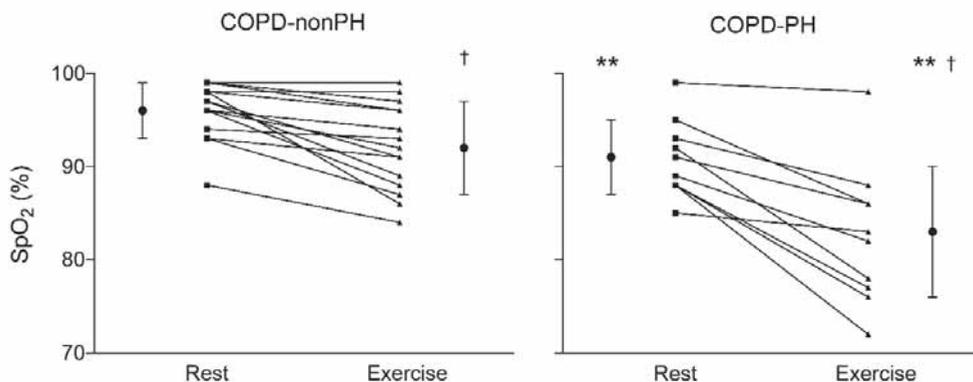


FIGURE 2. Arterial oxygen saturation (SpO_2) at rest and during maximal exercise in COPD-nonPH (left) and COPD-PH patients (right). COPD-PH patients showed a significantly reduced SpO_2 at rest and during exercise. Note that during maximal exercise all but one COPD-PH patients showed a SpO_2 below 90%. ** $p < 0.01$, versus COPD-nonPH, † $p < 0.01$, versus rest.

Pulmonary Artery Pressure and CPET characteristics

As shown in Figure 3, in the whole group resting mPpa was inversely related to resting PaO_2 and DLCO ($r = -0.70$, $p < 0.001$ and $r = -0.58$, $p < 0.01$, respectively), as well as to SpO_2 at rest and during peak exercise ($r = -0.58$ and $r = -0.63$, $p < 0.01$, respectively). Furthermore, our data showed a correlation between mPpa and exercise ventilatory efficiency (V_E/VCO_2 nadir, $r = 0.43$, $p < 0.05$).

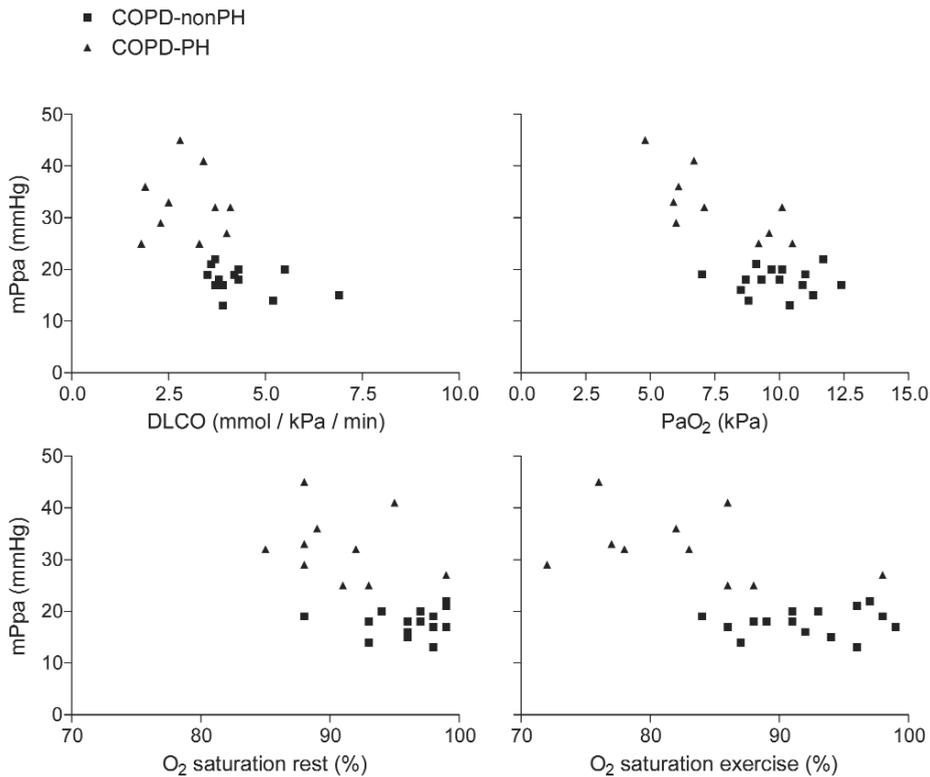


FIGURE 3. In the whole group resting mPpa was inversely related to diffusion capacity (DLCO, top left) and resting PaO₂ ($r = -0.58$, $p < 0.01$ and $r = -0.70$, $p < 0.001$, top left and top right, respectively). Furthermore, mPpa showed a correlation with arterial oxygen saturation (SpO₂) at rest and during peak exercise ($r = -0.58$ and $r = -0.63$, $p < 0.01$, bottom left and bottom right, respectively).

DISCUSSION

The present study sought to investigate whether the presence of PH in COPD is reflected by specific exercise gas exchange characteristics. Characteristic findings in idiopathic PAH are a reduced peak work capacity, reductions in VO₂ at the anaerobic threshold and at peak exercise, a diminished peak oxygen pulse (O₂-pulse), a diminished ventilatory efficiency and a gradual decrease in SpO₂ [13]. Here we show that the presence of PH in COPD only results in a few alterations in CPET patterns, with considerable overlap between PH and non-PH patients. PH was associated with a reduced SpO₂ at baseline, a further reduction in SpO₂

during exercise and an increased V_E/VCO_2 nadir (Table 2). These parameters were related to mPpa measured at rest. COPD-PH patients demonstrated a reduced PaO_2 and a trend to a lower diffusion capacity as compared to the COPD-nonPH patients. Furthermore, a weak inverse correlation of mPpa with PaO_2 at rest and diffusion capacity was shown. Most gas exchange variables showed a large overlap in both groups.

The patients we studied were part of a cohort of COPD patients screened for PH. In this cohort, right heart catheterization is performed in case of increasing symptoms on exertion despite stable pulmonary function tests. We included all patients who had undergone both CPET and right heart catheterization. The separation of COPD with and without associated PH resulted in 2 groups with a reduced (not significant) airflow obstruction in COPD-nonPH patients, and on average a significantly lower PaO_2 in COPD-PH patients. Two out of 10 COPD-PH patients were normoxic ($PaO_2 > 10$ kPa) and 2 patients only showed mild hypoxemia, as shown by a $PaO_2 > 9$ kPa. Moreover, 7 out of 15 COPD-nonPH patients had a $PaO_2 < 10$ kPa, suggesting that hypoxemia is not the only factor leading to PH in COPD. COPD-PH patients had moderate PH (mPpa = 33 ± 6 mmHg), although 2 patients had a mPpa of more than 40 mm Hg. The latter may be explained by a selection bias in the present study; we specifically included patients with progressive exercise intolerance despite stable pulmonary function tests. The 40% prevalence of PH in our COPD patients is comparable to that in other studied COPD populations [4;5;9].

Gas exchange measurements

It is known that exercise often induces an abnormal rise in mPpa in COPD patients [10;20], which may in part explain that, in the present study, only V_E/VCO_2 nadir and slope were found to differ between COPD-nonPH and COPD-PH patients. An increased nadir of the V_E/VCO_2 curve has been proposed as an index of ventilatory efficiency [21]. The index is known to be consistently elevated in idiopathic PH [13]. An important determinant of this nadir is the degree of dead space ventilation due to loss of pulmonary vascular bed. A decreased $PaCO_2$ set point (i.e., the ventilatory center regulates $PaCO_2$ at a lower value), such as in chronic psychogenic hyperventilation and metabolic acidosis, will also result in a higher V_E/VCO_2 nadir. The weak correlation between resting mPpa and V_E/VCO_2 nadir in this study suggests that loss of pulmonary vascular bed only partially explains the inefficient ventilation in these patients. The decreased ventilatory efficiency at peak exercise in COPD-PH patients might also explain their comparable aerobic capacity, despite lower peak workloads, through an increased work of breathing. Exercise characteristics at the anaerobic threshold (AT) were not provided since AT, assessed by the V-slope method [22], could not be determined, i.e. no VO_2 level at which VCO_2 began to increase with an inflection could be determined in almost half of the patients. Our find-

ings confirm previous studies that showed that in patients with moderate to severe COPD the AT is not reached in approximately half of the patients [23;24]. Absence of the AT in COPD patients can indicate that exercise was terminated before significant metabolic acidosis occurred. In addition, in COPD gas exchange methods for determination of the anaerobic threshold do not agree very well with methods that are based on the assessment of anaerobic metabolism in venous blood [25].

It is well known that an increased right ventricular afterload leads to an impaired stroke volume response (SV) to exercise [26]. Accordingly, Sun and co-workers [13] found a reduced peak O_2 -pulse in PH patients. The O_2 -pulse can be used as an estimator of the SV response to exercise on the assumption that O_2 extraction is unaltered [18]. In COPD patients, peak O_2 -pulse is usually reduced and related to exercise capacity [27;28]. Hypoxic pulmonary vasoconstriction [29] and a reduced pulmonary capillary reserve capacity result in increased right ventricular afterload during exercise, impairing SV. This increase in afterload is augmented by increased intrathoracic pressure swings, which have also been shown to be related to peak O_2 pulse [27;28]. Although functional residual capacity was not different at rest between both groups, we have no data on dynamic hyperinflation during exercise. Our study confirmed findings of a reduced O_2 pulse, but could not demonstrate that the presence of PH in COPD is associated with a further decrease in O_2 -pulse at maximal exercise.

Pulse oximetry

SpO_2 at rest was reduced in COPD-PH patients, and showed a further significant decrease during exercise; SpO_2 dropped below 90% in all but one COPD-PH patient. Furthermore, in accordance with previous studies [1], SpO_2 and PH were closely associated. Although this study does not clarify whether hypoxemia is cause or consequence of PH, hypoxemia should be considered as the main cause for the development and progression of PH in COPD [2]. Ventilation/perfusion inequality results in a low SpO_2 during exercise in COPD [30], and these factors were likely to be more impaired in the COPD-PH group, given a lower DLCO and larger $D(A-a)O_2$ at rest in these patients.

Clinical implications

In general, the increase in Ppa in COPD patients tends to be modest (mPpa, 20-35 mmHg), and the progression of PH in COPD is slow [4]. The relevance of PH in COPD was emphasised by Kessler and coworkers [12] who showed that the presence of PH in COPD is associated with an increased risk of hospitalisation. It has furthermore been shown that in COPD, PH results in shorter survival [1;9]. Hence, simple noninvasive tools pointing to the presence of PH in COPD patients are warranted. Gas exchange measurements during exercise may be useful in the recognition of PH [11]. Surprisingly, COPD-PH patients in our study had

a similar exercise capacity compared to COPD-nonPH, and showed only a reduced ventilatory efficiency during exercise. However, the individual values in both groups showed a large overlap. Therefore, gas exchange measurements during CPET do not seem to have an additive value over exercise pulse oximetry. The latter can e.g. easily be performed during a six minute walk test.

Study limitations

A larger number of patients may have resulted in significant differences between both groups. However, our results clearly show that there is a considerable overlap between the parameters in the nonPH and PH group, demonstrating the heterogeneity within COPD patients. It is therefore unlikely that a larger sample size in our study would have shown more diagnostic relevancy of CPET in the diagnosis of COPD related PH. In our study, we compared patient groups with different degrees of airway obstruction, as COPD patients with associated PH showed less severe airway obstruction. Although one could argue that it is an unjustified comparison, it followed automatically from our stratification of COPD patients according to presence or absence of PH. A relatively preserved FEV₁ in COPD patients with PH has also been found by other investigators [31;32]. Thabut et al. (2005) identified a subgroup of COPD patients characterized by an elevated pulmonary artery pressure and a marked hypoxemia, contrasting with moderate bronchus obstruction [5]. The observation that patients with PH showed less severe bronchus obstruction, but comparable peak VO₂, suggests that in these patients exercise is not impaired by airflow limitation only. If the patients in both groups would have shown similar degrees of airflow obstruction, differences in peak VO₂, VE/VCO₂ and SpO₂ would possibly have been larger between the two groups. It is very likely, however, that still there would have been a considerable overlap of these parameters in patients with and without PH.

Conclusion

During exercise in this cohort of COPD patients, the existence of PH was associated with hypoxemia and a reduced ventilatory efficiency. Gas exchange parameters measured during CPET showed a large overlap between COPD patients with and without PH. We therefore conclude that to detect PH in COPD, gas exchange measurements during CPET have no additive value to exercise pulse oximetry.

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CHAPTER SEVEN

Summary, conclusions and future perspectives

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SUMMARY

In patients with chronic obstructive pulmonary disease (COPD), a disease state characterized by airflow limitation, maximal exercise capacity is often reduced. Although the impaired exercise tolerance is generally attributed to a reduction in ventilatory capacity and excessive dyspnea, other factors may be contributory. These factors include deconditioning, peripheral muscle dysfunction and abnormal hemodynamic response to exercise. The latter may be due to the development of pulmonary hypertension (PH), an under-recognised but not uncommon feature in COPD patients. An increase in pulmonary vascular resistance may hamper cardiac function at rest, but more specifically during exercise, which leads to exercise limitation. In this respect, little is known about the cardiovascular response to exercise in these patients and to what extent it contributes to exercise limitation. With the availability of new sophisticated techniques, such as magnetic resonance imaging (MRI), and suitable therapy that produces pulmonary vasodilation, it is possible to elucidate the influence of a cardiovascular limitation in exercise tolerance in COPD patients. The objective of this thesis is to describe the cardiac and pulmonary hemodynamic response to exercise in COPD patients, and how these interact. **Chapter 1** of this thesis deals with pulmonary hypertension associated with COPD and gives an overview of the current knowledge on cardiac function and pulmonary hemodynamics at rest and during exercise in this patient group.

Chapter 2 presents a study about adaptation of the right ventricle (RV) in 25 COPD patients without clinical signs of pulmonary hypertension. Changes of the structure and function of the right ventricle have been well described in COPD patients with severe hypoxemia. Whether these changes occur in patients with normoxia or mild hypoxemia is unclear. Therefore, our aim was to determine if early right ventricular adaptive changes affect both right and left ventricular (LV) function in COPD patients with normoxemia and mild hypoxemia. The results were compared against an age-matched control group. Using MRI it was found that the COPD patients showed marked hypertrophy which is accompanied by decreased RV end-diastolic volume. The hypertrophy is classified as concentric hypertrophy, that is probably due to intermittent increases in pulmonary artery pressures that occur during exercise and/or sleep. Although stroke volume was reduced in comparison with the healthy controls, the finding of concentric hypertrophy did not impair RV or LV systolic function.

The effects of an increased pulmonary vascular resistance and hence pulmonary artery pressure (Ppa) on cardiac performance in response to exercise are described in **Chapter 3**. In ten patients with idiopathic PAH ($mPpa = 51 \pm 18$ mmHg) the effects of submaximal exercise on stroke volume (SV) and RV and LV

function were evaluated. In addition to these patients, cardiac MRI was also performed for 10 healthy age-matched controls both at rest and during submaximal exercise (40% of maximal workload). For both groups, right and left ventricular dimensions and stroke volume were assessed. In healthy controls all cardiac parameters increased significantly to exercise, with the exception of RV and LV end-diastolic volume. In iPAH stroke volume was low at rest and remained unaltered during exercise (61 ± 27 and 60 ± 31 mL, not significant, for rest and exercise respectively), with significant decrease in LV end-diastolic volume to exercise (88 ± 24 and 76 ± 29 mL, $p < 0.05$). Two mechanisms may be responsible for a reduction in LV end-diastolic volume. First, the RV and LV are enclosed in a relatively non-distensible pericardium and separated by the interventricular septum. Hence, changes in right ventricular volume will directly influence left ventricular volume. Therefore, exercise-induced changes in RV end-diastolic volume and pressure-mediated septal curvature will interfere with LV diastolic filling. Second, forward failure of the RV, as indicated by a reduced RV ejection fraction during exercise, will hamper an adequate filling of the LV. In conclusion, an exercise-induced increase in Ppa results in impairment of RV function and underfilling of the LV, leading to a failing stroke volume response.

In COPD the levels of PH are mild to moderate, but Ppa can increase excessively during exercise. Therefore in the study of **Chapter 4** we investigated cardiac response to exercise and determined if changes in cardiac function were related to changes in Ppa, measured at comparable exercise level. Right heart catheterisation was performed in 16 COPD patients and Ppa's were assessed both at rest and during exercise. For comparison, cardiac MRI was performed in 8 age-matched healthy controls both at rest and during submaximal exercise. All COPD patients showed a significant exercise-induced increase in mPpa (21 ± 8 to 33 ± 11 mm Hg, $p < 0.01$) and pulmonary vascular resistance remained unchanged. In comparison with healthy controls, the COPD patients showed reduced SV at rest and during exercise. The small increase in SV to exercise was solely dependent on an increased RV end-diastolic volume, whereas in the healthy subjects SV was augmented to exercise by both an increase in RV end-diastolic volume and a decrease in RV end-systolic volume. Furthermore, the results showed that Ppa at rest was related to SV during submaximal exercise. We concluded that as a consequence of an unaltered pulmonary vascular resistance to exercise, the right ventricle was unable to increase its contractility during exercise.

Sildenafil is recognised as a specific pulmonary vasodilator. In **Chapter 5** its aim was to determine if a single dose of sildenafil could attenuate the exercise-induced increase in pulmonary artery pressure, thereby allowing augmentation of stroke volume (SV), and improving maximal exercise capacity. 17 COPD patients (GOLD III-IV) underwent right heart catheterisation at rest and submaximal exercise. Resting and exercise measurements were repeated 60 minutes after oral intake of 50 mg sildenafil. Also, patients performed two maximal exercise tests

(CPET)- randomly, one hour after placebo and after 50 mg sildenafil. In 4 COPD patients pulmonary hypertension was apparent at rest ($mPpa > 25$ mmHg) and 6 patients developed pulmonary hypertension during exercise ($mPpa > 30$ mmHg). Sildenafil did not alter resting $mPpa$ (20 ± 9 mmHg), but during exercise $mPpa$ was significantly attenuated (28 ± 12 mmHg, $p < 0.01$) as compared with baseline exercise measurements, regardless of $mPpa$ at rest. The reduced augmentation in $mPpa$ was not accompanied by an increased SV, and CO. In addition, maximal exercise capacity and cardiopulmonary exercise characteristics were unchanged after acute sildenafil intake. However, the effects of chronic treatment with sildenafil on stroke volume response during exercise are unclear. In addition, since most of the patients studied in chapter 5 had no pulmonary hypertension, it is of interest whether COPD patients with significant pulmonary hypertension will show a more favourable response to pulmonary vasodilator therapy. Future studies are planned to elucidate these aspects.

It has been suggested that exercise testing may be useful in early diagnosis of PH in COPD patients. The objective of the study as described in **Chapter 6** was to verify whether the existence of PH in COPD was related to characteristic CPET findings. More specifically, we investigated whether gas exchange measurements during CPET could lead to a better recognition of PH in COPD than exercise pulse oximetry. Data from maximal cardiopulmonary exercise tests (CPET) of 25 COPD patients were retrospectively analysed. Differences in gas exchange and pulse oximetry were assessed between COPD patients with associated PH (COPD-PH, $n = 10$) and COPD patients without associated PH (COPD-nonPH, $n = 15$). COPD-PH patients showed a not significantly lower maximal workload. The only difference in gas exchange between the two groups was found in the ventilatory efficiency. COPD-PH patients demonstrated a less efficient ventilation during exercise, as reflected by an increased ventilatory equivalent for CO_2 at nadir and an increased slope of the ventilation versus CO_2 output. Pulse oximetry showed that arterial oxygen saturation was reduced both at rest and at maximal exercise in COPD-PH group. A high resting $mPpa$ was associated with a reduced arterial oxygen saturation (at rest and during exercise) and a reduced ventilatory efficiency. It can be concluded that the existence of PH in COPD is associated with a significantly reduced ventilatory efficiency during CPET. However, in this cohort of COPD patients a low SpO_2 at rest and a further decrease during exercise similarly suggest the presence of PH in COPD. Gas exchange parameters measured during CPET showed a large overlap between COPD patients with and without PH. We therefore conclude that to detect PH in COPD, gas exchange measurements during CPET have no additive value to exercise pulse oximetry.

Conclusions and future perspectives

One of the most important findings of this thesis is that COPD patients have an impaired stroke volume response to exercise, which can be attributed to the

inability of the right ventricle to improve its contractility during exercise, due to an increased right ventricular afterload. This finding confirms earlier studies that showed that cardiovascular limitation plays a role in the lowered oxygen delivery and thus exercise limitation [1-4]. Further research is warranted, and should be aimed at gaining insight in 1) the cause of pulmonary vascular damage, and 2) mechanisms of right ventricular failure in COPD.

Causes of pulmonary vascular damage

Different causes for the increased right ventricular afterload during exercise have been identified in COPD patients, as briefly discussed in chapter 1. In summary, changes in structure and damage of the micro arterial bed lead to a reduction in the pulmonary vascular bed, causing an increased pulmonary artery pressure [5]. Exercise induces several reactions that cause a rise in pulmonary artery pressure. First, due to diffusion disturbances patients with COPD often show a significant desaturation during exercise, that augments hypoxic pulmonary vasoconstriction [6]. Second, dynamic hyperinflation of the lungs during exercise could, by directly compressing the heart and intrathoracic vessels, elevate intracardiac pressures [7]. In addition, mechanical stress or inflammatory reaction due to repeated stretching of hyperinflated lungs may be involved in the pathobiology of pulmonary artery remodeling [8]. Third, recent studies have shown that exercise induces an abnormal systemic inflammatory and oxidative response in COPD patients, which is seen in both the circulation and peripheral muscles [9-11]. Next to inflammatory cells, increased levels of cytokines have been reported, including increased concentrations of tumor necrosis factor (TNF)- α , interleukin (IL)-6 and IL-8. These factors may play a role in the overall remodeling response of the pulmonary vascular bed [12].

The contribution of these factors to an increased pulmonary artery pressure are not known in individual patients. Recent developments in MRI offer unique possibilities in the study of pulmonary vascular diseases, since new techniques make it possible to not only calculate pulmonary blood flow content [13], but also to measure hemodynamic characteristics of the blood flow in the small pulmonary vasculature, and transit times of blood in the pulmonary capillaries. An example of a pulmonary perfusion image by MRI is given in Figure 1. It shows an emphysema patient with alpha-1-antitrypsin deficiency. The typical panlobular emphysema in these patients more commonly involves the lung bases [14]. Due to the disease process the pulmonary vasculature has been severely damaged in this area, as is clearly shown in Figure 1.

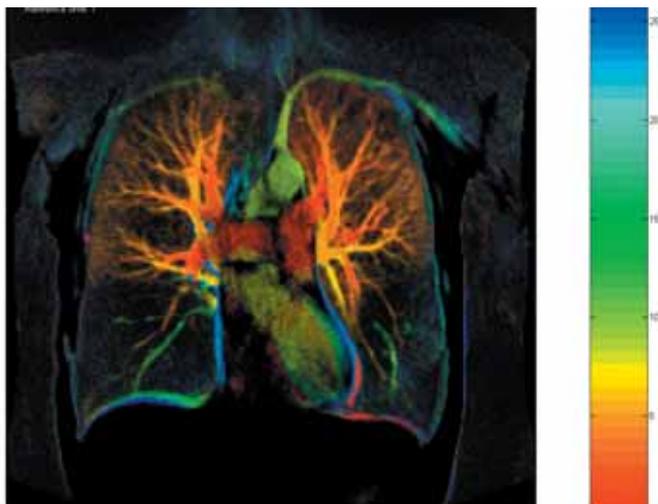
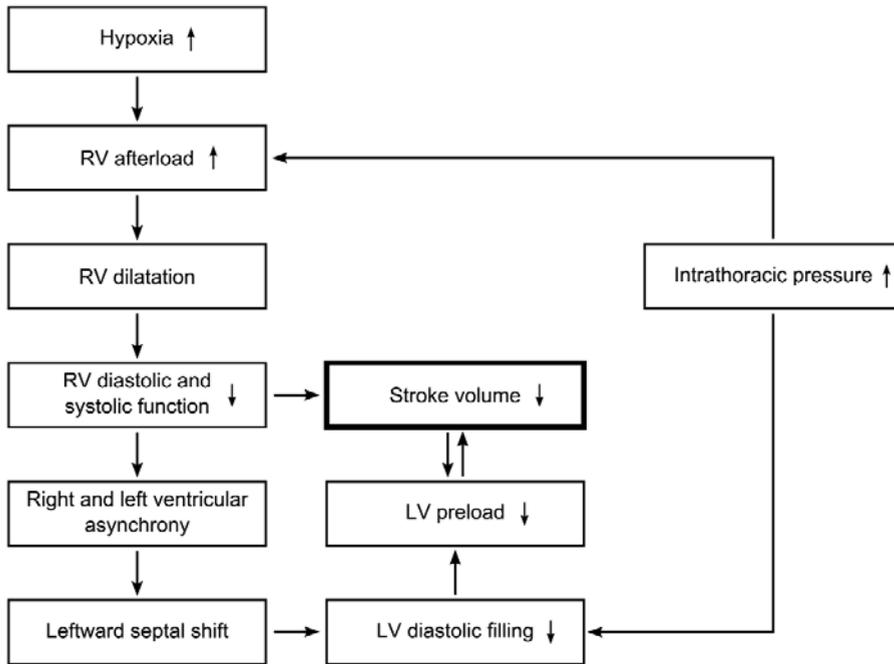


FIGURE 1. Pulmonary perfusion image of a female patient with emphysema (alpha-1-antitrypsin deficiency). Gadolinium contrast agent was injected as a bolus in the brachial veins. The colours reflect the arrival time of the maximum contrast: red means early and blue means late arrival. The image clearly illustrates that in this patient only the upper parts of the lung are perfused by the pulmonary circulation (orange) whereas the basal parts are only perfused in the aortic phase (green) by the bronchial circulation. Pulmonary mean transit time can be calculated by subtracting the arrival time of maximum contrast in the pulmonary artery from the arrival time in the aorta curve. The pulmonary transit time multiplied by cardiac output gives total pulmonary blood volume. (Courtesy of J.G. Korpelaar)

Mechanisms of right ventricular failure.

In the past, RV failure was considered as systolic dysfunction as a consequence of increased RV afterload, and the only effective treatment, a reduction of right ventricular afterload. Currently, other factors have been recognized in right ventricular failure such as RV diastolic dysfunction and interventricular interdependency leading to left ventricular underfilling and by that contributing to the decreased stroke volume in these patients. The proposed mechanisms that can lead to heart failure during exercise in patients with chronic pressure overload are summarized in Figure 2. In short, progressive increase in pulmonary vascular resistance will lead to RV dilatation and impaired systolic function. For this reason progressive RV dilatation, defined as an increase of RV end-diastolic volume over time is a clear sign of RV failure and predicts a poor prognosis in patients with pulmonary arterial hypertension [15]. Although most of the research has been focused on impairment of systolic function in RV failure, it is currently well recognised that diastolic dysfunction might play an important role in RV failure. RV



Figuur 2. Pathophysiological mechanisms involved in right ventricular (RV) heart failure and a reduced stroke volume (SV) during exercise in COPD patients. Exercise induces hypoxia and, consequently, hypoxic pulmonary vasoconstriction that increases RV afterload. As a result of dynamic hyperinflation during exercise, intrathoracic pressure will increase, thereby affecting RV afterload, but also reducing venous return and diastolic filling. An increased afterload may impair both RV diastolic and systolic function, and may cause interventricular asynchrony leading to a leftward shift of the interventricular septum. This may lead to underfilling of the left ventricle (LV). In addition, a low RV output directly causes a reduced LV preload. These factors may all be involved in patients with COPD when stroke volume is impaired at rest, but especially during exercise.

hypertrophy and increased pulmonary vascular resistance are associated with impaired myocardial relaxation duration [16].

The effects of treatment focussed on the improvement of right ventricular relaxation might thus be beneficial in patients with more advanced pulmonary hypertension. In addition, exercise increases heart rate and hence diastolic filling time is reduced. The effects of exercise on diastolic function in COPD remain unclear. With right ventricular pressure overload the septum tends to be displaced towards the left ventricle, which causes a distortion of the left ventricle [17]. This, together with a reduced stroke volume, causes a decreased LV preload. Decreased left ventricular preload will directly impair left ventricular output

according to the Frank–Starling mechanism. As a consequence, the increased oxygen demand of both ventricles may not be compensated for.

Future studies, should focus on the mechanisms responsible for the low stroke volume response during exercise in COPD patients, as described in this thesis, and the possibility of therapy to improve this condition. One important aspect is the possibility of reducing RV afterload by pulmonary vasodilation. This is especially challenging, since in COPD patients vasodilator therapy need to be pulmonary specific in order to avoid pulmonary shunting. In addition, the results described in this thesis show that the effects of pulmonary vasodilation should be assessed during exercise. This way the deleterious effects of hypoxic pulmonary vasoconstriction and dynamic hyperinflation can also be accounted for.

In addition, molecular insights came available on the mechanisms of myocyte adaptation and maladaptation in conditions of pressure overload [18]. These insights make the right ventricle itself a target for treatment with the purpose to improve pump function by improving myocyte adaptation. For instance, a recent study of our group showed that by means of sildenafil relaxation function of the right ventricle can be improved [16]. Therefore, future therapy should not only focused on the pulmonary vascular bed but also the right ventricle itself. The influence of pulmonary vascular damage and right ventricular involvement in COPD on exercise tolerance can only be elucidated when it is possible to improve pulmonary hemodynamics, including right ventricular function in these patients.

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NEDERLANDSE
SAMENVATTING

SAMENVATTING

Luchtwegobstructie is een van de belangrijkste kenmerken van de longziekte 'chronic obstructive pulmonary disease' (COPD). Patiënten met COPD hebben over het algemeen een beperkt inspanningsvermogen, wat voornamelijk wordt toegeschreven aan een afname in ventilatoire capaciteit en overmatige kortademigheid. Naast deze ventilatoire beperkingen zijn ook andere factoren van invloed op de inspanningstolerantie, zoals de perifere skeletspierfunctie en de hartfunctie.

Het functioneren van het hart kan belemmerd worden door de ontwikkeling van pulmonale hypertensie (PH), een te hoge bloeddruk in de longslagader. Deze drukstijging wordt veroorzaakt door een toename in de pulmonale vaatweerstand die op zijn beurt voortkomt uit verlies van en abnormale vernauwingen van de bloevaten in het longvaatbed. Met name tijdens inspanning kan de bloeddruk in de longslagader abnormaal snel stijgen. De rechter hartkamer, die het bloed door de longen pompt, wordt door deze drukstijging in zijn pompfunctie belemmerd. Dit zou van invloed kunnen zijn op de inspanningstolerantie bij patiënten met COPD. Met de komst van nieuwe technieken als MRI en medicatie gericht op het longvaatbed is het mogelijk onderzoek te doen naar de potentiële rol van het hart bij de inspanningsbeperking van COPD patiënten. Het doel van dit proefschrift is dan ook om de betekenis van de veranderingen in het longvaatbed op het functioneren van het hart en de inspanningstolerantie te beschrijven en de potentiële mogelijkheden van therapeutische interventie te onderzoeken bij patiënten met COPD.

Hoofdstuk 1 van dit proefschrift biedt een overzicht van de huidige kennis van hartfunctie en pulmonale vaatbedschade in rust en tijdens inspanning bij COPD patiënten.

In **Hoofdstuk 2** worden de verandering in de structuur en functie van het hart beschreven bij 25 patiënten met COPD met een normaal of licht verlaagd zuurstofgehalte in het bloed. Al eerder werden veranderingen in de structuur en functie van de rechter hartkamer beschreven bij een ernstiger groep COPD patiënten met een te laag zuurstofgehalte in het bloed en een verhoogde bloeddruk in de longslagader. Doel van ons onderzoek was om middels MRI-metingen de veranderingen in structuur en functie van het hart in een vroeger stadium van COPD te beschrijven. Een opvallende bevinding was dat de rechter hartkamer van de onderzochte patiëntengroep al aanzienlijk aangepast was in vergelijking met de gezonde controlegroep. De belangrijkste verschillen tussen patiënten en gezonden bestonden uit een verdikking van de wand en een afname van het eind-diastolische volume van de rechter hartkamer. Hoewel het slagvolume in vergelijking met de gezonde proefpersonen verlaagd was, bleek de systolische functie van zowel de linker als rechter hartkamer niet afwijkend.

Het effect van een ernstig verhoogde druk in de longslagader - ten gevolge van inspanning - op de prestatie van het hart wordt beschreven in **Hoofdstuk 3**. Aangezien de ernstige vorm van pulmonale hypertensie zeldzaam is bij COPD patiënten onderzochten wij een groep van tien patiënten met zogenaamde idiopathische pulmonale arteriële hypertensie (iPAH): een ernstige en levensbedreigende vorm van pulmonale hypertensie. De gemiddelde bloeddruk in de longslagader bij deze groep was 51 ± 18 mmHg (normaal $\cong 12 - 18$ mmHg). Middels MRI-bepalingen zijn de effecten van submaximale inspanning op het slagvolume en de linker en rechter hartkamer bestudeerd. Naast deze 10 patiënten hebben nog eens 10 gezonde proefpersonen van dezelfde leeftijd een MRI van het hart ondergaan in rust en tijdens submaximale inspanning (40% van maximale belasting). Tijdens deze metingen werden volumes van de rechter en linker hartkamer en het slagvolume bepaald. Bij de gezonde proefpersonen namen slagvolume, hartfrequentie en cardiac output significant toe tijdens inspanning. De eind-diastolische volumes van zowel rechter als linker kamer bleven onveranderd. Het slagvolume was laag bij de patiënten met iPAH en bleef onveranderd tijdens inspanning (61 ± 27 en 60 ± 31 ml, niet significant verschillend, voor respectievelijk rust en inspanning). Het eind-diastolisch volume van de linker kamer nam significant af tijdens inspanning (88 ± 24 and 76 ± 29 ml, $p < 0.05$). Er zijn twee mogelijke verklaringen voor deze afname in linker kamer eind-diastolisch volume. Ten eerste zijn de rechter en linker ventrikel omsloten door een relatief onuitrekbaar pericard (hartzakje) en gescheiden door een wand, het interventriculaire septum. Zodoende zullen veranderingen in rechter kamer volume direct het linker kamer volume beïnvloeden. Veranderingen in rechter ventrikel eind-diastolisch volume en septumkromming ten gevolge van inspanning kunnen op deze manier de linker ventrikelvulling belemmeren. Ten tweede kan een beperkte rechter ventrikel functie tijdens inspanning leiden tot inadequate vulling van het linker ventrikel. Concluderend kan gesteld worden dat een door inspanning geïnduceerde stijging van de druk in de longslagader leidt tot een afname in rechter ventrikel functie en een ondervulling van het linker ventrikel, die beide resulteren in een falend slagvolume respons.

De mate van PH in COPD patiënten – mits aanwezig - is mild tot matig, maar deze kan excessief stijgen tijdens inspanning. **Hoofdstuk 4** bespreekt de resultaten van een studie naar de respons van het hart op inspanning bij COPD patiënten met en zonder PH. Tevens is bepaald of veranderingen in hartfunctie gerelateerd zijn aan veranderingen in de druk van de longslagader, gemeten op een zelfde inspanningsniveau (40% van maximale belasting). Bij 16 COPD patiënten werd een rechter hartcatheterisatie uitgevoerd en werd de druk in de longslagader bepaald in rust en tijdens submaximale inspanning. Van alle patiënten werd bovendien een MRI-bepaling van het hart in rust en tijdens inspanning gemaakt. Deze MRI-metingen werden ook uitgevoerd bij 8 gezonde proefpersonen van dezelfde leeftijd. Alle COPD-patiënten lieten een significante toename zien in de

gemiddelde druk in de longslagader tijdens inspanning (21 ± 8 mmHg in rust en 33 ± 11 mmHg bij inspanning, $p < 0.01$); de pulmonale vaatweerstand bleef onveranderd. In vergelijking met gezonden vertoonden de COPD-patiënten een kleiner slagvolume in rust en tijdens inspanning. Bij de gezonden werd het slagvolume tijdens inspanning vergroot door zowel een afname in rechter ventrikel eind-systolisch volume als een toename in rechter ventrikel eind-diastolisch volume (preload). De kleine slagvolumetoename tijdens inspanning van de patiëntengroep was slechts afhankelijk van een toename in rechter ventrikel eind-diastolisch volume. Daarnaast bleek de druk in de longslagader in rust gerelateerd te zijn aan het slagvolume bij inspanning. We concluderen dat slagvolumetoename tijdens inspanning beperkt is bij patiënten met COPD en dat deze toename het resultaat is van het vergroten van het eind-diastolisch volume van de rechter kamer en niet van een afgenomen eind-systolisch volume.

Sildenafil is een erkend medicijn voor de behandeling van PH, dat specifiek in de longen vaatverwijding geeft. In de studie van **Hoofdstuk 5** is bepaald of een eenmalige dosis sildenafil de door inspanning geïnduceerde toename in druk in de longslagader kan beperken en daarmee de slagvolumetoename en de inspanningscapaciteit kan verbeteren. 17 COPD patiënten (GOLD stadium III-IV) ondergingen rechter hartcatheterisatie, waarbij pulmonaaldrukken (Ppa) werden bepaald in rust en tijdens submaximale inspanning. Bepalingen tijdens rust en inspanning werden 60 minuten na orale inname van 50 mg sildenafil herhaald. Binnen een week na de catheterisatie werden, in willekeurige volgorde en op verschillende dagen, twee maximale inspanningstests uitgevoerd; de ene één uur na placebo en de andere één uur na sildenafil. Vier COPD patiënten hadden PH in rust ($mPpa > 25$ mmHg) en 6 patiënten ontwikkelden PH tijdens submaximale inspanning ($mPpa > 30$ mmHg). De gemiddelde Ppa in rust was onveranderd na sildenafil, maar ongeacht de Ppa in rust was bij alle COPD-patiënten de gemiddelde Ppa tijdens inspanning minder hoog na sildenafil dan tijdens inspanning zonder sildenafil. De verlaagde Ppa tijdens inspanning resulteerde niet in een vergroot slagvolume en hartminuutvolume. Ook de maximale inspanningscapaciteit en de verschillende inspanningskarakteristieken bleven ongewijzigd na sildenafil. Of chronische behandeling met sildenafil effect heeft op de slagvolumerespons tijdens inspanning is onbekend. Aangezien deze populatie COPD patiënten relatief lage drukken in de longslagader lieten zien, blijft de vraag of patiënten met ernstiger PH meer baat zouden kunnen hebben bij vaatverwijdende therapie.

Bij patiënten met COPD kan met name tijdens inspanning de druk in de longslagader abnormaal toenemen. Om deze reden zouden de resultaten van cardio-pulmonale inspanningstests behulpzaam kunnen zijn bij vroege herkenning van PH bij COPD-patiënten. In **Hoofdstuk 6** wordt onderzocht of de aanwezigheid van PH ($mPpa \geq 25$ mm Hg) bij COPD gerelateerd is aan karakteristieke cardio-pulmonale bevindingen van een maximale-inspanningstest. Data van maximale-inspanningstests van 25 patiënten met COPD werden retrospectief geanalyseerd.

Verschillen in gaswisseling en polsoximetrie werden bepaald tussen COPD-patiënten met PH (COPD-PH, n = 10) en tussen COPD-patiënten zonder PH (COPD-nonPH, n = 15). De maximale belasting van COPD-PH patiënten was lager dan die van patiënten zonder PH. Dit verschil was echter niet significant. Het enige verschil in gaswisseling tussen beide groepen werd gevonden in de ventilatoire efficiëntie. COPD-PH patiënten lieten een minder efficiënte ventilatie tijdens inspanning zien, weergegeven door een verhoogd ventilatoir equivalent voor CO₂ en een toegenomen helling op de curve van de ventilatie versus de CO₂ output. De arteriële zuurstofsaturatie, gemeten met polsoximetrie, was zowel in rust als bij maximale inspanning verlaagd bij de COPD-PH groep. Een hoge druk in de longslagader in rust was gerelateerd aan een lage arteriële zuurstof saturatie (in rust en tijdens inspanning) en aan een verminderde ventilatoire efficiëntie. De resultaten van dit onderzoek suggereren dat de aanwezigheid van PH bij COPD patiënten geassocieerd is met een verminderde ventilatoire efficiëntie. Daarnaast bleek bij dit cohort van COPD patiënten een lage arteriële zuurstofsaturatie en een verdere afname tijdens inspanning ook de aanwezigheid van PH bij COPD te suggereren. De gaswisselingskarakteristieken verkregen tijdens de cardiopulmonale inspanningstest lieten een grote overlap tussen beide groepen zien. Voor detectie van PH bij COPD-patiënten lijken gaswisselingsbepalingen tijdens inspanning geen toegevoegde waarde te hebben ten opzichte van polsoximetrie tijdens inspanning.

Conclusie

Een van de belangrijkste bevindingen van dit proefschrift is dat patiënten met COPD tijdens inspanning een beperkte slagvolumerespons hebben. Dit kan worden toegeschreven aan het onvermogen van de rechter kamer om de contractiliteit tijdens inspanning te laten toenemen, wat mede wordt veroorzaakt door een toename van de pulmonale vaatweerstand tijdens inspanning. Deze bevindingen bevestigen eerdere studies die aantoonde dat cardiovasculaire beperkingen een rol spelen bij een verminderde zuurstofvoorziening en dus bij inspanningslimitatie. Echter, een acute daling van de druk in de longslagader tijdens inspanning na vaatverwijdende medicatie, leidt niet tot een vergroting van slagvolume of maximale inspanningscapaciteit.. Toekomstig onderzoek zou verder gericht kunnen zijn op het vergaren van nieuwe inzichten in enerzijds de oorzaak van pulmonale vaatschade, en anderzijds de mechanismen van rechter ventrikel falen bij patiënten met COPD.

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CURRICULUM VITAE

Sebastiaan (Bas) Holverda was born on May 6th 1975 in Apeldoorn, The Netherlands. He graduated from secondary school (VWO) in 1994 at the Veluws College, Apeldoorn. Subsequently, he started his study of Human Movement Sciences at the Vrije Universiteit Amsterdam. During his fourth year he participated in a research project for six months at the Department of Medicine, Division of Physiology at the University of California San Diego (UCSD). This study, led by Prof. Dr. John B. West, focused on the effects of sleeping in oxygen-enriched air on the control of ventilation in subjects exposed to high altitude hypoxia. In 2002 he received his M.Sc. degree and started working in the pulmonary function lab at the department of pulmonary diseases (head Prof. Dr. P.E. Postmus) at the VU University medical center, Amsterdam. In the following years, under supervision of Prof. Dr. Postmus and Dr. A. Vonk-Noordegraaf he conducted the investigations to the effects of exercise on cardiac function and pulmonary hemodynamics in COPD patients, described in this thesis. As from November 2007 Bas Holverda will start a post-doc appointment at the Division of Physiology at UCSD under supervision of Dr. S.R. Hopkins, studying the role of perfusion heterogeneity in the development of high-altitude pulmonary edema.

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