Cardiac function and pulmonary hemodynamics during exercise in COPD

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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 is 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 funtion 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± 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 paramaters 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 seperated 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 healty 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.

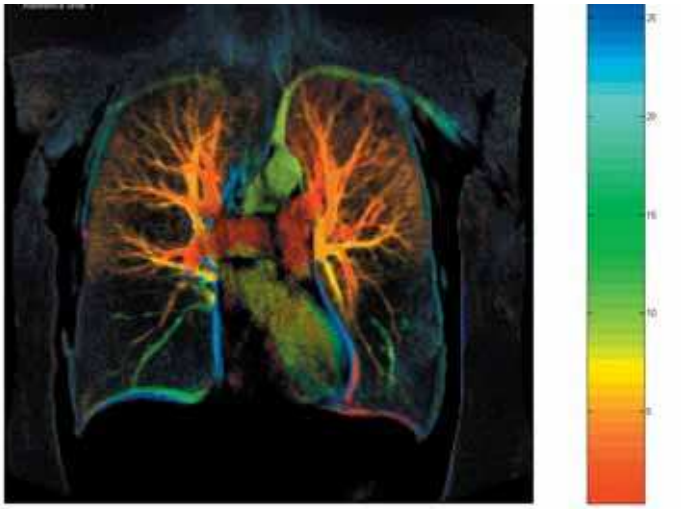
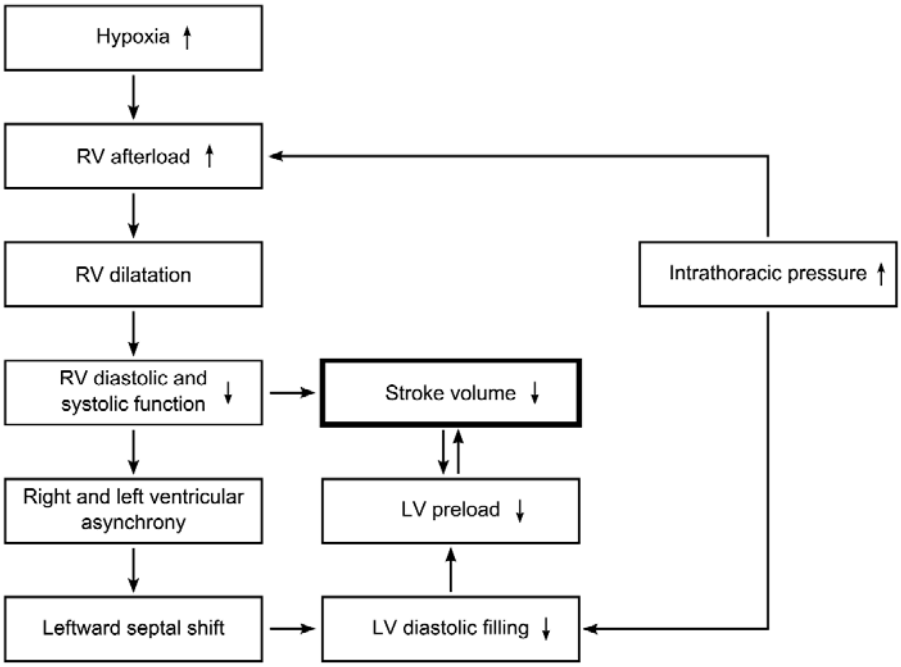


FIGURE 1. Pulmonary perfusion image of a female patient with emphysema (alpha-1-antitrypsin deficiency). Gadolineum contrast agent was injected as a bolus in the brachial veins. The colours reflect the arrival time of the maximum contrast: red means early and blue means late arrival. The image clearly 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 substracting 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. Korporaal)

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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