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Clinical relevance of exercise testing in pulmonary hypertension

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Summary,
conclusions and
future perspectives



SUMMARY AND CONCLUSIONS

The studies in this thesis aim to provide insight into the clinical relevance of different exercise profiles in pulmonary hypertension. Exercise testing in pulmonary arterial hypertension (PAH) is the main focus of this thesis. PAH is a disease state defined by an increased pulmonary arterial pressure and is characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure, exercise intolerance and ultimately death (1). Even in advanced stages of the disease, PAH patients have no symptoms at rest. However, symptoms develop during exercise when pulmonary vascular resistance increases and cardiac output can not rise. As a consequence, gradually progressive exercise intolerance with symptoms of breathlessness and fatigue are common in PAH patients. The prognostic relevance of maximal functional capacity has been shown in several clinical trials in PAH patients (2, 7). The six minute walk test and /or maximal cardiopulmonary exercise test (CPET) are frequently chosen to estimate maximal functional capacity in PAH drug trials (3). The pathophysiological exercise profile of PAH patients measured by CPET is characterized by a low aerobic capacity and decreased ventilatory efficiency (5). In addition to PAH, my research has involved two other categories of PH with global clinical relevance: pulmonary hypertension associated with chronic obstructive pulmonary disease (COPD) and with chronic mountain sickness (CMS).

Chapter 1 starts with an overview of the exercise pathophysiology in PAH and CMS and continues by providing a rationale for exercise testing in the clinical setting. The chapter concludes with a brief introduction of the two most commonly used exercise tests in clinical trials in PAH: the six minute walk test and CPET.

Non-invasive determination of stroke volume during CPET can contribute to the detection of heart failure. However, none of the variables measured during CPET are direct measurements of cardiac output or stroke volume. In **chapter 2** we compared stroke volume measured by magnetic resonance imaging (MRI) to the data provided by an intra-breath technique measuring acetylene absorption, a technique which offers the possibility to determine the augmentation of pulmonary blood flow per heart beat. Both methods were compared at rest and during sub maximal exercise in healthy subjects (n=10) and PAH patients (n=10). The intra-breath technique showed that PAH patients have a smaller exercise induced change in stroke volume compared to healthy controls. These results were similar to the exercise induced changes of stroke volume measured by MRI. In conclusion, the intra-breath measurement of acetylene absorption can be of value to estimate the stroke volume response during exercise and can detect differences in stroke volume between PAH and healthy subjects.

A reduced exercise performance due to a reduced stroke volume response is also seen in chronic left heart failure (6). Dissimilar stroke volume and heart rate responses in PAH and left heart failure could have important therapeutic implications, for example in predicting the response of patients to beta-blocker therapy. In the study presented in **chapter 3**, exercise

oxygen pulse (which estimates stroke volume) and heart rate are compared between a group of PAH patients (n= 28) and left heart failure patients (n=18), matched for maximal aerobic capacity. I showed that patients with PAH demonstrate a smaller stroke volume response and a greater heart rate response during exercise compared to left heart failure patients.

Mortality in PAH patients is strongly associated with right ventricle dysfunction (4), but accurate determination of hemodynamic parameters requires an invasive right heart catheterisation. Exercise parameters could serve as good non-invasive alternatives. Although the correlations with hemodynamic parameters are weak, the 6MWD (2) and maximal oxygen uptake (VO_{2max}) measured during CPET (7) predict survival in PAH. CPET has the advantage over 6MWD to describe pathophysiological abnormalities characterizing the limitation of exercise (5). However, it remains unclear whether gas exchange parameters measured during CPET yield additional prognostic value after determination of the 6MWD, which is less technically demanding. This study question was answered in **chapter 4**. In this retrospective survival study we determined the additional prognostic value of different CPET parameters to 6MWD in a cohort of PAH patients (n=115). The conclusion of this study was that CPET parameters reflecting a low aerobic capacity or a decreased ventilatory efficiency predict survival in PAH. However, only the exercise induced change in oxygen pulse improved the univariate 6MWD prediction model significantly. As such, CPET variables predict survival in PAH, but add only marginally to the prognostic value of the 6MWD.

Although it is clear that several CPET variables have prognostic value when measured at baseline, it is unknown whether these variables have also prognostic value when measured as changes over time. The aim of the study described in **chapter 5** was to determine changes in CPET variables in PAH patients treated with specific therapy and to relate these changes to long term survival. Baseline CPET variables were available from 65 PAH patients. The same CPET variables were available one year later in a sub group of 39 patients. Survival analysis in this study showed that from all CPET variables studied at base line, only maximal heart rate and the slope relating ventilation to carbon dioxide production were significant predictors of survival. After follow-up, only the change in VO_{2max} and oxygen pulse predicted survival. It was concluded that CPET parameters with prognostic value at baseline are not necessarily predictive for survival when measured as changes over time.

Traditionally, exercise training was contraindicated in PAH due to the risk of sudden death. With the knowledge that an improved functional status improves prognosis, the role of exercise training in PAH is being reconsidered. In **chapter 6**, we assess the effects of 12 weeks of exercise training (3 times per week) in 19 stable PAH patients. Before and after the training program, measurements were made of exercise endurance, maximal exercise tolerance and quadriceps muscle strength and endurance. In a subset of 12 PAH patients we were able to obtain quadriceps muscle biopsies before and after training to analyse the effects of exercise training on skeletal muscle morphology. Our study revealed that exercise training improves exercise endurance and quadriceps muscle function in patients with

stable PAH. Enhanced quadriceps muscle function after exercise training was associated with improvements in oxygen handling of the quadriceps muscle fibres.

COPD patients may develop pulmonary hypertension during the progression of their disease. CPET could serve as an important tool in the early diagnosis of pulmonary hypertension in this patient group. The objective of the study described in **chapter 7** was to verify whether the existence of pulmonary hypertension in COPD was related to characteristic CPET findings. More specifically, we investigated the additional value of gas exchange parameters to pulse oximetry during exercise to recognize pulmonary hypertension in COPD patients. CPET data from 25 COPD patients were retrospectively analysed. Differences in gas exchange and pulse oximetry were assessed between COPD patients with associated pulmonary hypertension (n=10) and COPD patients without associated pulmonary hypertension (n=15). The patients with pulmonary hypertension showed a significantly lower maximal exercise tolerance accompanied by a lower ventilatory efficiency. Pulse oximetry was reduced at rest and during exercise in the COPD patients with associated pulmonary hypertension. Mean pulmonary arterial pressure at rest was inversely associated with oxygen saturation (at rest and during peak exercise) and exercise ventilatory efficiency. It can be concluded that COPD patients with associated pulmonary hypertension show a significantly decreased ventilatory efficiency. However, our results also show that a low saturation at rest and a further decrease in saturation during exercise suggest the existence of pulmonary hypertension in COPD patients. CPET gas exchange parameters showed a large overlap between COPD patient with and without associated pulmonary hypertension. We therefore conclude that to detect pulmonary hypertension in COPD, gas exchange measurements during CPET have no additive value over exercise pulse oximetry.

Like COPD patients, patients with chronic mountain sickness (CMS) may suffer from pulmonary hypertension. Pulmonary hypertension in CMS is caused by a reduced hypoxic ventilatory drive compensated by excessive erythrocytosis. The objective of the study presented in **chapter 8** was to improve the understanding of the exercise physiology of CMS patients. 13 CMS patients, 15 healthy highlanders and 15 newcomer lowlander controls were investigated at an altitude of 4350m in Peru. All included subjects performed single breath diffusion measurements corrected for haemoglobin concentration at rest. Echocardiography was used to estimate mean pulmonary arterial pressure and cardiac output values at rest and during exercise. CPET measurements were performed to measure gas exchange variables and arterial oxygen saturation. All three study groups reached a similar VO_{2max} . Both highlander groups showed an increased diffusion capacity. Due to the excessive erythrocytosis and despite a decreased arterial oxygen saturation, CMS patients had a significantly elevated arterial oxygen content (at rest and during exercise) compared to both other study groups. As hypothesized, the CMS patients showed the highest mean pulmonary arterial pressures at peak exercise and a reduced ventilatory drive, reflected by a decreased ventilatory equivalent for carbon dioxide at the anaerobic threshold. From these results we concluded that the aerobic capacity of CMS patients is preserved in spite of

severe pulmonary hypertension and relative hypoventilation, probably by a combination of an increased oxygen carrying capacity of the blood and an increased lung diffusion capacity.

FUTURE RESEARCH PERSPECTIVES

This thesis shows that patients with pulmonary hypertension have a decreased maximal exercise tolerance measured by 6MWD and CPET. The characteristic CPET profile of a decreased maximal aerobic capacity and reduced ventilatory efficiency has an important clinical value. Non-invasive estimates of cardiac output including the intra-breath acetylene absorption technique could have additional value, although the accuracy of these techniques remains questionable. As long as accurate non-invasive measurements of cardiac output and stroke volume during exercise remain unavailable, maximal aerobic capacity, oxygen pulse and estimates of ventilatory efficiency remain good alternatives. An important research question to answer in the near future is whether exercise stroke volume responses show additional clinical significance to the standard CPET measurement of oxygen pulse.

As was done in other papers, this thesis highlights a decreased ventilatory efficiency as an important clinical hallmark in PAH. Although this decreased ventilatory efficiency could be explained by increases in dead space ventilation and ventilatory drive, future research should be designed to address the question which mechanism is primarily responsible for an increased ventilatory drive. Moreover, it also remains to be determined whether the increased ventilatory requirement contributes to patients' symptoms and exercise intolerance.

In addition to estimations by 6MWD and CPET, functional status can be assessed by determining exercise endurance on a cycle ergometer. In the exercise training study, endurance had the highest sensitivity to detect changes in functional status over time. By using exercise endurance testing with additional gas exchange measurements, new surrogate end-points could be developed, to be used in clinical trials.

Our retrospective study showed that changes in functional capacity have additional prognostic value over baseline measurements. A prospective study in a bigger cohort would provide the necessary data to validate this concept.

Although exercise training improves functional status in PAH patients, it is currently unknown whether the improvements sustain after cessation of the rehabilitation program. Future research should address this question and should also be directed at further developing integrated training programs and optimizing schedules for training and maintaining physical fitness.

Although we showed that COPD patients with associated PH have a different ventilatory response than COPD patients without PH, the measurement of gas exchange did not provide additional diagnostic information to oxygen saturation measurements in the detection of PH. A simple six minute walk test combined with pulse oximetry measurements could be developed as a tool to detect PH in COPD patients. However, future studies also need to address the question whether COPD patients would benefit from PH detection, as treatment options for these patients are still very limited.

In the final study of this thesis we showed that CMS patients have a CPET profile characterized

by decreases in oxygen saturation and ventilatory drive. It is unknown whether CPET variables predict survival in CMS. An epidemiological study to determine the prognostic value of CPET in CMS could be of great importance. However, the prognostic value of a simple six minute walk test with additional measurements of HR and pulse oximetry could be of much greater relevance, because CPET is too demanding and expensive for most mountainous regions of the world.

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