Summary, conclusions and implications
SUMMARY

One of the major complaints of patients with advanced chronic obstructive pulmonary
disease (COPD) is an impaired exercise capacity and a limitation in daily activities. Elu-
cidating the factors contributing to the exercise impairment is required to develop strat-
egies to improve exercise capacity. Cardiac function during exercise is a potential target
by which exercise capacity could be improved. Cardiac output in COPD can be affected in
several ways. One well known complication of COPD is Pulmonary hypertension (PH).
The effect of PH on exercise capacity, and through the frequently found excessive rise of
pulmonary artery pressure during exercise, is largely unknown. If PH or the “exercise in-
duced-PH”, of which currently no definition exists, indeed contributes to exercise impair-
ment, patients may benefit from pulmonary vasodilating therapy. There are, however, also
other mechanisms by which cardiac output can be impaired in COPD. Understanding these
mechanisms is important to develop strategies to improve cardiac output and, perhaps,
exercise tolerance. The effect of lung hyperinflation and the associated increased pleural
pressure swings, both induced by airflow limitation, on cardiac function received interest
recently. The altered pulmonary mechanics are thought to adversely effect cardiac output
by, among others, impairing venous return. The objective of this thesis was twofold. First,
which patients exercise is terminated due to a lowered cardiac output, as in these patients
improving cardiac function could increase exercise capacity.

In Chapter 2 we showed that the high intrathoracic pressure which develops in patients
with COPD hampers stroke volume during expiration. Although it was known that posi-
tive pressure mechanical ventilation can impair venous return and consequently cardi-
ac output, this phenomenon this effect had not been shown in spontaneously breathing
COPD-patients. We assessed the effects of intrathoracic pressure on pulmonary artery and
right atrial pressure in twenty-one patients with stable COPD, at rest and during exercise.
Beat-to-beat analysis of pulmonary artery pulse pressure during expiration showed that
the high intrathoracic pressure hampers stroke volume by impairing venous return. The
depressive effect of intrathoracic pressure on stroke volume persisted during exercise.
Patients with a low right atrial filling pressure showed the largest negative effects of an
increased expiratory intrathoracic pressure on stroke volume.

The sometimes impressive effect of severe airflow limitation on the pulmonary circula-
tion was further illustrated in the appendix of Chapter 2, where we described the pres-
sure changes in the pulmonary artery, right ventricle, right atrium, oesophagus and radial
artery during spirometry in a patient with severe COPD. The maximal expiration acted
as a Valsalva maneuver which impaired venous return, thereby severely reducing right
ventricular stroke volume and subsequently left ventricular stroke volume and systemic
blood pressure until the next inspiration.

Because we found evidence of significant negative effects of a high intrathoracic pressure
during expiration on cardiac function, we wanted to evaluate whether we could improve
cardiac function by reducing expiratory intrathoracic pressure. In the study described in
chapter 3 we measured stroke volume in patients at rest and during exercise, both while
breathing room air and while breathing a helium-oxygen mixture (Heliox). This mixture is
known to improve airflow and reduce expiratory intrathoracic pressure in COPD-patients.
We confirmed that a reduction in intrathoracic pressure with heliox improves stroke volume at rest. This provided additional evidence that cardiac function is indeed adversely affected by airflow limitation. Interestingly, the improvement did not last during exercise, which suggests that a relatively small change in intrathoracic pressure is not sufficient to affect exercise cardiac output in COPD.

In Chapter 4 we showed that the marked increases in expiratory intrathoracic pressure can lead to significant errors in measurements of mean pulmonary artery pressures (mPAP) during exercise, when pressures are measured at end-expiration. Incorrect estimation of mPAP led to a wrong diagnosis in a substantial part of the patients. Averaging pulmonary pressure over the full respiratory cycle and a correction for intrathoracic pressure (estimated using a right atrial pressure waveform) resulted in a better but still imperfect estimation of intravascular pressure. The effect of intrathoracic pressure was similar on mPAP and pulmonary capillary wedge pressure (PCWP). Therefore, the transpulmonary pressure gradient and pulmonary vascular resistance are not affected by intrathoracic pressures as long as mPAP and PCWP are measured at the exact same time point in the respiratory cycle. Including pulmonary vascular resistance in the definition of exercise induced pulmonary hypertension therefore avoids misdiagnosis if intrathoracic pressure or PCWP is taken into account.

In chapter 5, an integrated approach consisting of cardiopulmonary exercise testing and right heart catheterisation at rest and during exercise was used to identify a subgroup of COPD patients in whom the presence of PH impaired exercise tolerance. We describe the ventilatory and cardio-circulatory exercise profiles of forty-seven COPD patients divided in three subgroups, no PH, moderate PH and severe PH. We were able to demonstrate that only patients with severe PH showed at the end of exercise evidence of exhaustion of the cardiac reserve in combination with a continuing ventilatory reserve. In patients with no or only moderate PH, exercise termination was associated with an exhausted ventilatory reserve and evidence of a cardio-circulatory reserve. This implies that only in patients with severe PH, defined as a resting mean pulmonary artery pressure above 40 mmHg, exercise capacity might improve with therapeutic interventions aiming to reduce pulmonary artery pressure.

The complexity of the interactions between cardiac function and pulmonary function in COPD is further exemplified in chapter 6. We describe the cases of two patients suffering from severe COPD in combination with a patent foramen ovale. In both cases, hypoxemia due to right-to-left shunting aggravated the degree of PH, whereas the presence of PH by itself worsened right-to-left shunting and hypoxemia. The vicious circle of PH and hypoxemia was felt to significantly worsen the degree of dyspnea in both patients, and was therefore interrupted in two different ways. In the first patient, the foramen ovale was closed during a percutaneous intervention. In the second patient, the pulmonary artery pressure was pharmacologically reduced, which resulted in a physiological closing of the patent foramen ovale. A dramatic improvement of symptoms was noted in both patients.

In chapter 7 we evaluated in fifty-one patients with pulmonary arterial hypertension without evidence of parenchymal lung disease how pulmonary hypertension affects the size of the pulmonary arteries. We found that the ratio of the diameters of the pulmonary artery trunk and ascending aorta is useful for the detection of PH, with a positive predictive value of 92% when the ratio is greater than 1. The pulmonary artery exhibited progressive
CONCLUSIONS AND IMPLICATIONS

**Pulmonary hypertension and pulmonary vasodilating therapy in COPD**

The identification of those patients whose exercise capacity is limited by pulmonary hypertension (chapter 5) is an important step forward in identifying COPD patients who may benefit from pulmonary vasodilating therapy. Previous trials using pulmonary vasodilators in COPD included patients with less severe pulmonary hypertension and showed no beneficial effects of therapy on exercise capacity [1, 2, 3]. Our study shows that only patients with out-of-proportion pulmonary hypertension may be candidates for trials of using PAH specific drugs. Such a study in these patients is therefore justified. Whether pulmonary hypertension during exercise matters is debatable. Recently, emphasis is put on the slope of mPAP increase related to cardiac output increase with exercise. [4, 5] Future studies should evaluate whether an increased slope of mPAP contributes to exercise intolerance and whether it can lead to identification of more patients who potentially benefit from vasodilating therapy. Therefore, measurement of the mPAP/cardiac output slope combined with measures of ventilatory and circulatory reserves at the end of exercise are needed. This is especially interesting in patients with borderline elevated pulmonary artery pressure at rest and less severe airflow limitation. In these patients the ventilatory problems may be less overwhelming, thereby creating a potential role for the pulmonary circulation in limiting exercise.

**Diuretic use in COPD**

In the past, the low stroke volume in COPD was mainly attributed to an increased right ventricular afterload. The normal response to maintain right ventricular output when the afterload is increased, is to increase preload. In chapter 2, 2a and 3 we found signs of an impaired right ventricular preload in COPD-patients without overt pulmonary hypertension. This is the consequence of the high intrathoracic pressures (chapter 3) and hyper-inflation [6]. A higher venous or right atrial pressure is necessary to maintain sufficient venous return. The use of diuretics, frequent in COPD, may interfere with this compensatory mechanism [7]. Tailored use of diuretics might therefore be necessary for an optimal cardiac function in COPD-patients, and a study is required and advised.

**Hemodynamic measurements during exercise in COPD**

We showed in chapter 3 that increased intrathoracic pressure during exercise results in a marked overestimation of intravascular pressure when pulmonary artery pressure is measured at end-expiration. We therefore recommend to average pulmonary artery pressure over the respiratory cycle, when invasive hemodynamic measurements are performed during exercise. It is therefore advised that pulmonary vascular resistance should be added to the definition of exercise induced pulmonary arterial hypertension, as its determination is not affected by intrathoracic pressure.
Patent foramen ovale in COPD
In chapter 6 we showed that the combination of COPD and a patent foramen ovale (PFO) can lead to severe complaints in some patients. It is therefore tempting to state that, when present, closure of a PFO should be considered in COPD. It is however debated whether a PFO affects dyspnea and exercise tolerance in the general COPD population [8,9] and a PFO might even be beneficial in more severe pulmonary hypertension [10]. We therefore need more information about the prevalence and relevance of PFO's in COPD, before we start studying the effects and risks of PFO closure.

Pulmonary artery dilatation
Pulmonary artery dilatation was shown as an inevitable consequence of long-standing pulmonary hypertension, and was even persisting when treatment effectively reduced pulmonary artery pressure (chapter 7). Some rare but severe consequences of pulmonary artery dilatation might complicate pulmonary hypertension. Rupture [11] and dissection [12] of the pulmonary artery and also compression of the coronary arteries [13] or bronchi [14] are all described in pulmonary hypertension and may explain why pulmonary artery dilatation is related to sudden death in pulmonary hypertension [15]. As some are treatable, Higher awareness of the complications of pulmonary artery dilatation is indicated and may contribute to a better survival in pulmonary hypertension.
REFERENCES


