Summary
Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by persistent airflow limitation and impaired exercise capacity. Chronic bronchitis and pulmonary emphysema are the two main conditions included in COPD. Patients with COPD demonstrate a generally impaired health status and have increased rates of morbidity and mortality. Dyspnea is the cardinal symptom in COPD, which results in impaired exercise capacity and has a negative impact on daily life activities and quality of life. The perception of dyspnea is exaggerated in those patients during physical activity or exercise due to reduced breathing efficiency that results from the deteriorating ventilatory mechanics and the increased ventilatory requirement. Moreover, pathophysiological effects of cardiovascular and peripheral muscle abnormalities can further explain and intensify dyspnea as well as increased muscle fatigue in COPD. As a consequence, exercise capacity in those patients is symptom-limited and determined by a complex interaction of several pathophysiological factors in COPD. Therefore, exercise capacity can reflect the impact of disease severity on patients with COPD and can provide clinicians and health professionals with important clinical information.

Clinical exercise testing has become an important clinical tool to assess and evaluate exercise capacity and predict outcomes in patients with COPD. Therefore, this thesis focused on field exercise testing and specifically on the six-minute walk test (6MWT) aiming at extending the clinical information derived from the 6MWT and at increasing test utilization in clinical practice. After describing the overall burden of COPD disease and its negative impact on exercise capacity in patients, Chapter 1 introduced the field tests and demonstrated the clinical and prognostic value of the 6MWT as reliable clinical instrument according to the recent evidences in literature. Indeed, 6MWT has been shown to provide useful information for the impact of disease severity in patients’ functional status, the effectiveness of therapeutic interventions and can predict mortality and hospitalization. The main outcome of the 6MWT is the six-minute walk distance (6MWD) which represents exercise capacity and can change after therapeutic intervention or across the progress of disease severity influencing the clinical decision-making process.

Several determinants of exercise performance can affect 6MWD. Chapter 2 aimed at investigating the characteristics of functional exercise performance and determinants of the cycle endurance test (CET) and 6MWT in a large clinical cohort of COPD patients. A retrospective analysis in a large dataset of 2050 patients demonstrated different determinants of exercise performance between CET and 6MWT. The main findings were that the overall perception of dyspnea and sex-related differences determine the CET-T\textsubscript{end} but BMI, FEV\textsubscript{1} and FRC influence the 6MWD. Chapter 2 suggested that CET and 6MWT are not interchangeable exercise tests; gender difference should temper the interpretation of CET and that even though the fixed proportion of workload capacity does not provide the same physiological stress among patients, improvement in CET-
T_{end} after a therapeutic intervention such as a pulmonary rehabilitation (PR) program are responsive of improvements in clinical status of patients with COPD.

Several reference equations for the 6MWT have been formulated to facilitate the interpretation of the walked 6MWD and help to estimate the degree of exercise tolerance in patients. However, applying different reference equations could result in different 6MWD values of predicted leading to misinterpretation of the levels of exercise capacity or improvements of physical performance after therapeutic interventions. Therefore, Chapter 3 investigated the impact of several 6MWD reference equations and factors accountable for different 6MWD %predicted values in a large dataset of 2757 patients with COPD. Chapter 3 reported that existing 6MWD reference equations will give varying results and highlighted the importance of the selection of an appropriate reference equation. It suggested that the choice of 6MWD reference equation should consider the consistency 6MWT operating procedures and at least be specific for the country/region of origin.

Besides the interpretation of 6MWD, the estimation of prognosis according to walking performance is clinically important. In addition to the 6MWD, other 6MWT derived variables, such as mean walk-speed (6MWSpeed), 6-min walk-work (6MWW), distance-saturation product (DSP), exercise-induced oxygen desaturation (EID), and unintended stops seems to be useful for the prediction of mortality and hospitalization in COPD. Chapter 4, explored the association between 6MWT-derived variables and mortality as well as hospitalization and compared it with the BODE index using the ECLIPSE cohorts in a three-year follow-up. Cox’s proportional-hazard regressions were performed to estimate 3-year mortality and hospitalization and demonstrated that the 6MWT-derived variables have an additional predictive value of mortality in patients with COPD. Chapter 4, indicated the DSP as the strongest predictor of mortality and the BODE index as the most sensitive tool for assessing the risk of hospitalization while suggested that unintended stop(s) during the 6MWT can refine the prognosis of mortality in COPD.

Impaired gas exchange can produce varying degrees of V'/Q' inequalities, diffusion impairment, and hypoxemia during exercise. Chapter 5, aimed at investigating the prevalence of exercise-induced desaturation (EID), the relative-weight of several physiological determinants of EID including pulmonary emphysema, and the relationship of EID with certain patients' clinical characteristics using a dataset of 2050 COPD patients from the ECLIPSE cohort. Chapter 5 demonstrated that 21% of patients exhibited EID in the ECLIPSE cohort and showed that advanced emphysema, obesity, severe airflow limitation, and low resting oxygen saturation are associated with EID. Chapter 5 also suggested that emphysematous patients with high ADO-score should be monitored for EID.

In clinical practice, several screening tests have been proposed to predict EID, including FEV_{1}, DLCO and baseline-SpO_{2}. Chapter 6 aimed to validate a proposed cut-off
of baseline-SpO$_2$ ≤95% as simple screening procedure to predict EID during 6MWT and investigated the prevalence and characteristics of patients exhibited EID to SpO$_2$ nadir ≤88% using 402 non-hypoxemic COPD patients referred for pulmonary rehabilitation (PR). Chapter 6 reported that 39% of those patients, who were referred for PR, exhibited EID and that those patients may be suitable candidates for ambulatory oxygen therapy. Chapter 6 did not corroborate baseline SpO$_2$ ≤88% as highly accurate in predicting EID, and thus concluded that baseline SpO$_2$ solely is not adequate to predict EID. In contrast, a combination of several clinical characteristics including DLCO, FEV$_1$, PaO$_2$, baseline-SpO$_2$, and sex, increases substantially the odds for EID and can facilitate the prediction of EID in COPD.

Besides the EID, the variable of carbon-dioxide partial pressure (PCO$_2$) has been also reported as prognostic factor in COPD. Chapter 7, aimed to define patterns of transcutaneous carbon-dioxide partial-pressure (T$_{c}$PCO$_2$) trends during 6MWT and to study determinants of CO$_2$-retention and exercise-induced hypercapnia (EIH) using a group of 62 patients with very severe COPD. Chapter 7 demonstrated that 50% of the patients with COPD exhibited CO$_2$-retention, 26% preserved and 24% reduced T$_{c}$PCO$_2$ levels while in all group 31% patients presented EIH during the 6MWT. Chapter 7 also showed that even though PCO$_2$ response to 6MWT is highly heterogeneous, a very low FEV$_1$ and increased baseline-P$_c$CO$_2$ together with pre-walk dyspnea increase the risk for CO$_2$-retention and EIH. Moreover, chapter 7 revealed that an overweight BMI seems to carry a protective effect against EIH in very severe COPD.