TIME SERIES ANALYSES OF PHYSIOLOGICAL VARIABLES IN PATIENTS WITH COPD

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Preface

It all seems ages ago: the first time I got an e-mail from Jean-Marie about a PhD opportunity, the first trips to VITO, delving into literature about COPD, trying to pronounce 'exacerbation', … A lot has changed over these 4.5 years. When I started, I was pretty clueless about more or less everything. Now I dare to say that I do have some clues about at least some things. Working on a PhD is always a bumpy ride, but it turned out to be the perfect opportunity for me to develop myself, both professionally and personally.

My quest towards getting a PhD had 2 very distinct phases. Boldly put, there were 2 years of suffering and 2 years of joy! I am very happy that the suffering came first, so I could enjoy the second part even more. I started enjoying it so much that, against all odds, I decided to stay in research for at least a little longer.

Many people played an important role during my quest. For starters, my 'raad der wijzen': Jean-Marie, Jan, Patrick and Martijn. Initially, it was a bit of a challenge to have 4 supervisors. Later on, I realised it was a privilege to have 4 mentors that were so closely engaged with my project! All 4 brought different, compatible things to the table. I would not have gotten to this point in my career and personal life if it weren't for them.

Besides having 4 supervisors, I also had 3 work environments: KU Leuven, VITO (who I would like to thank for funding my quest) and CIRO. This resulted in quite some hours on the road, but it also gave me some well-appreciated variation. I will certainly remember the quizzes and nice evenings with the 'Schaambrokjes' from VITO, and the great team buildings with M3-BIORES. I went less often to CIRO, but I always felt very welcome.

A big thanks to my friends as well, who helped me to forget about my PhD once in a while. I especially would like to thank Freek, Dre, Max and Wokke. You guys had to endure quite some complaining during the first 2 years of my PhD, but you always listened to my concerns. Without your support, I don't think I would have completed my quest successfully!

Estoy muy agradecido a mi familia politica, por haber sido tan fantásticos desde la primera vez que los vi! Natuurlijk speelde ook mijn eigen familie een heel belangrijke rol. Niet alleen tijdens mijn doctoraat, maar minstens even zeer in de jaren ervoor. Ik heb altijd alle kansen gekregen om te doen en laten wat ik wou. Daarnaast hebben ze mij de juiste waarden en kwaliteiten meegegeven die nodig waren om mijn queeste tot een goed einde te brengen. Ik zal ze daar altijd dankbaar voor zijn!

Not least but last, my guardian angel Raquel. She was the one who had to endure my different moods and stress levels the most. She is also the one that is teaching me more and more to not lose myself into my work. Without her, I would definitely not have gotten to where I am today!

Joren
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Summary

Chronic obstructive pulmonary disease (COPD) is a complex, highly prevalent, non-communicable respiratory disease that is manifested through a variety of respiratory and non-respiratory pathologies. Accordingly, different types of interventions are available for individualised treatment and management of the disease (e.g. smoking cessation, medication, pulmonary rehabilitation (PR) and telemonitoring). These interventions are furthermore based on a variety of clinical assessments (e.g. pulmonary function testing, symptom questionnaires and physical performance testing). Despite this wide variety of currently available interventions and clinical assessments, we hypothesised that time series analyses of continuously measured physiological variables can still enhance interventions and clinical assessments of patients with COPD. More specifically, this dissertation focussed on enhancements of telemonitoring applications and physical performance testing.

The first objective of this dissertation was to evaluate whether the accuracy of telemonitoring applications and desaturator classifications of patients with COPD could be affected by natural peripheral oxygen saturation (SpO_2) fluctuations. Therefore, a systematic review summarised the scientific literature on the use of SpO_2 measurements in telemonitoring applications of patients with COPD. In addition, 20 stable patients with COPD performed continuous SpO_2 measurements over one week during daily home routines in order to assess natural SpO_2 fluctuations within and between multiple days and nights (telemonitoring study).

The results of the systematic review indicated that alerts for exacerbations were mainly raised when SpO_2 spot check values were below fixed thresholds. This approach, however, is unable to account for the multiple sources of SpO_2 variability that were identified in the telemonitoring study: i) large differences between mean daytime SpO_2 values in rest of different patients (between 84.7% and 96.0%), ii) large SpO_2 fluctuations over the course of a single day for individual patients (SpO_2 values during rest ranged on average over 10.8±4.4% within one day), and iii) large day-to-day SpO_2 differences of individual patients (mean SpO_2 in rest ranged on average over 1.9±1.5% over the course of one week).

Consequently, telemonitoring applications should apply individualised approaches, which should furthermore be able to capture the identified intraday and day-to-day SpO_2 fluctuations. In a similar way, large night-to-night differences of SpO_2 were observed for the included patients (e.g. the cumulative time spent with SpO_2 below 90% ranged on average over 28±25% over the course of one week). As a result, 50% of the patients changed category between desaturator and non-desaturator over the course of one week.

These results confirm that natural SpO_2 fluctuations can indeed affect telemonitoring applications and desaturator classifications in patients with COPD. Continuously measuring SpO_2 over prolonged time periods, combined with suitable analyses of the resulting time series, can therefore enhance current telemonitoring applications and desaturator classifications for patients with COPD. Similar results and recommendations can be expected for other chronic disease states that can also suffer from impairments of oxygen homeostasis.

The second objective of this dissertation was to examine whether physiological exercise responses during a constant work rate test (CWRT) can be analysed more reliably by using an alternative data analysis technique that is able to account for the natural fluctuations that are inherent to physiological exercise responses. Therefore, kinetic analyses of oxygen uptake ($\dot{V}O_2$) responses during a CWRT of patients with COPD (n=18) were compared between three conventional exponential models and Box-Jenkins transfer function (BJ-TF) models. Kinetic analyses characterise the fundamental component of a physiological exercise response, based on features such as mean response time (MRT; assessing the response rate) and response gain (quantifying the physiological increase per unit increase in external work rate). Autocorrelation tests and normalised root-mean-squared error values (BJ-TF: 2.8±1.3%; exponential methods A, B and C: 10.5±5.8%, 11.3±5.2% and 12.1±7.0%; $p<0.05$) confirmed that BJ-TF models were indeed able to account for the most important physiological fluctuations, in contrast to the conventional exponential models. As a result, BJ-TF models provided more reliable kinetic feature values compared to exponential methods A and B (e.g. MRT: BJ-TF, 74±20 s; method A, 100±56 s; and method B, 88±52 s; $p<0.05$). Only the kinetic feature values of exponential method C were comparable to

feature values from BJ-TF models (e.g. MRT method C: 75±20 s). Nevertheless, on an individual level, kinetic feature values still differed between BJ-TF models and exponential method C (e.g. an average difference of 7±8 s for MRT). Therefore, it can be argued that, based on theoretical considerations, BJ-TF models generate more reliable kinetic feature values than the conventional exponential models.

The third objective of this dissertation was to enrich clinical assessments of physical performance by characterising physiological exercise responses during CWRT of patients with COPD. Therefore, kinetic analyses were performed on a large sample of patients with COPD (n=256). It was shown that kinetic analyses are unlikely to be reliable for patients that are severely physically impaired (i.e. patients exhibiting a peak work rate < 45 W). For patients that could be included for kinetic analyses (n=209), gains of $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) were mainly associated with cardiac function and ventilatory constraints, representing both response efficiency and limitation. $\dot{V}O_2$ MRT showed potential to serve as a motivation-independent, physiological indicator of physical performance, as it was associated with both ventilatory (e.g. FEV_1%predicted: $p<0.001$; $r=-0.35$) and physical (e.g. $VO_{2,peak}$%predicted: $p=0.009$; $r=-0.18$) impairments.

Most of these patients furthermore completed a PR program, of which 183 patients could be used to examine whether changes in physiological exercise responses following PR differed between responders (i.e. patients improving CWRT endurance time following PR with more than 105 s; n=117) and non-responders to PR (n=66). Only the group of responders, in contrast to non-responders, decreased $\dot{V}O_2$ mean response time (75±21 to 70±17 s; $p<0.05$), $\dot{V}CO_2$ gain, $\dot{V}_E$ gain and isotime values of $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ following PR (all $p<0.001$), while also improving their breathing pattern (e.g. breathing frequency isotime value: 28.8±6.2 to 25.0±5.4 breaths·min^{-1}; $p<0.0001$). These changes were furthermore correlated with changes in physical performance (e.g. correlation between changes in $\dot{V}O_2$ mean response time and endurance time: $p<0.001$, $r=-0.32$). These results indicate that PR-induced changes in physiological exercise responses differed between responders and non-responders to PR, and that physiological improvements are important in explaining the variable improvements of physical performance following PR in patients with COPD.

Overall, the performed analyses demonstrate that the continuously measured physiological variables during a CWRT did not reveal all their secrets yet. Consequently, clinical assessments of physical performance can still be enhanced by characterising physiological exercise responses during CWRT of patients with COPD. Similar enhancements can be expected for other chronic disease states or in sport applications.

In conclusion, the results of this dissertation demonstrate that (i) telemonitoring applications and desaturator classifications can be affected by natural SpO_2 fluctuations. Therefore, continuous SpO_2 measurements over prolonged time periods, combined with suitable analyses of the resulting time series, can enhance desaturator classifications and telemonitoring applications for patients with COPD; (ii) BJ-TF models generate more reliable kinetic feature values than conventional exponential models; and (iii) characterising physiological exercise responses during CWRT can enrich clinical assessments of physical performance in patients with COPD.

Altogether, these results show that, indeed, clinical assessments and interventions of patients with COPD can still be enhanced by including time series analyses of physiological variables. Many of the results can furthermore be translated to other chronic diseases states or healthy populations.

Samenvatting

Chronisch obstructief longlijden (COPD) is een complexe, veelvoorkomende, niet-overdraagbare longaandoening ten gevolge van verschillende respiratoire en niet-respiratoire pathologieën. Verschillende interventies zijn momenteel voorhanden die zorgen voor een geïndividualiseerde behandeling van de ziekte (bv. stoppen met roken, medicatie, pulmonale rehabilitatie (PR) en telemonitoring). Deze interventies zijn bovendien gebaseerd op allerhande klinische testen (bv. longfunctietesten, symptoomvragenlijsten en fysieke inspanningstesten). De algemene hypothese van dit proefschrift was dat, ondanks de verscheidenheid aan beschikbare interventies en klinische testen, deze interventies en testen nog steeds verbeterd kunnen worden door gebruik te maken van tijdreeksanalyses van continu gemeten fysiologische variabelen. Meer specifiek richtte dit proefschrift zich op verbeteringen voor telemonitoring applicaties en fysieke inspanningstesten.

Het eerste objectief van dit proefschrift was om te evalueren of de accuraatheid van telemonitoring applicaties en desaturator classificaties van COPD patiënten beïnvloed kunnen worden door natuurlijke fluctuaties van de perifere zuurstofsaturatie (SpO_2). Daarom werd de wetenschappelijke literatuur over het gebruik van SpO_2-metingen in telemonitoring applicaties van COPD patiënten samengevat in een systematische review. Daarnaast werd er ook een telemonitoring studie uitgevoerd waarbij 20 stabiele COPD patiënten gedurende een week continue SpO_2-metingen uitvoerden tijdens hun dagelijkse routines met als doel om de natuurlijke SpO_2 fluctuaties doorheen de dag en tussen meerdere dagen en nachten in kaart te brengen.

De resultaten van de systematische review gaven aan dat alarmsignalen, die waarschuwden voor exacerbaties, werden ingesteld om af te gaan wanneer spotmetingen van SpO_2 onder vaste drempelwaardes vielen. Deze aanpak kan echter niet overweg met de verschillende bronnen van SpO_2 variabiliteit die geïdentificeerd werden in de telemonitoring studie: i) grote verschillen tussen de gemiddelde SpO_2 dagwaardes in rust van verschillende patiënten (tussen 84.7% en 96.0%), ii) grote SpO_2 fluctuaties in de loop van één enkele dag voor individuele patiënten (SpO_2 waardes in

rust varieerden gemiddeld over 10.8±4.4% binnen één dag), en iii) grote dag-tot-dag SpO_2 verschillen voor individuele patiënten (gemiddelde SpO_2 in rust varieerde over 1.9±1.5% in de loop van één week). Bijgevolg is het belangrijk dat telemonitoring applicaties een geïndividualiseerde aanpak hebben, die bovendien ook rekening kan houden met de waargenomen SpO_2 fluctuaties binnen één dag en tussen verschillende dagen. Op vergelijkbare wijze werden grote nacht-tot-nacht SpO_2 verschillen waargenomen voor de bestudeerde patiënten (bv. de cumulatieve tijd doorgebracht met een SpO_2 waarde lager dan 90% varieerde gemiddeld over 28±25% in de loop van één week). Het resultaat hiervan is dat 50% van de patiënten in de loop van één week van categorie veranderden tussen desaturator en niet-desaturator.

Deze resultaten bevestigen dat natuurlijke SpO_2 fluctuaties inderdaad invloed kunnen hebben op telemonitoring applicaties en desaturator classificaties bij COPD patiënten. Continue SpO_2 metingen over langere tijdsperiodes, gecombineerd met geschikte analyses van de resulterende tijdreeksen, kunnen daarom de huidige telemonitoring applicaties en desaturator classificaties voor COPD patiënten nog verbeteren. Gelijkaardige resultaten en aanbevelingen zijn te verwachten voor andere chronische ziektes die ook kunnen lijden aan een verstoorde zuurstofhomeostase.

Het tweede objectief van dit proefschrift was om na te gaan of de fysiologische responsen tijdens een fysieke inspanningstest met een constante belasting (CWRT) meer betrouwbaar geanalyseerd kunnen worden op basis van alternatieve data analyse technieken die rekening kunnen houden met de natuurlijke fluctuaties van deze fysiologische responsen. Daarom werden kinetische analyses van de zuurstofopname ($\dot{V}O_2$) tijdens een CWRT van COPD patiënten (n=18) vergeleken tussen drie conventionele exponentiële modellen en Box-Jenkins transfer functie (BJ-TF) modellen. Kinetische analyses karakteriseren de fundamentele component van een fysiologische respons door gebruik te maken van features zoals de gemiddelde responstijd (MRT; geeft de snelheid van de respons weer) en respons gain (geeft de toename van fysiologische respons weer per eenheid toename in externe belasting). Autocorrelatie testen en normalised root-mean-squared error waardes (BJ-TF: 2.8±1.3%; exponentiële methodes A, B and C: 10.5±5.8%, 11.3±5.2% en 12.1±7.0%;

p<0.05) bevestigden dat BJ-TF modellen inderdaad in staat waren om rekening te houden met de belangrijkste fysiologische fluctuaties, in tegenstelling tot de conventionele exponentiële modellen. Bijgevolg zorgden de BJ-TF modellen voor betrouwbaardere kinetische feature waardes in vergelijking met exponentiële methodes A en B (bv. MRT: BJ-TF, 74±20 s; methode A, 100±56 s; en methode B, 88±52 s; p<0.05). Enkel de kinetische feature waardes van exponentiële methode C waren vergelijkbaar met de feature waardes van BJ-TF modellen (bv. MRT methode C: 75±20 s). Desalniettemin verschilden de kinetische features waardes op individueel niveau nog steeds tussen BJ-TF-modellen en exponentiële methode C (bv. een gemiddeld verschil van 7±8 s voor MRT). Daarom kan op basis van theoretische overwegingen gesteld worden dat kinetische feature waardes meer betrouwbaar berekend kunnen worden met BJ-TF-modellen dan met de conventionele exponentiële modellen.

Het derde objectief van dit proefschrift was om fysieke inspanningstesten van COPD patiënten te verrijken door hun fysiologische responsen tijdens een CWRT te karakteriseren. Daarom werden kinetische analyses uitgevoerd bij een groot aantal COPD patiënten (n = 256). Er werd aangetoond dat kinetische analyses waarschijnlijk onbetrouwbaar zullen zijn voor patiënten met ernstige fysieke beperkingen (d.w.z. bij patiënten met een piekvermogen < 45 W). Kinetische analyses van patiënten die geïncludeerd konden worden voor deze analyses (n=209) gaven weer dat gains van $\dot{V}O_2$, koolstofdioxideproductie ($\dot{V}CO_2$) en minuutventilatie ($\dot{V}_E$) voornamelijk geassocieerd waren met hartfunctie en ventilatoire beperkingen. Hieruit blijkt dat respons gain zowel de efficiëntie alsook de restricties van fysiologische responsen kunnen weergeven. $\dot{V}O_2$ MRT toonde potentieel om gebruikt te kunnen worden als een motivatie-onafhankelijk, fysiologische indicator van fysieke capaciteit, aangezien het geassocieerd was met zowel ventilatoire (bv. FEV_1%voorspeld: p<0,001; r = -0,35) alsook fysieke (bv. $VO_{2,piek}$%voorspeld: p=0.009; r=-0.18) beperkingen.

De meerderheid van de patiënten voltooiden bovendien een PR programma. De data van 183 patiënten kon gebruikt worden om te onderzoeken of veranderingen van fysiologische responsen na PR verschilden tussen responders (d.w.z. patiënten die hun de CWRT-uithoudingsduur met meer dan 105 s verbeterden na PR; n=117) en non-

responders (n=66). Enkel de groep van responders, in tegenstelling tot de groep non-responders, hadden een snellere $\dot{V}O_2$ respons ($\dot{V}O_2$ MRT daalde van 75±21 tot 70±17 s; $p<0.05$), een lagere $\dot{V}CO_2$, $\dot{V}_E$ en $\dot{V}_E/\dot{V}CO_2$ respons, en een verbeterd ademhalingspatroon (bv. ademhalingsfrequentie bij isotime daalde van 28.8±6.2 tot 25.0±5.4 ademhalingen.min^{-1}; $p<0.0001$) na PR. Deze veranderingen waren bovendien gecorreleerd met veranderingen in fysieke capaciteit (bv. correlatie tussen veranderingen in $\dot{V}O_2$ MRT en uithoudingsduur: $p<0.001$, $r = -0.32$). Deze resultaten tonen aan dat veranderingen van fysiologische responsen na PR verschillend zijn voor responders en non-responders. Fysiologische verbeteringen zijn dus belangrijk om de variabele verbeteringen van fysieke capaciteit na PR bij COPD patiënten te verklaren.

Over het geheel genomen tonen de uitgevoerde analyses aan dat de continu gemeten fysiologische variabelen tijdens een CWRT nog niet al hun geheimen hebben prijsgegeven. Bijgevolg kan er nog meer informatie gehaald worden uit fysieke inspanningstesten van COPD patiënten door de fysiologische responsen tijdens een CWRT te karakteriseren. Soortgelijke verbeteringen kunnen verwacht worden voor andere chronische ziektes of in sport applicaties.

Samenvattend tonen de resultaten van dit proefschrift aan dat (i) telemonitoring applicaties en desaturator classificaties beïnvloed kunnen worden door natuurlijke SpO_2 fluctuaties. Bijgevolg kunnen continue metingen van SpO_2 over langere tijdsperioden, gecombineerd met geschikte analyses van de resulterende tijdreeksen, desaturator classificaties en telemonitoring applicaties voor COPD patiënten verbeteren; (ii) BJ-TF-modellen genereren betrouwbaardere kinetische feature waardes dan conventionele exponentiële modellen; en (iii) het karakteriseren van fysiologische responsen tijdens een CWRT kan fysieke inspanningstesten van COPD patiënten verrijken.

In zijn geheel tonen deze resultaten aan dat, inderdaad, klinische testen en interventies van COPD patiënten nog verbeterd kunnen worden door gebruik te maken van tijdreeksanalyses van fysiologische variabelen. Veel van de resultaten kunnen bovendien ook vertaald worden naar andere chronische ziektes of gezonde populaties.

List of abbreviations

Amp	Response amplitude
AUC	Area under the curve
AR(1)	Autocorrelation value with lag 1
BJ-TF	Box-Jenkins transfer function
BP	Blood pressure
CAT	COPD assessment test
CHANCE	COPD, health status and comorbidities study
CITD	Complex, individual, time-varying and dynamic
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CT90	Cumulative time spent with SpO_2 below 90%
CWRT	Constant work rate test
EE	Energy expenditure
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
HR	Heart rate
ISO	International organisation of standardisation
LIPA	Low-intensity physical activity
LVEF	Left ventricular ejection fraction
MET	Metabolic equivalent of task
mMRC	Modified medical research council
MRT	Mean response time
MVPA	Moderate-to-vigorous physical activity
MVV	Maximal voluntary ventilation
NRMSE	Normalised root-mean-squared error
O_2	Oxygen
PEF	Peak expiratory volume
PPG	Photoplethysmography
PR	Pulmonary rehabilitation
$\dot{Q}CO_2$	Muscle carbon dioxide production
$\dot{Q}_l$	Leg blood flow
$\dot{Q}O_2$	Muscle oxygen consumption
$\dot{Q}_p$	Pulmonary blood flow

RR	Respiratory rate
RV	Residual volume
Seff	Sleep efficiency
SD	Standard deviation
SpO_2	Peripheral oxygen saturation
TC	Time constant
TD	Time delay
TLCO	Transfer factor for carbon monoxide
TM	Telemonitoring
TNST	Total night sleeping time
UC	Usual care
$\dot{V}CO_2$	Carbon dioxide production
$\dot{V}_E$	Minute ventilation
$\dot{V}O_2$	Oxygen uptake
WASO	Wake after sleep onset
WR	Work rate
YIC	Young identification criterion
6MWD	Six-minute walking distance

Table of contents

Chapter 1 – General introduction 1

1. Chronic obstructive pulmonary disease 2
2. Patho(physio)logy 3
3. Interventions for treating and managing COPD 6
   - 3.1. Smoking cessation, medication, long-term oxygen therapy, endobronchial valves and surgery 6
   - 3.2. Self-management, education, nutritional intervention, physical activity and exercise training 7
   - 3.3. Pulmonary rehabilitation 8
   - 3.4. Telemonitoring 9
4. Clinical assessment of patients with COPD 10
   - 4.1. Pulmonary function testing 10
   - 4.2. Symptom questionnaires 11
   - 4.3. Arterial blood gas analyses and pulse oximetry 11
   - 4.4. Physical performance testing 12
5. Problem statement, hypotheses, objectives and framework 13
   - 5.1. Telemonitoring – Problem statement and hypotheses 15
   - 5.2. Physical performance testing – Problem statement and hypotheses 16
   - 5.3. General and specific objectives 17
   - 5.4. Framework of this dissertation 18

Chapter 2 – Oxygen saturation measurements in telemonitoring of patients with COPD: a systematic review 21

1. Abstract 22
2. Introduction 22
3. Methods 24
   - 3.1. Search strategy 24
   - 3.2. Information extraction 24
4. Results 25

4.1. Article selection 25
4.2. Study description 25
4.3. Measurements, oximeters, and telemonitoring systems 27
4.4. Application of SpO_2 measurements 27
4.5. SpO_2 alerts leading to immediate action 28
4.6. Exacerbation prediction through retrospective analysis 28
4.7. Value of SpO_2 measurements 30
5. Discussion 38
6. Conclusions 41
7. Expert commentary 42
8. Five-year view 43
9. Key issues 44

Chapter 3 – Wearable finger pulse oximetry for continuous oxygen saturation measurements during daily home routines of patients with Chronic Obstructive Pulmonary Disease (COPD) over one week: Observational study 45

1. Abstract 46
2. Introduction 47
3. Methods 48
3.1. Study design and participants 48
3.2. Wearable sensors and protocol 50
3.3. Data pre-processing 51
3.4. Data analyses 53
3.5. Statistical analyses 54
4. Results 55
4.1. Participants 55
4.2. Continuous SpO_2 measurements, pre-processing, and data quality 56
4.3. SpO_2 features and fluctuations 58
5. Discussion 61
6. Supplementary material 66
6.1. Supplementary Figure 3.1 66

6.2. Supplementary Text 3.2 67
6.3. Supplementary Figure 3.3 68

Chapter 4 – Box-Jenkins transfer function modelling for reliable determination of $\dot{V}O_2$ kinetics in patients with COPD 69

1. Abstract 70
2. Introduction 70
3. Material and methods 73
   3.1. Study design and participants 73
   3.2. Exercise testing 73
   3.3. Data pre-processing 73
   3.4. Kinetic analyses 74
   3.5. Statistical analysis 76
4. Results 77
   4.1. Exponential modelling 77
   4.2. Box-Jenkins transfer function modelling 80
   4.3. Kinetic features 82
5. Discussion 84

Chapter 5 – Kinetic analyses as a tool to examine physiological exercise responses in a large sample of patients with COPD 89

1. Abstract 90
2. Introduction 91
3. Material and methods 93
   3.1. Study design and participants 93
   3.2. Kinetic analyses 94
   3.3. Statistical analyses 95
4. Results 96
   4.1. Patient characteristics 96
   4.2. Kinetic analyses 99
   4.3. Mean response time 104
   4.4. Gains 104
5. Discussion 105

6. Supplementary material 110
6.1. Supplementary Text 5.1 110
6.2. Supplementary Text 5.2 111

Chapter 6 – Physiological changes differ between responders and non-responders to pulmonary rehabilitation in COPD 113

1. Abstract 114
2. Introduction 114
3. Material and methods 115
3.1. Study design and participants 115
3.2. Pulmonary rehabilitation 116
3.3. Physiological responses during a constant work rate test 117
3.4. Patient exclusion and unreliable kinetic feature values 118
3.5. Statistical analyses 118
4. Results 120
4.1. Patient characteristics 120
4.2. Physical performance and isotime values 120
4.3. Kinetic feature values 122
4.4. Correlations between changes in physiological exercise responses and physical performance 122
5. Discussion 126
6. Supplementary material 129
6.1. Supplementary Figure 6.1 129
6.2. Supplementary Text 6.2 131
6.3. Supplementary Tables 6.3 133
6.4. Supplementary Figure 6.4 135

Chapter 7 – General discussion and conclusions 137

1. Summary of main findings 138
2. COPD patients are complex, individual, time-varying and dynamic biological systems 139
2.1. Complex 139
2.2. Individually different 140
2.3. Time-varying and dynamic 141

3. Data analysis and modelling techniques 146
3.1. Explanatory models 146
3.2. Predictive models 152
4. Future perspectives - Telemonitoring 153
4.1. Increase transparency and standardisation of SpO_2 measurements 154
4.2. Implement continuous SpO_2 measurements over prolonged time periods 154
4.3. Combine multiple variables 155
4.4. Technological advancements of measuring devices 155
4.5. Explore and combine different data analysis and modelling techniques 156
4.6. Perform well-designed large-scale studies and examine patient subpopulations 156
5. Future perspectives - Physical performance testing 157
5.1. Compare $\dot{V}O_2$ gain during CWRT with $\Delta\dot{V}O_2/\Delta WR$ ratio during CPET 158
5.2. Compare $\dot{V}_E$ gain during CWRT with $\dot{V}_E/\dot{V}CO_2$ relationship during CPET 158
5.3. Model and examine other physiological variables 159
5.4. Model and examine physiological fluctuations 159
5.5. Examine changes of physiological exercise responses over the course of a PR program 160
5.6. Examine the prognostic value of physiological exercise responses 160
6. General conclusions 160

List of Figures

Figure 1.1: Simplified overview of the main characteristics of COPD. 2
Figure 1.2: The sigmoidal oxygen dissociation curve illustrates the association between oxygen partial pressure and oxygen saturation. 4
Figure 1.3: Overview of possible interventions for treating and managing COPD. 6
Figure 1.4: Overview of the main clinical assessments of patients with COPD. 10
Figure 1.5: The general hypothesis of this dissertation is based on specific problems and hypotheses related to telemonitoring (Section 5.1) and physical performance testing (Section 5.2) in patients with COPD. 14
Figure 1.6: Overview of the different chapters in this dissertation. 20
Figure 2.1: Article selection resulted in 71 included articles. 26
Figure 3.1: General overview of the applied methods. COPD = chronic obstructive pulmonary disease; SpO_2 = peripheral blood oxygen saturation; CT90 = cumulative time spent with SpO_2 below 90%.... 49
Figure 3.2: Visualization of the different pre-processing steps. Panel A shows all original data, containing error values, that are divided into daytime and nocturnal data. Panel B zooms in on the effect of data exclusion on a specific part of daytime peripheral blood oxygen saturation (SpO_2) data. Panel C zooms in on the effect of down-sampling and interpolating on the same part of daytime SpO_2 data.52
Figure 3.3: The amount of invalid data of continuous peripheral blood oxygen saturation (SpO_2) measurements for different activities. LIPA = low-intensity physical activity; MVPA = moderate-to-vigorous physical activity. 57
Figure 3.4: Mean nocturnal peripheral blood oxygen saturation (SpO_2) compared to mean daytime SpO_2 in rest. The dots indicate weekly averages of mean SpO_2 for every patient, lines indicate the standard deviation of the mean SpO_2 values over different days and nights, and the orange line is the line of equality. 58
Figure 3.5: Cumulative time spent with peripheral blood oxygen saturation (SpO_2) below 90% (CT90) values for every night of every patient showed that 50% (10/20) of the included patients changed category

between desaturator and non-desaturator. The number next to each dot indicates the corresponding night of the measuring week and the orange line indicates the threshold of CT90 (30%) that divides nights with and without desaturation. A missing night number indicates that no data was available for that night. 60
Figure 4.1: Graphical representation of the kinetic features that quantify the phase II response. The blue line represents the theoretical oxygen uptake ($\dot{V}O_2$) response, the orange line shows the phase II contribution that should be modelled, the black dashed line visualises the WR increase at t = 0 s. The blue and orange lines coincide during phase II. TD = Time delay; TC = time constant; MRT = mean response time; Amp = response amplitude; ΔWR = the step increase in work rate at t = 0 s; TD2 = time delay of phase III or the slow component, variable between 100-200 s [277]..... 72
Figure 4.2: Example plot of oxygen uptake ($\dot{V}O_2$) data and the three different exponential modelling methods. The estimated time delay values for methods B and C were 8.3 s and 20.3 s, respectively..... 78
Figure 4.3: Residual analyses of the residuals from (a) exponential method C (representative for methods A and B) and Box-Jenkins transfer function (BJ-TF) models with noise model orders (b) [2 0] and (c) [3 2]. Left: residual values divided by the response amplitude (Amp), plotted in function of time. Right: autocorrelation coefficients up to lag 10. 79
Figure 4.4: Example plot of oxygen uptake ($\dot{V}O_2$) data and the Box-Jenkins transfer function (BJ-TF) system and full (system + noise) model. The estimated time delay value was 20 s..... 81
Figure 4.5: Normalised root-mean-squared error (NRMSE) and kinetic feature values summarised as median (bar) and interquartile range (line) for exponential modelling methods A, B, C and the Box-Jenkins transfer function (BJ-TF) model with noise model order [2 0]. TD = Time delay; TC = time constant; MRT = mean response time; Amp = response amplitude. 83
Figure 5.1: Representation of a typical oxygen uptake ($\dot{V}O_2$) response at the onset of a constant work rate test (blue line) and the specific phase II contribution (orange line). Both lines coincide during phase II. The black dashed line visualises the WR increase at t = 0 s. MRT = mean response time; TD = time delay; TC = time constant; WR = work rate;

TD2 = time delay of phase III or the slow component, variable between 100-200 s [277]..... 92
Figure 5.2: Overview of patients included for general and kinetic analyses. CWRT = constant work rate test; $\dot{V}O_2$ = oxygen uptake; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}_E$ = minute ventilation..... 97
Figure 5.3: Representative examples of $\dot{V}O_2$ responses of patients exhibiting unreliable kinetic feature values due to a low $\dot{V}O_2$ increase above unloaded cycling (left), a poor $\dot{V}O_2$ system model fit (middle) or a severely slowed $\dot{V}O_2$ response. The orange dashed lines represents the Box-Jenkins transfer function system model. $\dot{V}O_2$ = oxygen uptake; NRMSE = normalised root-mean-squared error; MRT = mean response time.....101
Figure 5.4: A peak work rate (WR_{peak}) cut-off value of 45 W corresponded to a negative predictive value of 79% for the prediction of patients who exhibited unreliable kinetic feature values. Twenty-four patients (24/265=9%) had a WR_{peak} <45 W. A forced expiratory volume in 1 s (FEV_1) cut-off value of 1.3 L corresponded to a positive predictive value of 94% for the prediction of patients who exhibited reliable kinetic feature values. One hundred and forty-two patients (142/265=53%) had a FEV_1 >1.3 L.....102
Figure 5.5: Representative example of oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) responses above unloaded cycling at exercise onset of a patient that was included for kinetic analyses. The work rate increased from 0 W to 67 W at Time = 0 s. The orange dashed lines represents the Box-Jenkins transfer function system model. 103
Figure 6.1: Overview of patient numbers included for analyses of isotime values (n=183) and for subsequent analyses of kinetic feature values (n=127). PR = pulmonary rehabilitation; CWRT = constant work rate test. 119
Figure 6.2: Examples of changes in physiological exercise responses following pulmonary rehabilitation for responders and non-responders. For clarity reasons, responses of different responders and non-responders are shown. Symbols in between the plotted responses indicate increased (upward arrow), decreased (downward arrow) or unchanged values (equality sign) for responders (symbols on the left side) and non-responders (symbols on the right side)

following pulmonary rehabilitation. Framed symbols indicate differences between responders and non-responders for that specific variable. Similar examples of changes in minute ventilation/carbon dioxide production, breathing frequency and tidal volume are provided in Supplementary Figure 6.4.....125
Figure 7.1: Oxygen uptake ($\dot{V}O_2$) responses and corresponding fluctuations at the onset of a constant work rate test (CWRT) for three different patients with COPD. Fluctuations (lower plots) are calculated as the difference between the $\dot{V}O_2$ response (black line) and Box-Jenkins transfer function system model (orange dashed line). The fluctuations of the first two patients differ greatly in amplitude, while the fluctuations of the third patient exhibit a peculiar, spiked behaviour. 142
Figure 7.2: Illustration of how the cardiovascular system enables gas exchange between the ventilatory and muscular system. The figure is inspired by Figure 1 in the work of Wasserman [122]. O_2 = oxygen; CO_2 = carbon dioxide; $\dot{V}O_2$ = oxygen uptake ($ml.min^{-1}$); $\dot{V}CO_2$ = carbon dioxide output ($ml.min^{-1}$); $\dot{Q}O_2$ = muscle oxygen consumption ($ml.min^{-1}$); $\dot{Q}CO_2$ = muscle carbon dioxide production ($ml.min^{-1}$); $\dot{Q}_l$ = leg blood flow ($dl.min^{-1}$); $\dot{Q}_p$ = pulmonary blood flow ($dl.min^{-1}$). 147
Figure 7.3: Curve 1 represents the simulated oxygen uptake response based on the mechanistic model created by Barstow and Molé [303]. Curve 2 represents the simulated oxygen uptake response when only blood flow increased at CWRT onset, while muscle oxygen consumption was kept constant. Figure adapted from the work of Barstow and Molé. 149

List of Tables

Table 2.1: Overview of the 71 included articles, based on 50 individual studies. [a] 31
Table 2.2: Detection or prediction of exacerbations based on SpO_2 and other physiological measurements. 36
Table 3.1: Characteristics of the 20 included patients with moderate to very severe COPD. 55
Table 3.2: Summary of the amount of peripheral oxygen saturation (SpO_2) measurements that were included for further analyses. All 20 patients performed nocturnal measurements and 17 patients performed daytime measurements. Therefore, averages were calculated with n=17 for daytime measurements and n=20 for nocturnal and total measurements. 56
Table 4.1: Patient characteristics. 77
Table 4.2: Model performance characteristics for identification of the noise model order. Dark squares show noise model orders that resulted in visually inappropriate full model fits. Upper values for every noise model structure are Young Identification Criterion (YIC) values, and lower values are normalised root-mean-squared error values (NRMSE) (%). 81
Table 5.1: Characteristics of patients included for general analyses (first column), divided as patients exhibiting unreliable (second column; excluded for kinetic analyses) and reliable (third column; included for kinetic analyses) kinetic feature values. 98
Table 6.1: Pre-rehabilitation characteristics, presented as mean (standard deviation), of patients with COPD that performed a constant work rate test (CWRT) pre- and post-pulmonary rehabilitation, divided as patients with (responders) and without (non-responders) clinically relevant increase of CWRT endurance time following pulmonary rehabilitation (i.e. >105 s increase). 121
Table 6.2: Changes in physical performance and constant work rate test (CWRT) isotime values following pulmonary rehabilitation (PR), presented as mean (standard deviation). 123
Table 6.3: Changes in kinetic feature values following pulmonary rehabilitation (PR), presented as mean and standard deviation. 124

Chapter 1 – General introduction

This chapter will introduce the main topics of this dissertation. The chapter starts with a general introduction into chronic obstructive pulmonary disease (COPD), discussing the burden, main symptoms and causes of the disease. Hereafter, an overview of the most important patho(physio)logy will be provided, followed by a summary of interventions for treating and managing COPD. Next, different clinical assessments are introduced that are used for identifying appropriate intervention strategies. This chapter then concludes with a description of how these clinical assessments and interventions can still be improved, which finally leads to the objectives of this PhD research.

1. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a highly prevalent non-communicable respiratory disease that is characterised by persistent airflow limitation [1]. Figure 1.1 provides a simplified summary of the main characteristics of COPD. A more detailed description is provided throughout this section. Latest global estimates report almost 400 million people to suffer from COPD [2]. Consequently, COPD leads to more than 3 million annual deaths, making up 5% of all deaths worldwide [3]. Still, this can be considered as an underestimation of the true mortality rate due to the under-recognition and under-diagnosis of COPD [1]. Both prevalence and mortality rate of COPD are expected to keep increasing [2, 3], resulting in COPD to become the third leading cause of death worldwide by 2030 [3]. Naturally, these high numbers are related to significant economic costs (e.g. €141 billion annually in Europe [4]) and societal costs (e.g. fifth leading cause of years lived with disability [5]).

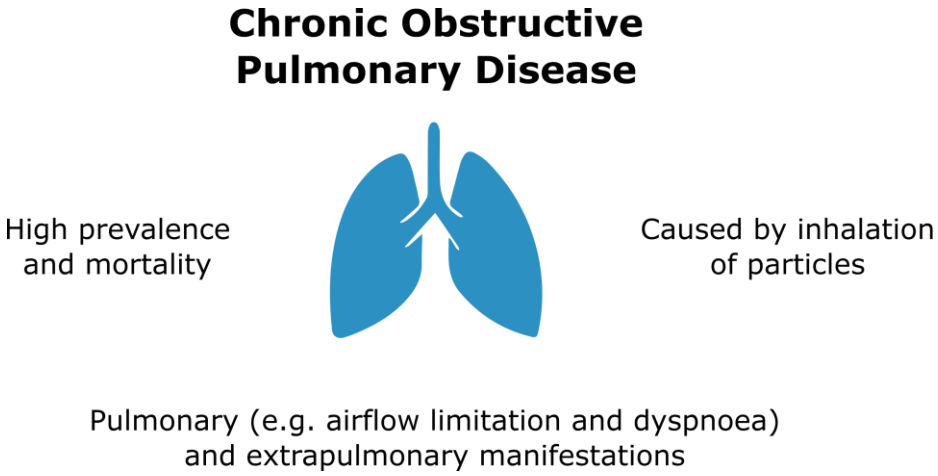


Figure 1.1: Simplified overview of the main characteristics of COPD.

The cardinal sign of COPD is chronic airflow limitation. This results in dyspnoea, possibly in combination with chronic cough, sputum production and/or wheezing [1]. The characteristic airflow limitation of patients with COPD is caused by a combination of airway and/or alveolar abnormalities, related to chronic inflammation, narrowing of peripheral airways and parenchymal destruction [1]. Exacerbations of COPD (defined as "a

sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations"[6]) are typically stressful events in the natural history of the disease that contribute to the high burden of COPD [7]. In addition, patients with COPD often suffer from extrapulmonary complications such as fatigue [8], weight loss [9], physical inactivity [10] and/or skeletal muscle dysfunction [11]. Also other chronic conditions (comorbidities), such as cardiovascular disease, osteoporosis, depression or diabetes, are common in patients with COPD, contributing to the overall severity of the disease [12, 13]. Altogether, COPD can be considered a complex, heterogeneous and multicomponent chronic condition [14, 15].

The most important risk factor for developing COPD is the inhalation of particles. This is most commonly related to cigarette smoking [16], but also other types of smoking (e.g. passive, cigar, water pipe or marijuana smoking [17–20]) are risk factors for COPD. Estimates indicate that 50% of elderly smokers develop COPD [21]. Other important sources of particle inhalation that increase the risk for developing COPD, are occupational exposure and in- and outdoor air pollution [22–24]. Occupational exposure is related to vapours, gas, dust or fumes in the work environment, while indoor air pollution is mainly related to biomass smoke. Besides these causal risk factors, which are all related to particle inhalation, also non-causal risk factors like age, body mass index, socioeconomical status and genetics can further increase the risk for developing COPD [20, 25, 26].

2. Patho(physio)logy

The main pathological characteristics of patients with COPD are chronic inflammation of the lungs and structural changes in the airways and lung parenchyma [27]. This chronic lung inflammation is due to an amplified inflammatory immune response towards the inhalation of particles. Structural changes include narrowing of peripheral airways and destruction of lung parenchyma (emphysema) [27]. These structural changes are responsible for the characteristic airflow limitation in patients with COPD [27–29]. The limited airflow during expiration consequently results in gas trapping and lung hyperinflation [1]. In addition, the described changes lead to a mismatch between local alveolar ventilation and pulmonary perfusion, impairing proper gas exchange between the

pulmonary and cardiovascular system [30]. This can lead to hypoxemia (low arterial oxygen levels) and hypercapnia (carbon dioxide retention) [1]. Oxygen homeostasis and hypoxemia are especially important in this PhD research and will be discussed in more detail below.

Impairments of oxygen transfer from the pulmonary to the cardiovascular system decreases both partial pressure of oxygen in arterial blood and arterial oxygen saturation (i.e. the percentage of haemoglobin binding sites that are occupied by oxygen) [31]. It is important to note that the relationship between oxygen partial pressure and oxygen saturation is not linear, as illustrated by the oxygen dissociation curve in Figure 1.2. Arterial blood of healthy individuals remains in the upper plateau of the oxygen dissociation curve. Consequently, small changes of arterial oxygen partial pressure will have a limited effect on arterial oxygen saturation. In capillary blood, however, oxygen extraction by the metabolising tissues will move oxygen partial pressure towards the steep portion of the sigmoidal curve. A small further decrease of oxygen partial pressure can therefore allow for a relatively large increase of oxygen extraction by the metabolising tissues, as indicated by the large decrease of oxygen saturation [31]. Conditions that prevail in metabolising tissues (e.g. low pH and high partial pressure of carbon dioxide) additionally shift the oxygen dissociation curve

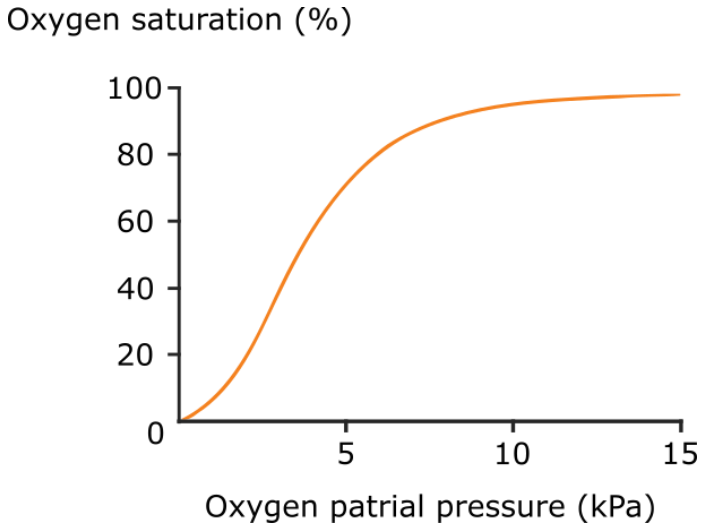


Figure 1.2: The sigmoidal oxygen dissociation curve illustrates the association between oxygen partial pressure and oxygen saturation.

to the right, further facilitating oxygen extraction by the metabolising tissues. Similarly, high pH and low partial pressure of carbon dioxide in pulmonary capillaries shift the curve to the left, facilitating the uptake of oxygen in the pulmonary blood flow [32].

Reduced oxygen partial pressure in patients with COPD results in arterial blood being closer to the steep portion of the idal curve compared to healthy individuals. Consequently, small changes of oxygen partial pressure or a small shift of the oxygen dissociation curve can induce large fluctuations of arterial oxygen saturation in patients with COPD. Reduced oxygen partial pressure due to nocturnal hypoventilation can therefore induce nocturnal desaturation [33]. Also the increased peripheral oxygen extraction and dynamic hyperinflation during exercise can lead to a decrease of oxygen partial pressure, resulting in exertional desaturation [34, 35].

Besides these effects on the respiratory system and oxygen homeostasis, COPD also affects cardiovascular and muscular systems. COPD is often associated with pulmonary hypertension, which can further lead to right ventricular hypertrophy [36]. Increased intrathoracic pressures can furthermore reduce left ventricular filling, stroke volume and cardiac output [37–39]. Also muscle dysfunction is common in patients with COPD, leading to muscle weakness and reduced muscle endurance. The underlying mechanisms include muscle atrophy, reduced capillary density, reduced oxidative capacity and a shift in muscle fibre type [11]. This wide variety of discussed respiratory and non-respiratory manifestations of COPD clearly illustrates the complex nature of the disease.

sigmo

3. Interventions for treating and managing COPD

Some possible interventions for treating and managing COPD are illustrated in Figure 1.3 and will be discussed below.

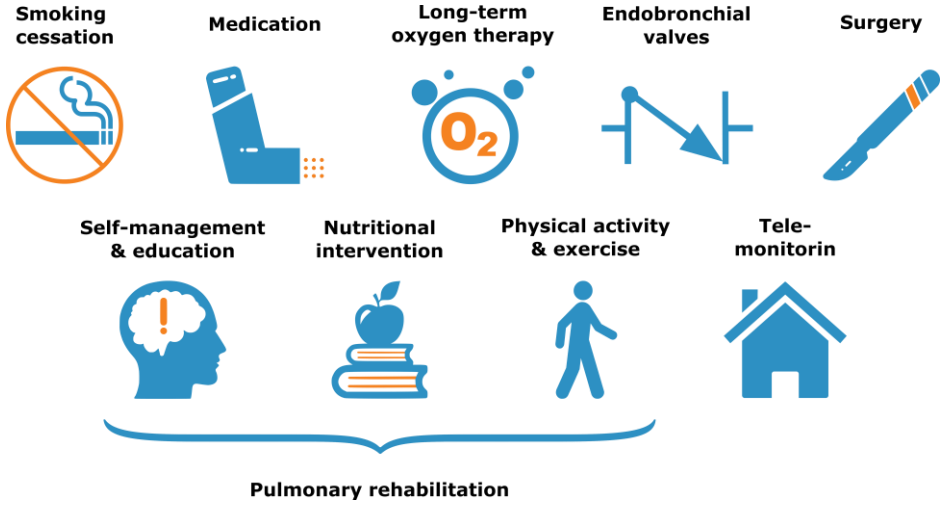


Figure 1.3: Overview of possible interventions for treating and managing COPD.

3.1. Smoking cessation, medication, long-term oxygen therapy, endobronchial valves and surgery

Smoking cessation is considered the most important intervention for slowing the progression of COPD and reducing morbidity and mortality [40]. Exposure to noxious occupational, indoor and outdoor particles should also be limited [1]. *Pharmacological treatment*, such as the use of bronchodilators or inhaled corticosteroids, is another important intervention to reduce COPD morbidity [1]. For patients with severe resting hypoxemia, mortality can be decreased by long-term administration of supplemental oxygen (*long-term oxygen therapy*) [41]. Oxygen supplementation during exercise can reduce dynamic hyperinflation, improve arterial oxygen saturation and increase exercise time for COPD patients with exercise-induced hypoxemia [42]. However, a recent study indicates that long-term benefits of acute oxygen supplementation during exercise are doubtful [43]. The bronchoscopic implementation of *endobronchial valves* is another method to reduce lung hyperinflation [44].

These one-way valves limit the inspiratory airflow to hyperinflated lung regions, while expiratory airflow can be maintained. In some carefully selected cases, *surgical interventions* can reduce morbidity and improve physical performance [45]. Lung volume reduction surgery can improve expiratory flow rates and reduce hyperinflation by removing diseased lung tissue [46]. Lung transplantations can improve quality of life in some patients with very severe COPD [45].

3.2. Self-management, education, nutritional intervention, physical activity and exercise training

Important non-invasive, non-pharmacological interventions for patients with COPD include self-management, education, nutritional interventions, increased physical activity and exercise training [1]. *Self-management and education* help patients to acquire knowledge about the disease, recognise and manage disease-related problems and improve health-related behaviour [47]. This has been associated with a reduction in hospital admissions and reduced economic costs [48, 49]. *Nutritional intervention* is mainly recommended for undernourished patients, preferably in combination with exercise training [50]. Maintaining a sufficient level of *physical activity* is also crucial for patients with COPD. Low levels of physical activity are associated with many detrimental effects, including impaired physical performance, dynamic hyperinflation, the presence of comorbidities, increased risk for hospitalisation and increased mortality [10]. A recent meta-analysis showed that any level of physical activity or a reduction of sedentary time is associated with a lower risk of premature mortality in middle aged and older adults [51]. Nevertheless, physical inactivity is common in patients with COPD [52]. This can lead to a further decline in lung function, which is the start of a deleterious vicious circle of deconditioning [10]. Besides merely increasing physical activity, *exercise training* provides additional benefits. It is considered the most effective intervention to improve muscle function [11], related to enhancements of muscle oxidative enzyme activity [53], increased capillary-to-fibre ratios [54] and/or enlarged muscle mass [55]. Furthermore, exercise training can improve cardiovascular function [56–58] and reduce ventilatory requirements, hyperinflation and dyspnoea [58–62]. Ultimately, exercise training also improves physical performance [57–62].

3.3. Pulmonary rehabilitation

Pulmonary rehabilitation (PR) is a comprehensive, interdisciplinary intervention that combines different non-pharmacological interventions (e.g. the interventions discussed in section 3.2; Figure 1.3) [63]. It is considered the most effective intervention to reduce physical impairments in patients with COPD [63, 64]. Nevertheless, additional behavioural changes are paramount for obtaining a lasting increase of physical activity levels after PR [64]. Besides improvements of physical activity levels and physical performances, PR has been associated with a wide variety of improvements, including increased quality of life [65, 66], reduced hospital admissions [65, 66], decreased symptom sensation [63], improved mental health [67], reduced fatigue [68], increased muscle function [11] and improved physiological responses during activities of daily living [69] or exercise [58].

Practical implementations of a PR program (e.g. in- or outpatient setting, duration, number of weekly sessions or staff-to-patient ratios) can vary, depending on preference and available resources [63]. Nevertheless, a minimum duration of 8 weeks is deemed necessary [70]. Physical activity and exercise training are considered to be the cornerstone of a PR program. Walking- or cycling-based endurance training is the most common modality of exercise training in PR programs [63]. Interval training, altering periods of high-intensity exercise with periods of rest, is an alternative training modality for patients that are not able to perform continuous endurance training exercises [54, 71]. Strength training of local muscle groups can be used to improve muscle mass and strength [72, 73]. Also, strength training can be more easily tolerated by COPD patients due to the reduced cardiopulmonary stress compared to endurance and interval training [74]. Neuromuscular electrical stimulation can be used to train skeletal muscles of severely limited COPD patients, as it only requires minimal efforts from the pulmonary and cardiovascular systems [63]. Overall, a combination of different exercise modes is recommended for a greater impact on physical performance [63, 72].

3.4. Telemonitoring

A more recent type of intervention for patients with COPD is telemonitoring. Telemonitoring can be described as the use of telecommunication technologies to provide and support health care at a distance [75]. It is expected to become a key component in future healthcare [76]. For patients with COPD, home monitoring could be a useful tool for early detection of exacerbations [77]. This could be of great importance, as early treatment of exacerbations has been shown to improve exacerbation recovery and quality of life in patients with COPD [78]. Exacerbation prediction, instead of merely early detection, could be even more beneficial, as this could prevent these detrimental episodes from happening. Although telemonitoring is a promising tool that can increase quality of life and reduce exacerbations, emergency room visits and hospitalisations [79–82], compelling evidence of the benefits of telemonitoring is still lacking [83–86]. Nevertheless, telemonitoring applications have been considered to facilitate the continuity of care after hospital discharge [87], facilitate adherence to chronic disease management [88], empower patients and influence their behaviour [89, 90], improve physical activity [91], detect exacerbations [92–100] and reduce hospitalisations [90, 99, 101].

Telemonitoring can be performed in many different forms. Some applications are merely serving as remote communication devices between patients and healthcare providers, while other require active (daily) data submission. Low-level telemonitoring interventions, such as regular phone calls or text messages, could already improve physical activity levels [91] or enhance chronic disease management adherence [88]. Nevertheless, (daily) transmission of symptoms or physiological variables seems necessary to detect or predict exacerbations. Symptoms are generally reported through (daily) questionnaires [77], while peripheral devices are used to perform (daily) spot check measurements of physiological variables, such as peripheral oxygen saturation (SpO_2), heart rate, lung function or breathing frequency [77, 102]. These spot check measurements generate alerts when reported values exceed predefined thresholds, which can help healthcare professionals to provide early interventions [103]. However, as indicated before, conclusive evidence of the benefits of telemonitoring interventions is still to be provided.

4. Clinical assessment of patients with COPD

Some of the main clinical assessments of patients with COPD are pulmonary function testing, symptom questionnaires, arterial blood gas analyses and physical performance testing (Figure 1.4), as will be described below.

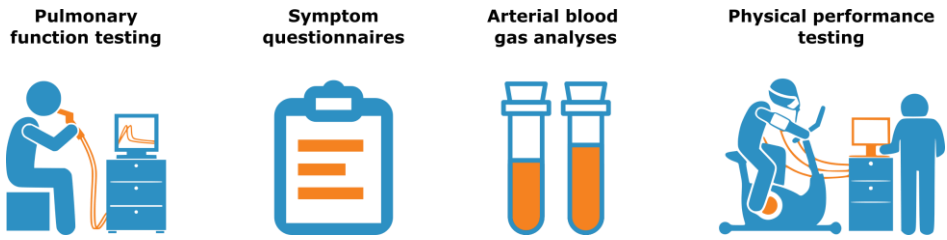


Figure 1.4: Overview of the main clinical assessments of patients with COPD.

4.1. Pulmonary function testing

Pulmonary function tests include spirometry, body plethysmography and single-breath diffusion capacity. Spirometry assesses the degree of airflow limitation, which is used to diagnose patients with COPD [1]. The main outcomes of spirometry are the volume of air that can be forcefully exhaled in 1 second (forced expiratory volume in 1 second, FEV_1) and the total volume of air that can be forcefully exhaled (forced vital capacity, FVC) after maximal inhalation. Subjects are diagnosed with COPD when they suffer from a post-bronchodilator FEV_1/FVC ratio lower than 70%, indicating airflow limitation [1]. In addition, '%predicted values' are obtained by comparing measured values with reference values that are based on gender, age, height and race [104]. Further classifications of disease severity (i.e. GOLD stages) are then based on the degree of airflow limitation, expressed as FEV_1%predicted:

GOLD 1	-	$FEV_1 \geq 80$%predicted	-	Mild COPD
GOLD 2	-	$50 \leq FEV_1 < 80$%predicted	-	Moderate COPD
GOLD 3	-	$30 \leq FEV_1 < 50$%predicted	-	Severe COPD
GOLD 4	-	$FEV_1 < 30$%predicted	-	Very severe COPD

Body plethysmography and the single-breath diffusion capacity can provide additional information about lung function impairment. Body plethysmography determines lung volumes, including the total lung capacity (volume of air in the lungs after maximal inhalation) and residual volume (volume of gas remaining in the lungs after maximal exhalation) [105]. Values > 120%predicted, based on the comparison with reference values [106], can indicate the presence of static lung hyperinflation [107]. Single-breath diffusion capacity assesses gas exchange abnormalities based on the inhalation of a small fraction of carbon monoxide during a single breath. Lung diffusion capacity is then expressed as the transfer factor for carbon monoxide (TLCO), often expressed as %predicted based on the comparison to established reference values [108].

4.2. Symptom questionnaires

Symptoms of COPD patients can be assessed by questionnaires. The modified Medical Research Council (mMRC) questionnaire provides a dyspnoea grading between 0 ('I only get breathless with strenuous exercise') and 4 ('I am too breathless to leave the house or I am breathless when dressing or undressing') [109]. A more comprehensive assessment of symptoms can be obtained by the St. George's Respiratory Questionnaire [110] or COPD assessment test (CAT) [111]. The short CAT questionnaire (8 questions) might be more suitable for clinical practice than the elaborate St. George's Respiratory Questionnaire (76 questions). These questionnaires are furthermore used in the 'ABCD' assessment tool for classifying COPD patients based on their symptom burden (using mMRC dyspnoea grading or CAT score) and exacerbation risk (based on exacerbation history). A refined classification of COPD patients can then be obtained by combining airflow limitation classifications (GOLD stages) with the 'ABCD' assessment tool [1].

4.3. Arterial blood gas analyses and pulse oximetry

Arterial blood gas analyses can be used to detect hypoxemia (low arterial oxygen partial pressure or saturation) or hypercapnia (high arterial carbon dioxide partial pressure). Patients with a partial pressure of oxygen lower than 55 mm Hg or arterial oxygen saturation lower than 88% can be considered for long-term oxygen therapy [1]. Alternatively, patients can initially be screened for low oxygen concentrations by a non-invasive pulse

oximeter, providing measurements of SpO_2 (i.e. peripheral oxygen saturation as measured with a pulse oximeter). An SpO_2 value below 92% indicates that arterial blood gas analyses are required to assess the need for long-term oxygen therapy [112]. Furthermore, pulse oximeters can identify patients that desaturate during exercise or sleep. An SpO_2 drop below 88-90% during a walking test has generally been used to identify exercise-induced desaturators [43, 113]. Patients with an SpO_2 value lower than 90% for more than 30% of the time in bed are considered nocturnal desaturators [114, 115]. Nevertheless, as previously mentioned, the benefits of oxygen administration during exercise or sleep are controversial [43, 116].

4.4. Physical performance testing

Physical performance of patients with COPD can be assessed through a variety of tests, including tests of muscle strength, six-minute walk test, cardiopulmonary exercise test (CPET) and constant work rate test (CWRT). Muscle strength of patients with COPD has mostly been assessed in the quadriceps by measuring the maximal isometric (constant muscle length) voluntary contraction or isokinetic (constant angular speed) peak torque [11]. Although assessing isokinetic peak torque requires more advanced measuring devices than assessing maximal isometric voluntary contraction, it has been shown to be very reliable [11, 117]. Physical endurance of patients with COPD can be assessed using walking or cycling tests. The most widespread walking test of patients with COPD is the self-paced six-minute walk test, indicating the maximal distance that can be walked in six minutes [118]. This test is practically simple, well-tolerated and closely reflects activities of daily living [119].

Besides walking tests, cycling tests such as CPET and CWRT are frequently used to assess physical endurance of patients with COPD [120]. Patients cycle until exhaustion while work rate (WR) increases linearly (CPET) or remains constant at a submaximal level (CWRT). Mostly, physiological variables such as oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) are measured continuously during these tests. Peak values of WR or $\dot{V}O_2$ that are reached during a CPET provide information about maximal physical performance and can be used

to optimise training intensities during a pulmonary rehabilitation program [120]. A CWRT is the preferred test to quantify improvements of physical performance following an intervention, such as oxygen breathing or pulmonary rehabilitation [121]. The continuous measurements of physiological variables that are collected during a CPET can furthermore help to identify underlying pathologies that lead to impaired physical performances or unexplained dyspnoea [120]. A nine-plot graphical display, plotting a variety of physiological variables in function of WR, $\dot{V}O_2$ or $\dot{V}CO_2$, is a useful tool to determine these pathologies for individual patients [122]. For example, the $\dot{V}CO_2$-$\dot{V}O_2$ plot during CPET can be used to determine the anaerobic threshold, while the $\dot{V}_E$-$\dot{V}CO_2$ relationship can identify ventilatory inefficiency [120].

5. Problem statement, hypotheses, objectives and framework

The description provided in the previous sections shows that COPD is a complex and heterogenous disease, manifested through a variety of respiratory and non-respiratory pathologies. Accordingly, different types of interventions are available for individualised treatment and management of the disease (Figure 1.3). These interventions are furthermore based on a variety of clinical assessments (Figure 1.4). However, despite this wide variety of available interventions and clinical assessments of patients with COPD, we hypothesise that improvements can still be obtained.

Concretely, the general hypothesis of this dissertation is that time series analyses of continuously measured physiological variables can enhance current interventions and clinical assessments of patients with COPD (Figure 1.5). This general hypothesis is based on specific problems and hypotheses related to telemonitoring and physical performance testing in patients with COPD, as will be discussed below. The identified problems are not necessarily limited to patients with COPD. Therefore, the stated hypotheses have a wider applicability in other chronic disease states, such as asthma or congestive heart failure, or healthy populations

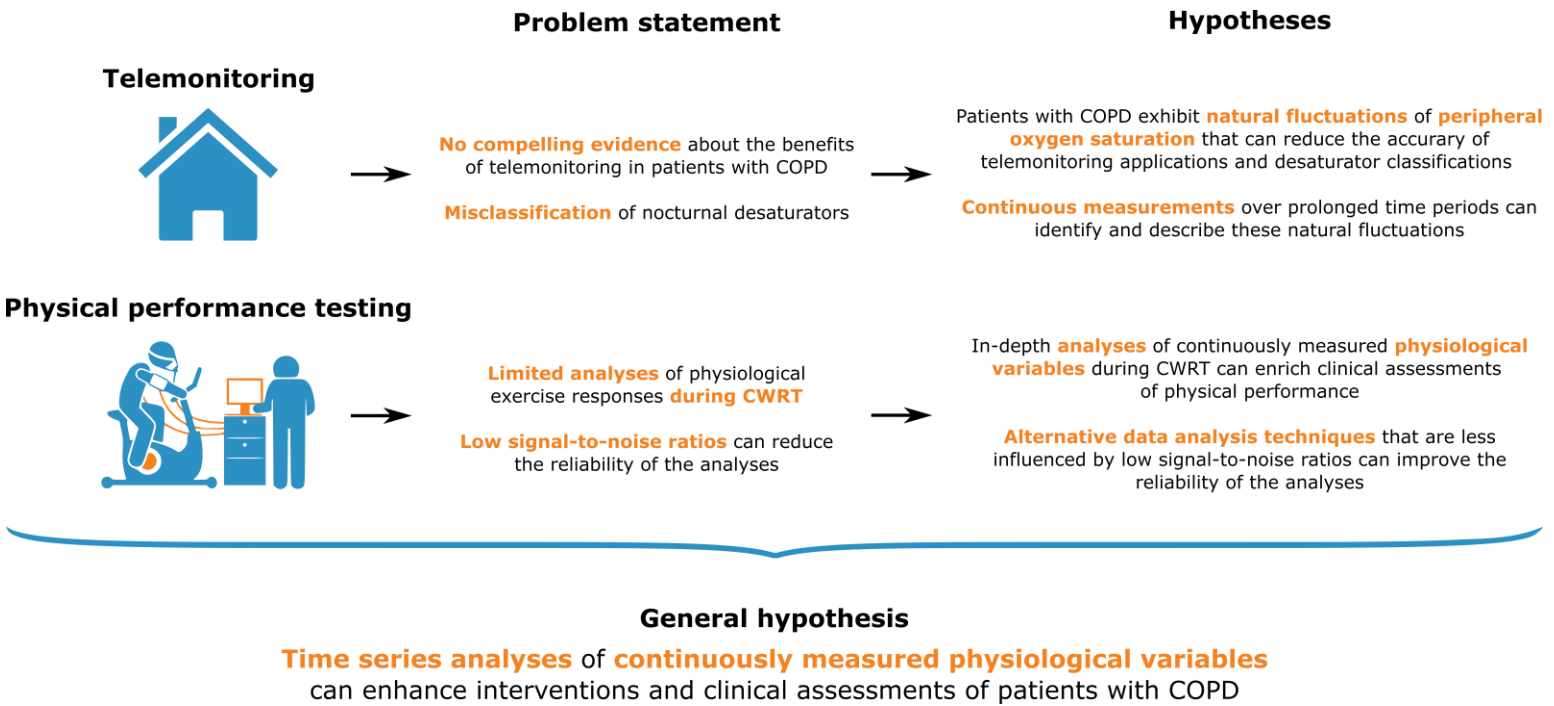


Figure 1.5: The general hypothesis of this dissertation is based on specific problems and hypotheses related to telemonitoring (Section 5.1) and physical performance testing (Section 5.2) in patients with COPD.

5.1. Telemonitoring – Problem statement and hypotheses

The main issue of telemonitoring applications for patients with COPD is that *no compelling evidence about its benefits* has yet been provided [83–86]. Different elements have been assumed to hamper the performance of telemonitoring applications in patients with COPD, including the complexity of the disease, difficulties of the patients to recognise symptom worsening, the absence of a clear predictor variable or the lack of reliable predictive algorithms [103, 123–125]. Furthermore, natural fluctuations of measured physiological variables (e.g. heart rate, SpO_2) could mask physiological changes that are induced by exacerbations [123]. The latter is especially problematic considering the fact that physiological variables are generally assessed through daily spot check measurements [77, 102], which are unable to capture these natural fluctuations. In addition, no proper characterisation of the magnitude, frequency and dynamic behaviour of these natural fluctuations has been performed yet. Although improved predictive algorithms have been suggested as the primary approach to increase telemonitoring performances [103, 124], even the most advanced algorithms will struggle with these natural fluctuations when physiological variables are only assessed through spot check measurements.

Capturing these natural physiological fluctuations can thus be considered as the first step towards more accurate telemonitoring applications in patients with COPD. This can be achieved by continuously measuring physiological variables over prolonged time periods. In a following step, these prolonged measurements can then be combined with more advanced predictive algorithms to really boost performance of telemonitoring applications in patients with COPD. It can be expected that the suggested approach can provide similar benefits to telemonitoring applications of other chronic disease states.

Although no clear predictor variable has yet been identified, SpO_2 is considered the physiological variable with the highest predictive power for exacerbations of patients with COPD [79, 126, 127]. Wearable pulse oximeters make it possible to measure SpO_2 continuously over prolonged time periods. In addition, continuous, nocturnal SpO_2 measurements can be used to identify nocturnal desaturators, which is usually based on nocturnal

SpO_2 measurements during at most two nights [114–116]. Similar to spot check measurements in telemonitoring applications, using measurements during only one or two nights might overlook the natural variability that could be present over multiple nights. This could lead to *misclassifications of nocturnal desaturators*, contributing to the controversy related to nocturnal oxygen administration [116].

Overall, we hypothesise that patients with COPD exhibit natural SpO_2 fluctuations within one day or over multiple days and nights, which can reduce the accuracy of telemonitoring applications and desaturator classifications. Continuous SpO_2 measurements over prolonged time periods can identify and describe these natural fluctuations.

5.2. Physical performance testing – Problem statement and hypotheses

Despite the wide variety of physiological variables (e.g. $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, breathing frequency or heart rate) that are measured continuously during a CWRT, *analyses of physiological exercise responses during CWRT remain limited*. In contrast, physiological exercise responses during CPET are more extensively studied. As previously described, physiological exercise responses during CPET are a useful tool to identify pathologies that underlie impaired physical performances or unexplained dyspnoea [120]. A CPET, however, is not representative for activities of daily living. Patients with COPD, as well as healthy individuals or patients with other chronic disease states, will rarely perform physical activities of increasing intensity in daily life.

A CWRT, representing the transition from rest to (constant) exercise, is more closely related to daily life routines [128]. Despite the large amount of data that is generated during a CWRT, endurance time remains the main output of the test [121]. The few small-scale studies that did examine physiological exercise responses at CWRT onset showed that patients with COPD exhibited a slower physiological exercise response compared to healthy subjects [129, 130]. Interventions such as oxygen administration, bronchodilator therapy or exercise training were found to increase the speed of this physiological response [57, 131–133]. Nevertheless, studies with larger samples sizes are needed to further explore causes and

consequences of impaired physiological exercise responses in patients with COPD.

It should furthermore be noted that the *low signal-to-noise ratios* (i.e. physiological response amplitude-to-fluctuations ratio) that can be observed in patients with COPD, a result of low tolerable WRs [120], can reduce the reliability of analysing physiological exercise responses during CWRT [134, 135]. This is especially important considering the fact that most studies relied on least-squares algorithms for parameter estimations, which can be susceptible to low signal-to-noise ratios [136, 137]. Alternative data analysis techniques that are less influenced by low signal-to-noise ratios (e.g. parameter estimations based on refined instrumental variable approach [137] or models that explicitly account for fluctuations [138]) can therefore improve the reliability of analysing physiological exercise response.

Overall, we hypothesise that in-depth analyses of the continuously measured physiological variables at the onset of a CWRT can enrich clinical assessments of physical performance by shedding light on the causes and consequences of impaired physiological exercise response in patients with COPD. Furthermore, alternative data analysis techniques that are less influenced by the high fluctuations, compared to the response amplitude, can improve the reliability of the analyses.

5.3. General and specific objectives

Based on these considerations, the general objective of this PhD research is to *enhance clinical assessments and interventions of patients with COPD by analysing time series of physiological variables.* More concretely, this can be translated into three specific objectives:

(i) Evaluate whether the accuracy of telemonitoring applications and desaturator classifications of patients with COPD could be affected by natural SpO_2 fluctuations (**Chapter 2 and 3**),

(ii) Examine whether physiological exercise responses during CWRT can be analysed more reliably by using an alternative data analysis technique that is able to account for natural physiological fluctuations (**Chapter 4**),

(iii) Characterise physiological exercise responses during CWRT of patients with COPD to enrich clinical assessments of physical performance (**Chapters 5 and 6**).

Although this dissertation focusses on patients with COPD, the outcomes will have a wider applicability. Other chronic disease states, such as asthma or congestive heart failure, can also suffer from low arterial oxygen saturation [139, 140] and, consequently, from high natural SpO_2 fluctuations. The reasoning presented in section 5.1 can furthermore be applied to alternative key variables for telemonitoring of other chronic disease states, such as blood pressure for patients with hypertension [141]. In addition, enhanced analyses of physiological responses during exercise can not only enrich clinical assessments of physical performance of patients with COPD and other (chronic) disease states, but it can also enrich physical assessments in recreational and professional sports. The results of this dissertation can therefore be interpreted in a context that is wider than merely patients with COPD.

5.4. Framework of this dissertation

The objectives of this PhD research will be addressed in the different chapters of this dissertation, as shown in Figure 1.6 and discussed below.

Chapters 2 and 3 – **Telemonitoring**

First, a systematic review will evaluate the scientific literature on the use of SpO_2 measurements in telemonitoring applications of patients with COPD (**Chapter 2**). Hereafter, the findings of a telemonitoring study will be discussed. During this study, 20 patients with COPD used wearable finger pulse oximeters to continuously measure SpO_2 over one week during daily home routines in order to assess natural SpO_2 fluctuations within and between multiple days and nights (**Chapter 3**). The combined results of these Chapters will be used to assess whether patients with COPD exhibit

natural SpO_2 fluctuations that could affect the accuracy of telemonitoring applications and desaturator classifications. Putting these findings into practice can improve telemonitoring applications and reduce desaturator misclassifications.

Chapters 4, 5 and 6 – **Physical performance testing**

The second part of this dissertation starts with introducing and evaluating an alternative data analysis technique, which is less influenced by low signal-to-noise ratios than conventional techniques, for analysing physiological exercise responses in patients with COPD (**Chapter 4**). The focus of this evaluation will be on the ability of this alternative technique to account for low signal-to-noise ratios that can be observed in patients with COPD. This technique will then be applied on an extended dataset of COPD patients (n=265) to examine whether impaired physiological exercise responses are associated with ventilatory, cardiovascular and/or physical impairments (**Chapter 5**). Most of these patients furthermore completed a PR program. The last chapter before the general discussion reports about whether PR-induced changes of physiological exercise responses differ between patients that do or do not improve physical endurance following PR (**Chapter 6**).

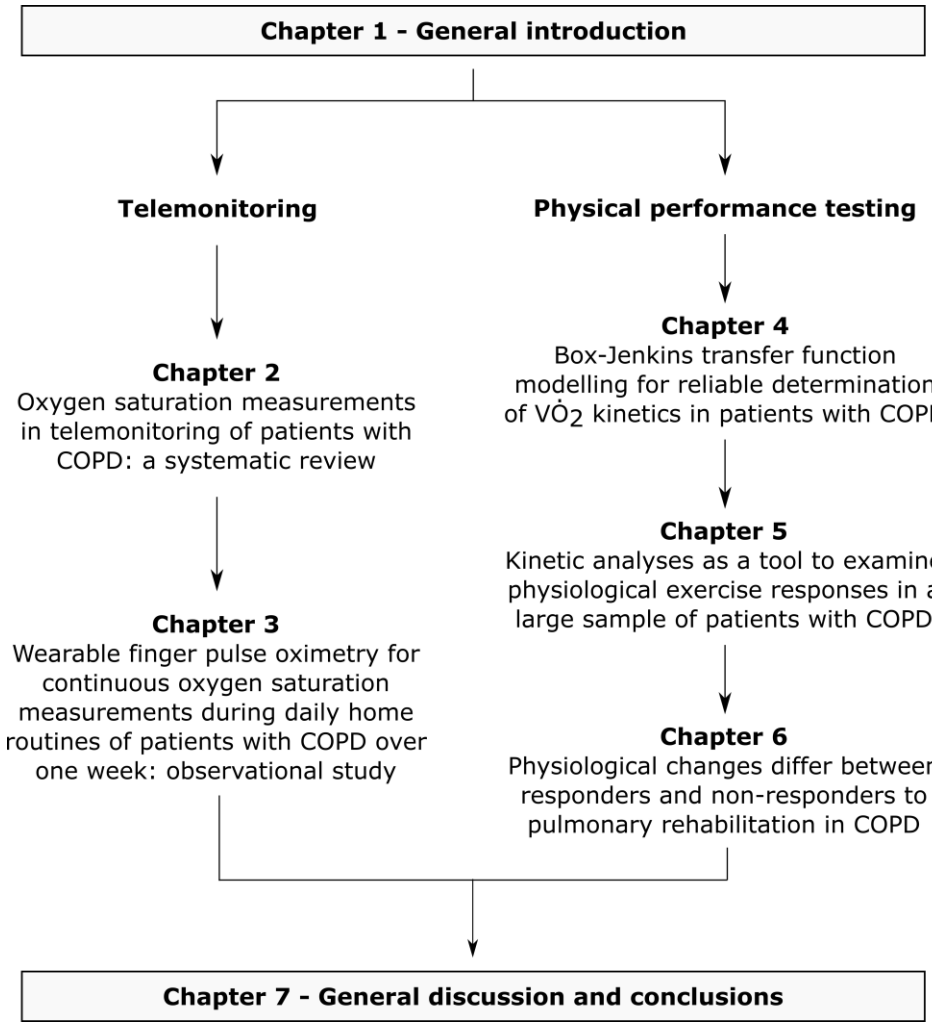


Figure 1.6: Overview of the different chapters in this dissertation.

Chapter 2 – Oxygen saturation measurements in telemonitoring of patients with COPD: a systematic review

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This Chapter reports on the results of a systematic review that was performed to evaluate the scientific literature on the application of SpO_2 measurements in telemonitoring of patients with COPD. The results of this Chapter, combined with the results of Chapter 3, address the first objective of this dissertation.

1. Abstract

Introduction: Telemonitoring applications are expected to become a key component in future healthcare. Despite the frequent use of SpO_2 measurements in telemonitoring of patients with chronic obstructive pulmonary disease (COPD), no profound overview is available about these measurements.

Areas covered: A systematic search identified 71 articles that performed SpO_2 measurements in COPD telemonitoring. The results indicate that long-term follow-up of COPD patients using daily SpO_2 spot checks is practically feasible. Very few studies specified protocols for performing these measurements. In many studies, deviating SpO_2 values were used to raise alerts that led to immediate action from healthcare professionals. However, little information was available about the exact implementation and performance of these alerts. Therefore, no firm conclusions can be drawn about the real value of SpO_2 measurements. Future research could optimise performance of alerts using individualised, time-dependent thresholds or predictive algorithms to account for individual differences and SpO_2 baseline changes. Additionally, the value of performing continuous measurements should be examined.

Expert commentary: Standardisation of the measurements, data science techniques and advancing technology can still boost performance of telemonitoring applications. All these opportunities should be thoroughly explored to assess the real value of SpO_2 in COPD telemonitoring.

2. Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic noncommunicable disease affecting 64 million people [142]. By 2030, COPD will become the third leading cause of death worldwide [3]. Total costs associated with this disease are estimated to be €141 billion in Europe [4]. Major contributors to the high economic and societal burden of COPD are exacerbations [7]. Exacerbations of COPD (defined as 'a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations') [6] are typically stressful events in the natural history of the disease [1]. Low blood oxygen concentrations (hypoxemia) increase the risk of exacerbation, while exacerbations can also

induce hypoxemia [34]. The risk of hypoxemia rises with increasing disease severity [1] and can lead to long-term adverse effects such as pulmonary hypertension and systematic inflammation, reducing quality of life in patients with COPD [34]. Long-term administration of oxygen decreases mortality in patients with severe resting hypoxemia [41] and is prescribed based on blood gas measurements [1].

Pulse oximetry is a non-invasive method to assess arterial blood oxygen concentrations that uses light absorption characteristics of haemoglobin [143]. Pulse oximeters produce a photoplethysmography (PPG) waveform, from which both peripheral oxygen saturation (SpO_2) and heart rate (HR) can be derived [144]. An SpO_2 value below 92% indicates blood gas measurements should be performed to assess the need for supplemental oxygen therapy [112]. Pulse oximetry is also used in telemonitoring applications [77, 102]. These applications make use of information technology to monitor patients at a distance without a healthcare professional present at the monitoring site [89]. Telemonitored patients are able to consult healthcare professionals through video or phone calls (remote consultations) or send information gathered via questionnaires or physiological measurements (e.g. HR or SpO_2) to healthcare professionals. In the case of management of COPD patients, this information can be used to detect exacerbations. Early detection of exacerbations can reduce hospitalisations and improve recovery and health-related quality of life [78]. Furthermore, it has been suggested that telemonitoring applications could even predict these events [102], which could lead to the prevention of detrimental hospitalisations [78]. Generally, telemonitoring applications are expected to become a key component in future healthcare [76].

Despite the frequent use of SpO_2 measurements in COPD telemonitoring [77], no profound overview is available about these measurements. Therefore, this systematic review will evaluate the scientific literature on the application of SpO_2 measurements in telemonitoring of patients with COPD.

3. Methods

3.1. Search strategy

The literature search was performed in PubMed and Web of Science on the 15th of March 2017. The systematic search terms consisted of the following keywords: (mHealth OR 'mobile health' OR tele(-)health OR tele(-)monitoring OR tele(-)medicine) AND (COPD OR 'chronic obstructive pulmonary disease'). Search terms were not narrowed down to only SpO_2 measurements to avoid exclusion of potentially valuable articles that did not mention SpO_2 measurements in the abstract. Meta-analyses and reviews were excluded a priori. Article screening excluded duplicates, non-English articles, editorials, conference proceedings, articles without full-text availability, and articles that were not applying SpO_2 measurements in telemonitoring of patients with COPD. Additional articles were included based on reference list screenings from the articles retrieved via PubMed or Web of Science. Results were discussed with all co-authors and inventoried by the first author.

3.2. Information extraction

First, articles originating from the same study were grouped. Then, studies applying remote consultations were identified, as they have significantly different characteristics compared to telemonitoring implementations not requiring personal contact. Afterwards, participant numbers were extracted and in the case of a randomised controlled trial, participant numbers of both telemonitoring and usual care group were denoted. When possible, the distinction between COPD patients and other participants was made. In a next step, characteristics of the studies were extracted by identifying study duration, SpO_2 measuring frequency, and type of oximeter and associated telemonitoring system (used for storage and/or transmission of SpO_2 data). Finally, information was extracted on the application and value of SpO_2 measurements.

This review specifically aims to provide an overview of the use of SpO_2 measurements in telemonitoring of COPD patients. However, most of the reviewed studies primarily focused on the results of whole telemonitoring systems, which depend on several technical and organisational factors of

the whole telemonitoring setup. Therefore, reporting on the overall results of the included studies is outside the scope of this systematic review.

4. Results

4.1. Article selection

The initial PubMed and Web of Science search retrieved 532 articles (Figure 2.1). After removal of duplicates (n = 169), non-English articles (n = 15), editorials (n = 13), conference proceedings (n = 12), and articles without full text availability (n = 11), 312 articles remained. Full text screenings excluded articles that were not applying telemonitoring in COPD or performing SpO_2 measurements (n = 243). Addition of articles from reference lists (n = 2) resulted in a final set of 71 articles.

4.2. Study description

Table 2.1 provides a description of the 71 included articles, originating from 50 distinct studies. The first article was published in 2004. Sixty-three of the 71 articles (89%) have been published after 2010.

The 50 included studies can be divided into studies with supervised measurements (during remote consultations; n = 6) and independent patient measurements (n = 44). Two types of remote consultations were performed: (i) short-term (≤14 days) follow-up of patients released from the hospital after an exacerbation [145–151] (n = 4); or (ii) long-term (12 months) remote monitoring [152–155] (n = 2). Regarding the 44 studies with independent patient measurements, most implemented telemonitoring for at least 2 months (n = 39) and almost two-thirds of the studies lasted for at least 6 months (n = 28). In almost half of the 50 included studies, less than 30 COPD patients were included for telemonitoring (n = 24). Very few studies reported on analyses of specific patient subpopulations (e.g. patients with and without oxygen therapy) and methods to characterise patients were not consistent. Therefore, no analyses of specific patient subpopulations could be made in this review.

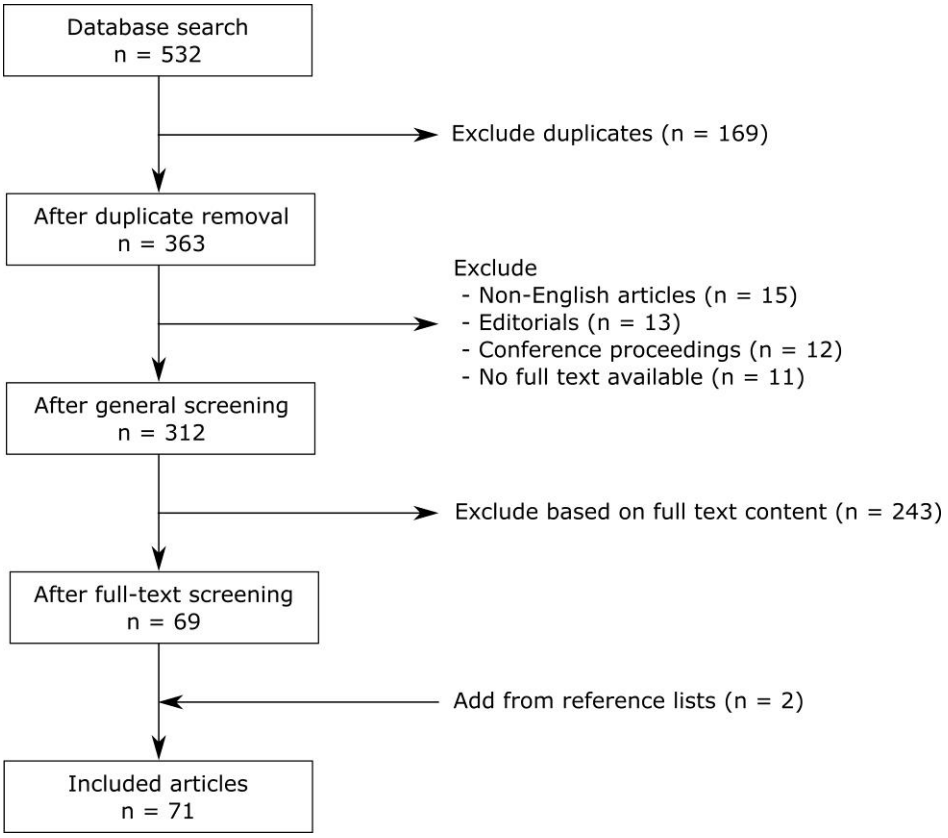


Figure 2.1: Article selection resulted in 71 included articles.

4.3. Measurements, oximeters, and telemonitoring systems

Forty-nine of the 50 included studies (98%) used pulse oximeters for spot check measurements. Continuous measurements were only performed in the study of Faria et al. [156] (sampling frequency not specified). Frequency of spot check measurements ranged from 3 times in 5 h to once weekly, with most of the studies measuring once daily (n = 38). Only three articles specified a protocol for performing the measurements. In Hurst et al. [95], participants performed SpO_2 measurements each morning at the same time after 10 min of rest, on the same finger, but before taking medication. The highest obtained value during the measurement was retained. Jódar-Sánchez et al. [157] specified that measurements were taken 20 min after taking medication while seated, rested, and on oxygen therapy. Shany et al. [158] had patients perform measurements after taking medications and while on oxygen therapy.

The pulse oximeter was specified in 26 of the 50 studies (Table 2.1). Almost half (n = 12) of the 26 specified oximeters are manufactured by Nonin Medical (7 Nonin Onyx; 1 Nonin Avant; 4 unspecified Nonin). Nonin Onyx is a finger clip oximeter for spot check measurements; Nonin Avant is a wrist worn device with a linked finger clip able to perform continuous measurements. Considering all studies, the oximeters were used in combination with 15 different types of telemonitoring systems (Table 2.1).

4.4. Application of SpO_2 measurements

In many studies, deviating SpO_2 values were used to raise alerts (SpO_2 alerts) that led to immediate action from healthcare professionals, ranging from phone calls to hospital admissions (n = 34; Table 2.1). Other studies developed methods to predict exacerbations through retrospective analysis of the measured SpO_2 values (n = 5). An additional retrospective analysis was also performed in three of the 34 studies that carried out immediate action [97, 126, 159]. The other 11 studies (i) did not specify the exact SpO_2 use during remote consultations (n = 5); or (ii) were set up for evaluation of a telemonitoring system and did not further use the measured SpO_2 values (n = 6).

4.5. SpO_2 alerts leading to immediate action

The SpO_2 alerts in the 34 studies that carried out immediate action were based on (i) abnormal values (n = 10; no further information was provided to describe what was considered to be an abnormal value), (ii) thresholds values (n = 23; as discussed in next paragraph), or (iii) the output of an algorithm (n = 1) (Table 2.1). This algorithm used oximetry measurements in combination with questionnaire answers and spirometry measurements to predict exacerbation probability. High probabilities raised alerts, but the exact algorithm was not further specified [160].

Two types of thresholds can be distinguished: generic (n = 6) or individualised (n = 12). Five studies did not specify the type of threshold (n = 5). Generic thresholds were fixed on one value (88% [161, 162], 90% [152–154] or 92% [163]) or on multiple values for a graded severity indication. Koff et al. [164] specified thresholds of 90% and 88%, Ho et al. [165] on 92% and 90% and Colantonio et al. [166] made the distinction between breathing room air (thresholds of 92% and 90%) and breathing O_2 (thresholds of 93%, 90% and 80%). Three studies that applied individual thresholds did not specify the method for determining the threshold values [127, 167, 168]**.** The other nine studies with individual thresholds based the threshold values on caregiver assessments or baseline measurements. Seven of these nine studies did not further clarify the exact determination of the threshold values. The other two studies denoted a quantitative method for determining the individualised threshold value: Segrelles Calvo et al. [169] set the threshold 3% below the average of first three measuring days. The articles originating from the EDGE project [126, 170–172] defined the threshold value as the 95% percentile of the cumulative density function of the measured values of the first six weeks.

4.6. Exacerbation prediction through retrospective analysis

Eight articles developed methods to predict exacerbations through retrospective analysis of the measured SpO_2 values: five originated from retrospective studies and three from studies that performed an additional retrospective analysis. Brown-Connolly used retrospective analysis to calculate the optimal generic threshold value by taking into account the accuracy of alerts to warn for hospitalisations, emergency admissions, and

home visits. A receiver operating characteristics analysis indicated 85–86% as the generic SpO_2 threshold with both the highest sensitivity (0.62) and specificity (0.91) [159].

The other seven articles extracted features from daily measured SpO_2 and used these features in addition to the measured SpO_2 values to retrospectively develop methods to predict exacerbations. Mohktar et al. [97] calculated four features, based on the combination of daily measurements and the measurements of the previous 30 days: 30-day distribution mean and standard deviation, percentage change of daily measured values compared to distribution mean, and the z-score of measured values compared to the 30-day distribution. The same features were calculated from five other variables (i.e. HR, blood pressure, lung function parameters, weight, and temperature), after which they were used as input for a classification and regression tree algorithm to predict next-day risk of exacerbation. Shah et al. [126] calculated mean and linear fit gradient from 7-day periods of SpO_2, HR, and respiratory rate to be used as input for a logistic classifier to predict exacerbations. Jensen et al. [173] and Riis et al. [98] calculated features based on differing types (mean, standard deviation, skewness, kurtosis or linear regression between SpO_2 and HR) and durations (ranging between 5 and 30 days) and used them for prediction of exacerbation risk in the following 30 days or as input for a k-nearest neighbour classifier for prediction of exacerbation onset, respectively. Hurst et al. [95] calculated an oximetry score, based on the z-scores of SpO_2 and HR from daily measurements compared to the distribution of measurements from the first 30 stable days. An oximetry-peak expiratory flow (PEF) score was calculated similarly by adding z-scores of PEF measurements to the equation. These scores were used to discriminate exacerbation onset from normal day-to-day symptom variations. Merone et al. [174] further specified this oximetry score by applying weights to the elements in the oximetry score formula and used this in a finite-state machine model for prediction of different types of adverse events (e.g. onset of exacerbation, hypoxemia, or dyspnoea). Last, Clarke et al. [175] decomposed time series of daily SpO_2 measurements of four patients in a long-term trend, a short-term trend, and a residual signal. In one patient, the declining long-term trend clearly indicated the worsening health status of this patient. The residual signal outperformed the short-term trend for exacerbation predictions.

4.7. Value of SpO_2 measurements

Most studies that carried out immediate action (n = 31) did not provide information about the correctness or effectiveness of the implemented SpO_2 alerts and only considered general, long-term outcomes of the whole telemonitoring setup (e.g. quality of life, morbidity, or healthcare costs). Three studies that carried out immediate action and five studies with retrospective analyses did quantitatively evaluate the performance of stand-alone SpO_2 measurement to detect or predict exacerbations (Table 2.2). Except for Hurst et al., alerts based on SpO_2 measurements performed better than alerts based on other physiological variables, as can be seen in Table 2.2 by means of the higher AUC [126, 159], the higher Cohen's kappa [97], because SpO_2 was better able to differentiate between exacerbation days or usual days [94], or because SpO_2 raised more accurate alerts [127, 169]. The four articles that examined the ability to predict exacerbations of both stand-alone SpO_2 measurements and of measurements of a combination of variables (including SpO_2), all found an increase in performance when other physiological variables were added to the measurements of SpO_2, indicated by the higher AUC [95, 126, 173] or Cohen's kappa [97] (Table 2.2).

Table 2.1: Overview of the 71 included articles, based on 50 individual studies. [a]

Author	Year	Participants (n)		FEV_1%pred (mean ± SD)		Study duration	Measuring frequency	Oximeter type	Telemonitoring systems	SpO_2 application
		TM	UC	TM	UC					
Vitacca [152]	2006	17 [b]		33 ± 16		176±69 days	1x/week	Nonin Onyx or 2500	Digicom 30 EM	Alert: Threshold – Generic (RC)
Vitacca [154]	2009	57[b]	44 [b]	39 ± 23	34 ± 16	12 months				
Vitacca [153]	2010	181 [b]		/		6/12 months				
Koizumi [155]	2005	2		/		12 months	1x/week	Nihon Kohden TX-001T	Nihon Kohden TMS 5002	No alert: Use not specified (RC)
Schou [146]	2013	22	22	39 ± 20	44 ± 15	2-8 days	Once daily	/	Touch screen PC	No alert: Use not specified (RC)
Schou [145]	2014	22	22	39 ± 20	44 ± 15	2-8 days				
Emme [148]	2014	25	25	31	29	1-11 days				
Jakobsen [147]	2015	28	29	/	/	/				
Sorknaes [151]	2013	132	134	33 ± 13	37 ± 14	5-9 days	Once daily	MIR Spirotel	/	No alert: Use not specified (RC)
Gottlieb [149]	2014	72		/		14 days	Once daily	/	/	No alert: Use not specified (RC)
Saleh [150]	2014	99		/		14 days	Once daily	/	Computer	No alert: Use not specified (RC)
Venter [176]	2012	10 [c]	10 [c]	/		12 months	/	TMC Health Monitor	TMC Health Monitor	Alert: Abnormal values
Jensen [173]	2012	57		/	/	4 months	Prescribed	Nonin Onyx	/	Retrospective analysis
Lilholt [177]	2015	60		/	/	2 months	2 weeks: 1x/day Afterwards: 1x/week	Nonin Onyx	Samsung Galaxy Tab 2	Alert: Abnormal values
Lilholt [178]	2016	60		/	/	2 months				
Haesum [179]	2016	60	56	48 ± 15	50 ± 18	2 months				
Stausholm [180]	2016	263	290	49 ± 17	48 ± 22	12 months				

Table 2.1: Continued.

Author	Year	Participants (n)		FEV_1%pred (mean ± SD)		Study duration	Measuring frequency	Oximeter type	Telemonitoring systems	SpO_2 application
		TM	UC	TM	UC					
Achelrod [160]	2016	651	7047	/	/	12 months	2x/week	/	/	Alert: Algorithm
Colantonio [166]	2015	26		38±10		115±40 days	3x/week	/	/	Alert: Threshold – Generic
Finkelstein [181]	2004	11 [b]	14 [b]	/	/	/	Once daily	Nonin	/	Alert: Threshold –Not specified
Finkelstein [182]	2006	11 [b]	14 [b]	/	/	/				
Lamothe [168]	2006	82 [c]		/		6-243 days	Once daily	Honeywell HomMed	Honeywell HomMed	Alert: Threshold – Individual
Smaradottir [183]	2015	6		/		7 days	Once daily	Nonin Onyx	Tablet	No alert: System evaluation
van der Heijden [184]	2013	5		/		9 days	Once daily	Nonin	Smartphone & Mobi	No alert: System evaluation
Cardozo [185]	2010	119[b]		/		60 days	Once daily	/	Bosch Health Buddy	Alert: Abnormal values
Hamad [186]	2016	183		/		80.7 days	Once daily	/	Docobo	Alert: Threshold – Not specified
Hurst [95]	2010	31		46 ± 23		87 days	Once daily	Nonin Onyx	/	Retrospective analysis
Davis [187]	2015	58 [b]	174 [b]	/		90 days	Once daily	/	Cardiocom	Alert: Abnormal values
Ho [165]	2016	53	53	62 ± 23	62 ± 21	2 months	Once daily	/	/	Alert: Threshold – Generic

Table 2.1: Continued.

Author	Year	Participants (n)		FEV_1%pred (mean ± SD)		Study duration	Measuring frequency	Oximeter type	Telemonitoring systems	SpO_2 application
		TM	UC	TM	UC					
Koff [164]	2009	20	20	34 ± 9	31 ± 10	3 months	Once daily	GE Healthcare Tuffsat	Bosch Health Buddy	Alert: Threshold – Generic
Gellis [188]	2012	11 [b]	15 [b]	/	/	3 months	Once daily	Honeywell HomMed	Honeywell HomMed	Alert: Abnormal values
Gellis [189]	2014	11 [b]	15 [b]	/	/	3 months				
Jodar-Sanchez [157]	2013	24	21	37 ± 13	38 ± 10	4 months	Once daily	MIR Spirotel	Aerotel TeleModem	Alert: Threshold – Individual
Jodar-Sanchez[190]	2014	24	21	/	/	4 months				
Ure [125]	2012	20		45 ± 21		6 months	Once daily	/	Touch screen PC	No alert: System evaluation
Burton [94]	2015	19		/		> 200 days				
Teijeiro [191]	2013	18		/		6 months	Once daily	/	Smartphone	No alert: System evaluation
De San Miguel [90]	2013	36	35	/	/	6 months	Once daily	/	Docobo	Alert: Threshold – Individual
Ding [192]	2014	10		51 ± 15		6 months	Once daily	/	Smartphone	No alert: System evaluation
Segrelles Calvo [169]	2014	29	30	/	/	6 months	Once daily	MIR Spirotel	Aerotel TeleModem	Alert: Threshold – Individual
MacNab [163]	2015	51		/		6 months	Once daily	/	/	Alert: Threshold – Generic
Kenealy [193]	2015	98 [c]	73 [c]	/		6 months	Once daily	/	Docobo	Alert: Threshold – Individual
McDowell [194]	2015	55	55	46 ± 14	43 ± 11	6 months	Once daily	Honeywell HomMed	Honeywell HomMed	Alert: Threshold – Individual

Table 2.1: Continued.

Author	Year	Participants (n)		FEV_1%pred (mean ± SD)		Study duration	Measuring frequency	Oximeter type	Telemonitoring systems	SpO_2 application
		TM	UC	TM	UC					
Chatwin [167]	2016	19 [b]	20 [b]	/		6 months	Once daily	/	Philips MOTIVA	Alert: Threshold – Individual
Brown-Connolly [159]	2014	34		/		> 6 months	Once daily	/	/	Alert: Threshold – Not specified
Zamith [195]	2009	21 [b]		/		9 months	Once daily	Smiths Medical BCI	Docobo	No alert: System evaluation
Steventon [196]	2016	467 [b]	446 [b]	/	/	10.4 months	Once daily	/	Tunstall MyMedic	Alert: Threshold – Not specified
Clarke [175]	2016	6		/		347.4 days	Once daily	/	/	Retrospective analysis
Martin-Lesende [127]	2013	28 [c]	30 [c]	/		12 months	Once daily	/	PDA	Alert: Threshold – Individual
Antoniades [197]	2012	22	22	/	/	12 months	Once daily	TMC Health Monitor	TMC Health Monitor	Alert: Abnormal values
Mohktar [97]	2015	21		34 ± 11		12 months				
Pinnock [84]	2013	128	128	44 ± 19	40 ± 17	12 months	Once daily	/	Touch screen PC	Alert: Threshold – Individual
Stoddart [198]	2015	128	128	44 ± 19	40 ± 17	12 months				
Steventon [199]	2012	739 [b]	786 [b]	/	/	12 months	Once daily	/	/	Alert: Threshold – Individual
Bardsley [200]	2013	549 [b]	520 [b]	/	/	12 months				
Henderson [201]	2013	334 [b]	244 [b]	/	/	12 months				
Rixon [202]	2015	334 [b]	244 [b]	/	/	4/12 months				
Vianello [87]	2016	230	104	/	/	12 months	Once daily	MCWC	/	Alert: Abnormal values

Table 2.1: Continued.

Author	Year	Participants (n)		FEV_1%pred (mean ± SD)		Study duration	Measuring frequency	Oximeter type	Telemonitoring systems	SpO_2 application
		TM	UC	TM	UC					
Shany [158]	2016	21	21	40 ± 13	32 ± 16	12 months	Once daily	TMC Health Monitor	TMC Health Monitor	Alert: Threshold – Not specified
Williams [172]	2014	19		/	/	6 months	Once daily	Nonin Onyx	Samsung Galaxy Tab 2	Alert: Threshold – Individual
Hardinge [171]	2015	18		/	/	6 months				
Velardo [170]	2017	110		/	/	12 months				
Shah [126]	2017	100		/	/	12 months				
Riis [98]	2016	108		/		2 years	Once daily	Nonin Onyx	Tunstall RTX 3371	Retrospective analysis
Esteban [203]	2016	119	75	46 ± 16	45 ± 15	2 years	Once daily	/	Smartphone	Alert: Threshold – Individual
Lewis [161]	2010	20	20	38 ± 16	40 ± 15	6 months	2x/day	Nonin	Docobo	Alert: Threshold – Generic
Chau [204]	2012	22	18	38 ± 13	38 ± 17	2 months	3x/day	IVT	Smartphone	Alert: Abnormal values
Merone [174]	2017	22		/		6 months	3x/day	/	Smartphone	Retrospective analysis
Pedone [205]	2013	50	49	53 ± 15	55 ± 16	9 months	5x/3hours	Nonin	Smartphone	Alert: Abnormal values
Faria [156]	2014	22 [b]		/		7.6 ± 4.5 days	Continuous	Nonin Avant	Smartphone	Alert: Abnormal values

SD = standard deviation; RC = remote consultation; TM = telemonitoring group; UC = usual care group; FEV_1%pred = percentage predicted of the forced expiratory volume in 1 s; MCWC = Medical Concierge Wrist Clinic. [a] Outdented articles originate from the same study as the article above. The articles are sorted by measuring frequency and study duration. [b] Non-COPD participants excluded. [c] Non-COPD participants included.

Table 2.2: Detection or prediction of exacerbations based on SpO_2 and other physiological measurements.

Author	Year	SpO_2	Other physiological variables	Combination of variables
Martin-Lesende [127]	2013	74.3% of all SpO_2-based alerts were generated in the five days prior to a hospitalisation	RR: 69.4% alerts generated prior hospitalisation Systolic BP: 38.9% alerts generated prior hospitalisation Diastolic BP: 36.1% alerts generated prior hospitalisation HR: 27.8% alerts generated prior hospitalisation Body weight: 31% alerts generated prior hospitalisation Temperature: 27.8% alerts generated prior hospitalisation	/
Segrelles Calvo [169]	2014	SpO_2 triggered an alert in 30 of 50 detected exacerbations	PEF: 7 of 50 alerts BP: 4 of 50 alerts	/
Burton [94]	2015	SpO_2 can differentiate between exacerbation days and usual days (p-value = 0.002) SpO_2 cannot differentiate between exacerbation days and isolated bad days (p-value = 0.61)	HR: cannot differentiate between exacerbation days and usual days (p-value = 0.12) HR: cannot differentiate between exacerbation days and isolated bad days (p-value = 0.22)	/
Brown-Connolly [159]	2014	Exacerbation prediction based on measured SpO_2 AUC = 0.693	Exacerbation prediction based on measured: BP: AUC = 0.553 HR: AUC = 0.540 Systolic BP: AUC = 0.540 Diastolic BP: AUC = 0.527	/
Shah [126]	2017	Exacerbation prediction based on mean and linear fit gradient over seven days of SpO_2: AUC = 0.658	Exacerbation prediction based on mean and linear fit gradient over seven days of: RR: AUC = 0.605 HR: AUC = 0.578	Exacerbation prediction based on mean and linear fit gradient over seven days of: SpO_2 + HR: AUC = 0.664 SpO_2 + RR: AUC = 0.672 SpO_2 + HR + RR: AUC = 0.682

Table 2.2: Continued

Author	Year	SpO_2	Other physiological variables	Combination of variables
Jensen [173]	2012	Exacerbation prediction based on SD over 25 days of SpO_2 AUC = 0.61	/	Exacerbation prediction based on linear regression between SpO_2 and HR over 30 days: AUC = 0.78 SpO_2 SD over 25 days + linear regression between SpO_2 and HR over 30 days: AUC = 0.73
Hurst [95]	2010	Exacerbation prediction based on measured SpO_2 AUC = 0.712	Exacerbation prediction based on measured: HR: AUC = 0.819 PEF: AUC = 0.805	Exacerbation prediction based on: oximetry score (SpO_2 + HR): AUC = 0.849 oximetry-PEF score (SpO_2 + HR + PEF): AUC = 0.897
Mohktar [97]	2015	Exacerbation prediction based on distribution mean of SpO_2 over 30 days Cohen's kappa = 0.27	Exacerbation prediction based on: FEV_1 SD: Cohen's kappa = 0.21 measured weight: Cohen's kappa = 0.21 measured FEV_1: Cohen's kappa = 0.18 weight distribution mean: Cohen's kappa = 0.15 weight SD: Cohen's kappa = 0.13 temperature percentage change: Cohen's kappa = 0.13 FEV_1 percentage change: 0.13 FEV_1 distribution mean: 0.11	Exacerbation prediction based on features of SpO_2, FEV_1, weight, temperature HR, RR: Cohen's kappa = 0.42 Accuracy = 71.8%

SpO_2: oxygen saturation; RR: respiratory rate; BP: blood pressure; HR: heart rate; PEF: peak expiratory flow; AUC: area under the curve; FEV_1: forced expiratory volume in 1 s; SD: standard deviation.

5. Discussion

This systematic review identified and evaluated the use of SpO_2 measurements in telemonitoring of patients with COPD. In many studies, daily SpO_2 measurements were performed for more than 6 months, indicating that long-term follow-up of COPD patients using daily SpO_2 measurements is practically feasible. However, very few studies specified protocols for performing the measurements. Often the used oximeter was not mentioned. When specified, the oximeters from Nonin Medical were most frequently used. Overall, participant numbers were relatively low and the articles had no consistent method for characterising the included patients.

In many studies, deviating SpO_2 values were used to raise alerts that led to immediate action from healthcare professionals (e.g. patient visits or hospital admissions). However, little information has been made available about the exact implementation of these alerts. Almost a third of the studies carrying out immediate action indicated that alerts were based on abnormal values, without further specifying when values were considered abnormal. Other alerts were based on exceeded threshold values, but these values were often not specified or only based on unspecified caregiver assessments. In addition, little attention was given to the optimal implementation of alerts. When generic threshold values were specified, they ranged between 88% and 92%. However, the retrospective analyses of Brown-Connolly suggested lower values (85–86%) as the optimal SpO_2 threshold [159]. Moreover, COPD patients are generally considered a very heterogeneous population [206] with an overall decline in health status [207] and a variable baseline SpO_2 [175]. Generic thresholds cannot take this variability into account. It can thus be assumed that individualised, time-dependent thresholds (i.e. personal thresholds that can change over time) will outperform generic thresholds [186]. Individualised thresholds were already implemented in some studies that carried out immediate action, but except for Segrelles Calvo et al. [169] and the articles originating from the EDGE project [126, 170–172], no information was provided on how these thresholds were determined. All these elements illustrate the current lack of knowledge and transparency concerning alert implementations.

The studies with retrospective analyses focused more on alert optimisations. Brown-Connolly used retrospective analyses to calculate the optimal generic threshold value [159]. The other retrospective studies calculated additional features from daily measured SpO_2 values and used these features to retrospectively predict exacerbations by applying thresholds to the feature values or by using the features as input for predictive algorithms. The calculated features were based on a combination of individual present-day values and individual values from the last week or month, which allowed accounting for both individual differences and longer-term health status changes. This is important because general health status changes can lead to a different baseline SpO_2 [175]. A decline in baseline SpO_2, not related to exacerbations, could thus lead to a high number of false alerts when the individual thresholds are not able to change accordingly. In addition, these features have the possibility to provide valuable information about the general, long-term health status of the monitored patients, as has been suggested by Clarke et al. [175]. Surprisingly, most of the calculated features were still based on simple, basic statistics such as mean, standard deviation or a linear fit gradient of past periods [97, 98, 126, 173]. Only Clarke et al. [175] approached the daily measurements as a time series. The authors proposed a method to monitor both health status and the onset of exacerbations by using specific time-series analyses. However, their method is derived from data of only 4 patients and thus needs further validation.

Little information was provided about the correctness and effectiveness of the SpO_2 alerts in studies that performed immediate action, as these studies mostly only considered general, long-term outcomes of the whole telemonitoring setup (e.g. quality of life, morbidity or healthcare costs). Nonetheless, the three articles that did evaluate the performance of SpO_2-alerts quantitatively, indicate that these alerts could have the potential to detect or predict exacerbations: Martin-Lesende et al. [127] found that SpO_2 alerts were mostly triggered in the 5 days prior to hospitalisation; Segrelles Calvo et al. [169] found that most alerts for exacerbations were triggered by SpO_2; and Burton et al. [94] indicated that SpO_2 measurements could differentiate between exacerbation days and regular days. The retrospective analyses provide more information about the value of SpO_2 measurements and indicate that stand-alone SpO_2 measurements could have predictive power for exacerbations. Furthermore, the results in Table

2.2 suggest that exacerbation predictions based on stand-alone SpO_2 measurements perform better than predictions based on measurements of other standalone physiological variables. Nevertheless, adding other physiological variables to SpO_2 measurements can increase performance. A combination of SpO_2 and HR might be especially valuable, having the additional advantage that both can be calculated from the same PPG signal as measured by oximeters [144].

Overall, this systematic review identified multiple shortcomings of the included articles concerning the SpO_2 measurements and applications: measurement protocols and used oximeters were often not specified, participant numbers were generally low, little information was available about the implementation and performance of the alerts and alert implementations were not optimised. Therefore, no firm conclusions can be drawn on the real value of SpO_2 measurements. Nevertheless, the few studies that assessed the value of SpO_2 measurements indicated that these measurements could be valuable for exacerbation detections or predictions. Still, future research could optimise alerts based on regular SpO_2 measurements by using individualised, time-dependent thresholds or predictive algorithms to account for individual differences and SpO_2 baseline changes.

This systematic review identified only one study that performed continuous SpO_2 measurements [156]. According to the authors of this review, future research should consider performing more continuous measurements of SpO_2 instead of spot checks, possibly in combination with measurements of other variables that acutely influence SpO_2 (e.g. physical activity and sleep [156])**.** This will provide a completer picture of the dynamics of SpO_2, which can further lead to new features that can be used to determine individualised and time-dependent thresholds or predictive algorithms. Additionally, these measurements and features could be used to optimise oxygen therapy or training intensities in tele-rehabilitation programs [208]. In the study of Faria et al., patients treated according to conventional methods for long-term oxygen therapy carried out simultaneous continuous measurements of SpO_2 and physical activity during activities of daily living, in combination with continuous SpO_2 measurements during sleep [156]. Low SpO_2 values were still found in continuous measurements during exercise, rest, and sleep, indicating that current long-term oxygen therapy guidelines (based on spot check

measurements) could further be optimised by using continuous measurements. The dynamics of continuously measured SpO_2 have so far only been examined during sleep in laboratory conditions, for example, in obstructive sleep apnoea [209] or apnoea-hypopnea syndrome diagnosis [210]. In these studies, new insights were obtained by calculating a variety of features from continuously measured nocturnal SpO_2.

Future research should assess the real value of continuous measurements through a formal comparison between spot check and continuous measurements, also considering differences in, for example, user acceptance or costs. Technological improvements can still increase the accuracy of continuous measurements taken with user friendly wearable devices (e.g. accurate measurements on the wrist, arm, or earlobe).

6. Conclusions

This review evaluates the scientific literature on the application of SpO_2 measurements in telemonitoring of patients with COPD. The results indicate that long-term follow-up of COPD patients using daily spot check SpO_2 measurements is practically feasible. However, very few studies specified protocols to perform SpO_2 measurements. In many studies, deviating SpO_2 values were used to raise alerts that led to immediate action from healthcare professionals. Other studies developed methods to predict exacerbations through retrospective analysis of the measured SpO_2 values.

Little information was available about the exact implementation and performance of these alerts. Therefore, no firm conclusions can be drawn about the real value of SpO_2 measurements. Nevertheless, the few studies that assessed the value of SpO_2 measurements indicated that these measurements could be valuable for exacerbation detections or predictions.

Future research could optimise alerts based on daily measured SpO_2 by using individualised, time-dependent thresholds or predictive algorithms to account for individual differences and SpO_2 baseline changes. Additionally, the value of performing more continuous measurements should be examined, as these can make it possible to examine the SpO_2 dynamics and account for factors that acutely influence the measurements (e.g. physical activity or sleep).

7. Expert commentary

The demographic shift toward an older population contributes to the increased burden of chronic noncommunicable diseases. These diseases are becoming more prominent causes of morbidity and mortality, and the treatment costs will keep increasing. New ways of managing chronic diseases are necessary to reach a sustainable healthcare system, including a shift in focus from treatment only toward prevention. Prevention does not only include keeping diseases from developing, it also includes preventive actions to gain control over the course of the disease. For the latter, telemonitoring can be used to timely indicate when preventive actions are required. Unfortunately, telemonitoring is not yet generally accepted because of a lack of compelling evidence of its beneficial long-term effects on healthcare costs, morbidity, or mortality.

This lack of evidence is not surprising. Until now, very little attention has been directed toward the optimal exploitation of the gathered data, as has been confirmed by the results of this review. Standardisations, data science techniques, and advancing technology can still boost performance of telemonitoring applications. Better performances will lead to higher acceptance, providing more opportunities to embed telemonitoring applications in daily practice, ultimately leading to a more sustainable healthcare system.

This review exposed some of the opportunities to increase performance of telemonitoring applications that measure SpO_2 in COPD patients. Telemonitoring of patients with COPD is mostly applied for detection of exacerbations to enable earlier and better treatment, but exacerbation detection has not been proven sufficiently accurate yet. A first step that must be taken to reach acceptable accuracies is the standardisation of the SpO_2 measurements. Very few articles provide information about a protocol to perform the measurements, which leads to unwanted variability in the measured values. Second, only articles with retrospective analyses explored some of the possibilities of data science techniques. This makes it impossible to assess the real added value of data science on longer-term outcomes such as healthcare costs or mortality. In addition, the applied techniques were mostly only based on simple, basic statistics such as means or standard deviations. More advanced data analysis techniques using time series analyses and predictive modelling should be applied in studies that

can initiate immediate action to explore the real potential of telemonitoring in patients with COPD. Last, the advancing technology can make it possible to accurately measure SpO_2 continuously instead of through spot checks only. This will allow exclusion of unwanted influences on the measurements (e.g. physical activity) and provide a completer picture of the dynamics of SpO_2 during the day and/or night. Applying the appropriate analyses on these continuous measurements can give rise to a whole new set of individualised and time-dependent features that can further improve the performance of telemonitoring applications. Only when all these opportunities are thoroughly explored, the real value of telemonitoring SpO_2 in COPD patients can be assessed.

8. Five-year view

No firm conclusions can be drawn about the real value of SpO_2 measurements in telemonitoring applications because many improvements that could lead to better performances are still underexplored. Therefore, the focus of future research will be increasingly on incorporating data science techniques in telemonitoring applications for COPD patients. The use of more complex predictive algorithms will improve exacerbation predictions and the constant technological advancements will make it possible to use wearables to continuously and accurately measure SpO_2 without interfering in the patient's daily life. Using appropriate data science techniques on these continuous SpO_2 measurements can further boost the performance of telemonitoring applications, which will ultimately lead to a higher acceptance of telemonitoring applications in daily practice.

9. Key issues

- Long-term follow-up of COPD patients using daily spot check measurements of SpO_2 is practically feasible.
- Very few studies specified protocols to perform SpO_2 measurements.
- In many studies, deviating SpO_2 values were used to raise alerts that led to immediate action from healthcare professionals. Other studies developed methods to predict exacerbations through retrospective analysis of the measured SpO_2 values.
- Little information was available about the exact implementation and performance of SpO_2 alerts.
- No firm conclusions can be drawn about the real value of SpO_2 measurements. Nevertheless, the few studies that assessed the value of SpO_2 measurements indicated that these measurements could be valuable for exacerbation detections or predictions.
- Future research could optimise alerts based on daily measured SpO_2 by using individualised, time-dependent thresholds or predictive algorithms to account for individual differences and SpO_2 baseline changes.
- The value of performing more continuous measurements should be examined, as these measurements can make it possible to examine the SpO_2 dynamics and account for factors that acutely influence the measurements (e.g. physical activity or sleep).

Chapter 3 – Wearable finger pulse oximetry for continuous oxygen saturation measurements during daily home routines of patients with Chronic Obstructive Pulmonary Disease (COPD) over one week: Observational study

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This Chapter reports on the findings of a telemonitoring study that was carried out during this PhD research. During this study, 20 patients with COPD used wearable finger pulse oximeters to continuously measure SpO_2 over one week during daily home routines in order to assess natural SpO_2 fluctuations within and between multiple days and nights. The results of this Chapter, combined with the results of Chapter 2, address the first objective of this dissertation.

1. Abstract

Background: Chronic obstructive pulmonary disease (COPD) patients can suffer from low blood oxygen concentrations. Peripheral blood oxygen saturation (SpO_2), as assessed by pulse oximetry, is commonly measured during the day using a spot check, or continuously during one or two nights to estimate nocturnal desaturation. Sampling at this frequency may overlook natural fluctuations in SpO_2. This study used wearable finger pulse oximeters to continuously measure SpO_2 during daily home routines of COPD patients and assess natural SpO_2 fluctuations.

Methods: A total of 20 COPD patients wore a $WristOx_2$ pulse oximeter for 1 week to collect continuous SpO_2 measurements. A SenseWear Armband simultaneously collected actigraphy measurements to provide contextual information. SpO_2 time series were pre-processed and data quality was assessed afterward. Mean SpO_2, SpO_2 SD, and cumulative time spent with SpO_2 below 90% (CT90) were calculated for every (1) day, (2) day in rest, and (3) night to assess SpO_2 fluctuations.

Results: A high percentage of valid SpO_2 data (daytime: 93.27%; nocturnal: 99.31%) could be obtained during a 7-day monitoring period, except during moderate-to-vigorous physical activity (MVPA) (67.86%). Mean nocturnal SpO_2 (89.9%, SD 3.4) was lower than mean daytime SpO_2 in rest (92.1%, SD 2.9; P<.001). On average, SpO_2 in rest ranged over 10.8% (SD 4.4) within one day. Highly varying CT90 values between different nights led to 50% (10/20) of the included patients changing categories between desaturator and non-desaturator over the course of 1 week.

Conclusions: Continuous SpO_2 measurements with wearable finger pulse oximeters identified significant SpO_2 fluctuations between and within multiple days and nights of patients with COPD. Continuous SpO_2 measurements during daily home routines of patients with COPD generally had high amounts of valid data, except for motion artefacts during MVPA. The identified fluctuations can have implications for telemonitoring applications that are based on daily SpO_2 spot checks. CT90 values can vary greatly from night to night in patients with a nocturnal mean SpO_2 around 90%, indicating that these patients cannot be consistently categorised as desaturators or non-desaturators. We recommend using wearable sensors for continuous SpO_2 measurements over longer time periods to determine the clinical relevance of the identified SpO_2 fluctuations.

2. Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent lung disease that is characterised by persistent airflow limitation due to a mixture of obstructive bronchiolitis and emphysema [1]. Morbidity and mortality of COPD are high and still increasing [7], leading COPD to become the third-leading cause of death worldwide by 2030 [3]. COPD patients can suffer from low blood oxygen concentrations due to gas exchange abnormalities [1]. Hypoxemia during the night (i.e. nocturnal desaturation) is also common in patients with COPD [114, 211, 212] due to nocturnal alveolar hypoventilation and ventilation-perfusion mismatching [213]. Hypoxemia can worsen with increasing disease severity [34]. Furthermore, it has been shown that hypoxemia is associated with lower exercise tolerance; decreased quality of life; increased risk for exacerbations, defined as "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations" [6]; and higher risks of death [34].

The presence of hypoxemia can be assessed by invasive blood gas analyses. A non-invasive method to assess peripheral blood oxygen saturation (SpO_2) is pulse oximetry. Spot check SpO_2 measurements with thresholds of 88%-92% have been suggested for the detection of hypoxemia [1, 112, 214]. In telemonitoring applications, daily SpO_2 spot checks are used to raise alerts for exacerbations when SpO_2 spot check values drop below predefined SpO_2 thresholds [215]. Nocturnal desaturation is usually defined as having an SpO_2 value below 90% for more than 30% of the time in bed, measured during one [115, 212, 216–218] or two nights [114, 116, 219–221].

The current SpO_2 monitoring strategies do not take into account natural fluctuations in SpO_2. Sampling SpO_2 with such a low time frequency or during such a short time period may thus lead to classification errors (i.e. hypoxemic or non-hypoxemic and nocturnal desaturator or non-desaturator) or false alerts in telemonitoring applications [215]. Wearable finger pulse oximeters provide the possibility to collect SpO_2 data at higher time frequencies and over longer time periods. This makes it possible to assess and account for oxygen saturation fluctuations in patients with COPD. Therefore, the objective of this study was to use wearable finger pulse oximeters to continuously measure SpO_2 during daily home routines

of COPD patients and assess natural SpO_2 fluctuations. We hypothesised that significant natural SpO_2 fluctuations are present within and between multiple days and nights, which may lead to classification errors (i.e. nocturnal desaturator or non-desaturator) or false alerts in telemonitoring applications.

3. Methods

3.1. Study design and participants

Figure 3.1 provides a general overview of the methods applied in this single-centre, 1-week observational study. COPD patients at Global Initiative for Chronic Obstructive Lung Disease stages II-IV (GOLD II-IV) were recruited at the Centre of Expertise for Chronic Organ Failure (CIRO), a COPD treatment centre located in Horn, the Netherlands, during a standard baseline assessment prior to pulmonary rehabilitation [222]. The target sample size was set a priori to 20 patients. COPD patients were eligible to enrol in the study based on the following criteria: (1) clinically stable (i.e. no exacerbation in the past 4 weeks), (2) no rollator use, and (3) no long-term oxygen therapy. Patients that were interested in participating were called a few days after the baseline assessment to schedule a home visit for the delivery of the wearable sensors. During this visit, the functioning of the sensors and data acquisition protocol were explained, written informed consent was obtained, and a new visit was planned for collection of the sensors at the end of the study period. During the 7-day study period, which took place before the start of pulmonary rehabilitation, two phone calls were made to resolve potential technical difficulties. Demographics, oxygen partial pressure in arterial blood (PaO_2), postbronchodilator pulmonary function data (i.e. forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], and transfer factor for carbon monoxide [TLCO]), six-minute walking distance (6MWD), and COPD assessment test (CAT) results were collected during the standard baseline assessment at CIRO. The study was approved by the Medical Research Ethics Committees United (MEC-U) (study approval number: NL58079.100.16) in the Netherlands and executed between December 2016 and April 2018.

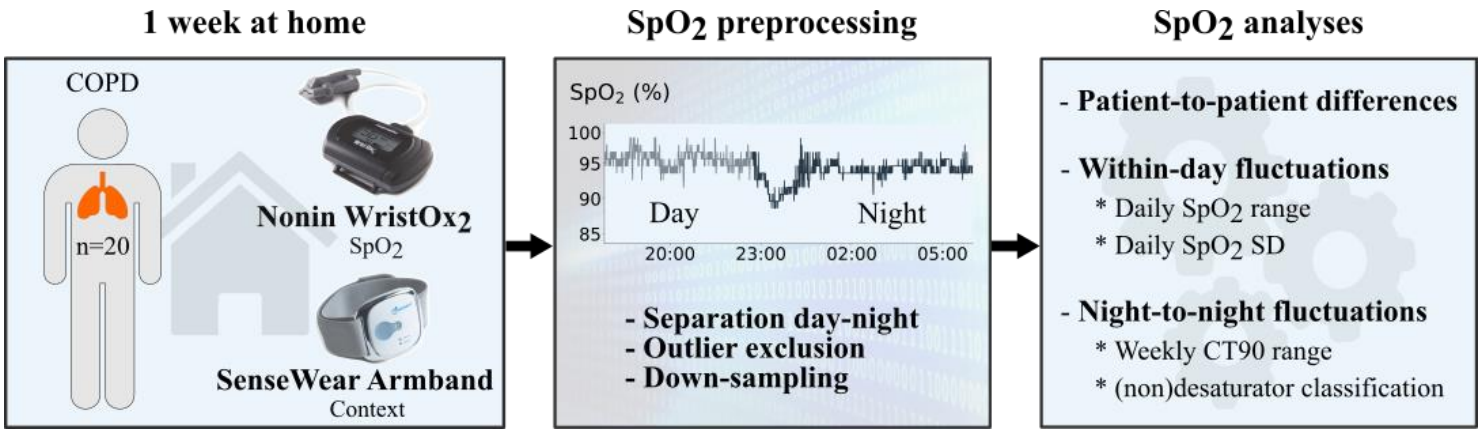


Figure 3.1: General overview of the applied methods. COPD = chronic obstructive pulmonary disease; SpO_2 = peripheral blood oxygen saturation; CT90 = cumulative time spent with SpO_2 below 90%.

3.2. Wearable sensors and protocol

Continuous SpO_2 measurements were performed for 1 week using a wearable finger pulse oximeter: $WristOx_2$ 3150 (Nonin Medical). Nonin oximeters have frequently been used for home monitoring of patients with COPD [215] and the $WristOx_2$ 3150 model complies with the International Organisation for Standardisation (ISO) standards ISO 10993-1 and ISO 80601-2-61. The manufacturer reports an accuracy of ±2% for SpO_2 measurements [223]. Sampling frequency was fixed at 1 Hz. Only the cumulative measurement time was visible for the participants. SpO_2 values were not shown on the $WristOx_2$ display to prevent patients from changing their behaviour when deviating SpO_2 values would occur. Every participant received three $WristOx_2$ devices to deal with the limited battery life (i.e. 48 hours of continuous measurements with one $WristOx_2$). Participants were instructed to wear the $WristOx_2$ on the index finger of their nondominant hand every night and as much as possible during the day, depending on their daily routines and comfort of wearing the finger clip. Raw data were stored on the internal memory of the $WristOx_2$ and downloaded at the end of the week using nVISION software, version 6.4.0.10 (Nonin Medical).

Simultaneously, actigraphy was performed with the SenseWear Armband (BodyMedia) for obtaining contextual information about physical activity levels and when the participants were lying down and/or asleep. The SenseWear Armband is a multisensory triaxial accelerometer, combining accelerometery with measurements of heat flux, galvanic skin response, and skin temperature. Based on these measurements, the armband provides information about, for example, energy expenditure (EE), expressed as metabolic equivalent of task (MET), or steps taken, while also indicating when the wearer is lying down and sleeping, at a standard sampling time of 1 sample per minute. Measurements of MET were used for classifying physical activity levels, whereas the indications of lying down and sleeping were used to separate daytime measurements from nocturnal measurements, as further described below. The SenseWear Armband has been shown to be accurate for measurements of both physical activity [224, 225], except when using a rollator [225], and sleep estimations [226]. Patients were asked to wear the armband on the left upper arm, except when there was contact with water (e.g. when taking a shower). Battery life

of one SenseWear Armband was sufficient for continuous 24-hour measurements with a 1-minute sampling time during the whole week. Data were stored on the internal memory and downloaded at the end of the week using the BodyMedia SenseWear 8.1 software (BodyMedia).

3.3. Data pre-processing

Figure 3.2 visualizes the pre-processing steps. The SenseWear Armband indications about lying down and sleep were used to determine the time of going to bed in the evening and the time of getting out of bed in the morning. These time stamps were used to divide SpO_2 data into nocturnal and daytime data (see Figure 3.2A). Only full-night nocturnal SpO_2 measurements were retained for further analyses and daytime SpO_2 measurements were retained if there was at least one hour of SpO_2 measurements during that day. One hour of daytime measurements was considered sufficient to examine whether significant fluctuations occurred in SpO_2 values during the day. Previous studies examining intraday fluctuations only examined measurements of one hour or less [227–230]. No days or nights had to be excluded due to lacking SenseWear Armband measurements. Days with at least one hour of measurements in both the afternoon and evening were used for the comparison between afternoon (i.e. 13:00-18:00) and evening (i.e. 18:00-going to bed) SpO_2 values. No comparison was performed between SpO_2 values in the morning (i.e. before 13:00) and the afternoon and evening, because SpO_2 measurements were often not performed before 13:00 (see Supplementary Figure 3.1).

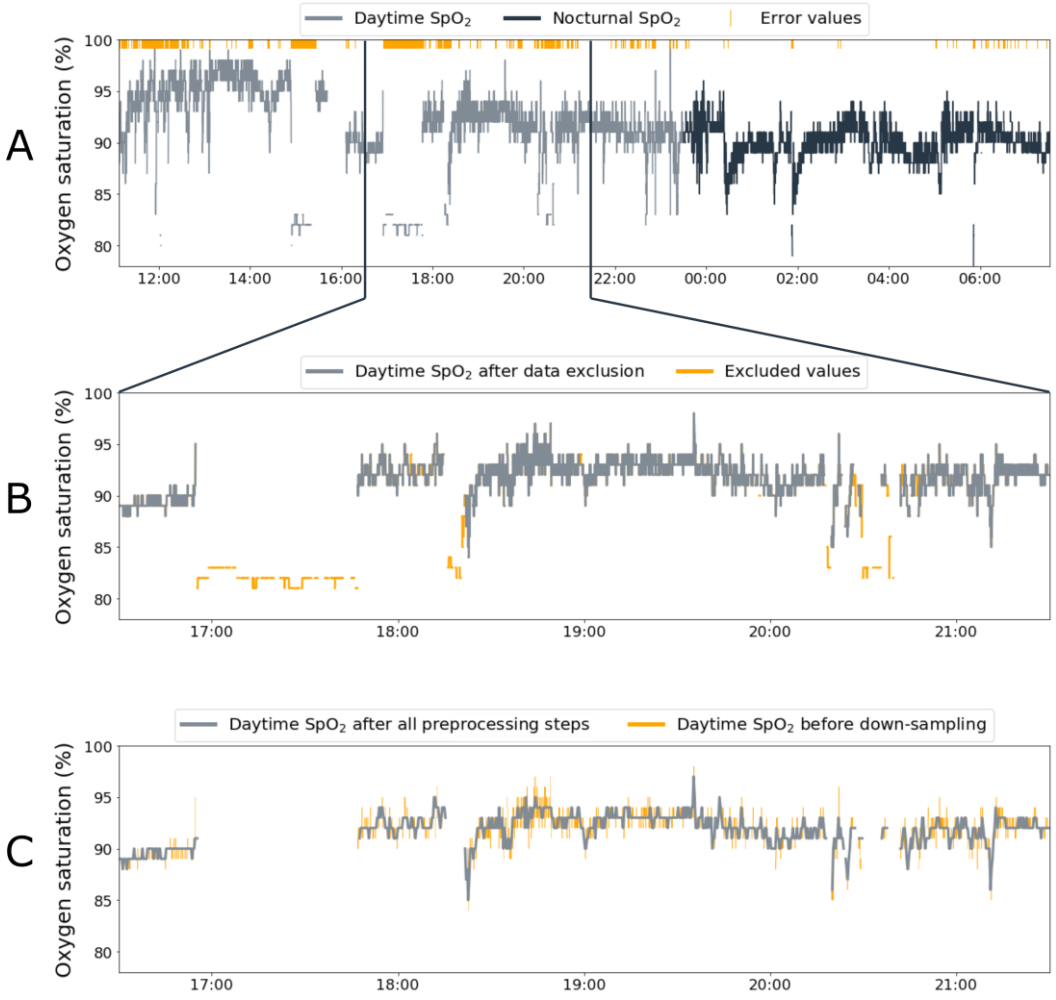


Figure 3.2: Visualization of the different pre-processing steps. Panel A shows all original data, containing error values, that are divided into daytime and nocturnal data. Panel B zooms in on the effect of data exclusion on a specific part of daytime peripheral blood oxygen saturation (SpO_2) data. Panel C zooms in on the effect of down-sampling and interpolating on the same part of daytime SpO_2 data.

The raw SpO_2 data contained error values (i.e. the number 500 was provided in the raw data file) when measurements were considered invalid by the algorithms of the $WristOx_2$ manufacturer (i.e. orange dashes in Figure 3.2A). However, close inspection of the time series indicated that invalid data (e.g. sudden low values) surrounded these error values. A data-cleaning algorithm was developed to exclude these invalid SpO_2 values as follows. First, small blocks of data (i.e. less than 20 samples) between error values were excluded. Second, bigger blocks of data (i.e. between 20 and 100 samples) between error values were excluded, only when the mean SpO_2 value of this data block was deviating more than 6% from the mean SpO_2 value of the full day or night under consideration: both steps are shown in Figure 3.2B. Thorough visual and raw data examination of both valid and invalid data led to the choice of this 6% threshold for excluding invalid blocks of data (e.g. Figure 3.2B**:** around 17:00-18:00). Third, remaining outliers were excluded by down-sampling the data (see Figure 3.2C). Autocorrelation analyses indicated that a sampling time of 20 seconds was appropriate (see Supplementary Text 3.2) and all data were thus down-sampled by taking the median SpO_2 value of each consecutive 20-second block. By taking the median value, the effect of outliers was excluded. As a last step, small gaps of SpO_2 data (i.e. 3 or fewer missing samples) were filled using linear interpolation (see Figure 3.2C). After application of the data-cleaning algorithm, all data were visually checked to ensure valid SpO_2 values were retained, while invalid values were removed.

3.4. Data analyses

The SenseWear Armband indications about lying down and sleep were used to calculate the total night sleeping time (TNST) (i.e. sum of all minutes indicated as sleep), wake time after sleep onset (WASO) (i.e. sum of all minutes spent awake during the time in bed, after the first onset of sleep), and sleep efficiency (Seff) (i.e. the ratio between TNST and time in bed) for every separate night. Weekly averages of TNST, WASO, and Seff were calculated to describe the sleep quality of the included patients.

Daytime SpO_2 data were divided into daytime data during rest ($EE \leq 1.5$ MET, while the patient was still awake), during low-intensity physical activities (LIPAs) ($1.5 \text{ MET} < EE \leq 3$ MET), and during moderate-to-vigorous intensity physical activities (MVPAs) ($EE > 3$ MET). Data quality of the

continuous SpO_2 measurements was assessed for both nocturnal and daytime data based on the amount of valid data (i.e. excluding error values and cleaned values). Furthermore, the effect of physical activity on the amount of valid data was examined by comparing data quality during MVPA with data quality during rest and LIPA (EE≤3 MET).

Mean SpO_2, SpO_2 SD, and cumulative time spent with SpO_2 below 90% (CT90) were calculated for every separate (1) day, (2) day in rest, and (3) night. Hereafter, the weekly average and weekly range (i.e. the difference between the maximum and minimum value over the different days or nights of the same patient) of these features were calculated for every patient.

Intraday and intranight fluctuations were quantified as the weekly average of the standard deviation of the SpO_2 measurements. The range of SpO_2 values during the day in rest, calculated as the difference between the maximum and minimum SpO_2 values of that day in rest, was determined to indicate how much spot-check values in telemonitoring applications could differ depending on the moment of the measurement. Only daytime SpO_2 in rest was considered because only at these moments could spot checks have been performed in a telemonitoring application. In addition, the difference between mean SpO_2 values in rest in the afternoon (i.e. between 13:00 and 18:00) and in the evening (i.e. between 18:00 and going to bed) was calculated for every day separately to examine differences in SpO_2 baseline levels during the day.

Night-to-night and day-to-day SpO_2 fluctuations were quantified as the weekly ranges of the three features (i.e. mean SpO_2, SpO_2 SD, and CT90). Furthermore, we examined how many of the included patients changed category between nocturnal desaturator and non-desaturator.

3.5. Statistical analyses

Patient characteristics, weekly averages, and weekly ranges were summarised for all patients as mean and SD. Paired-sample t tests were used to test for differences between weekly averages of nocturnal and daytime SpO_2 in rest. Pearson correlations assessed the relationship between mean SpO_2 and patient characteristics, intraday SpO_2 fluctuations, or intranight SpO_2 fluctuations. A P value of <.05 was considered statistically significant. All analyses were carried out in Jupyter Notebooks (Project

Jupyter) using the Python 3.5 programming language (Python Software Foundation).

4. Results

4.1. Participants

A total of 21 out of 41 patients that were approached accepted study participation. One patient suffered from an exacerbation before the start of the 7-day study period and was excluded. This finally led to the inclusion of 20 patients (14 males, 70%; 6 females, 30%) with moderate (8/20, 40%), severe (10/20, 50%), or very severe (2/20, 10%) COPD. General demographics, postbronchodilator lung function, resting arterial blood gases, 6MWD, CAT score, and sleep-quality characteristics are summarised in Table 3.1.

Table 3.1: Characteristics of the 20 included patients with moderate to very severe COPD.

	Value mean (SD)
Age (years)	63 (8)
Body Mass Index (kg/m^2)	26 (4)
Forced expiratory volume in 1 second (l)	1.4 (0.5)
Forced expiratory volume in 1 second (% predicted)	48 (15)
Forced vital capacity (l)	3.8 (1.1)
Forced vital capacity (% predicted)	97 (20)
Transfer factor for carbon monoxide (% predicted)	50 (16)
Partial pressure of oxygen (kPa)	8.7 (1.7)
Partial pressure of carbon dioxide (kPa)	5.2 (0.6)
Six-minute walking distance (m)	411 (59)
COPD assessment test	21 (5)
Total night sleeping time (min)	411 (72)
Wake after sleep onset (min)	74 (36)
Sleep efficiency (%)	83 (8)

4.2. Continuous SpO_2 measurements, pre-processing, and data quality

An overview of the amount of SpO_2 measurements that were included for further analyses is provided in Table 3.2 and Supplementary Figure 3.1. A total of 2 days and 2 nights of measurements from patient 4 were missing due to battery issues. A total of 3 days and 3 nights of measurements from patient 11 were excluded because correct time stamps were missing, due to the patient unintentionally resetting the time indication by taking out the batteries. The last day and night of patient 11's measurements could not be analysed because no clear distinction could be made between daytime and nocturnal data. Still, 3 days and 3 nights of patient 11's measurements were used for further analyses.

Table 3.2: Summary of the amount of peripheral oxygen saturation (SpO_2) measurements that were included for further analyses. All 20 patients performed nocturnal measurements and 17 patients performed daytime measurements. Therefore, averages were calculated with n=17 for daytime measurements and n=20 for nocturnal and total measurements.

	Value mean (SD)
Days per patient	5.3 (1.8)
Nights per patient	5.9 (1.2)
Hours per day	7.8 (3.9)
During rest (EE ≤ 1.5 MET)	6.1 (3.1)
During LIPA (1.5 MET < EE ≤ 3 MET)	1.5 (2.7)
During MVPA (EE > 3 MET)	0.2 (0.2)
Hours per night	8.0 (0.9)
Data samples per patient	296533 (95580)
During the day	149665 (88909)
During the night	169318 (35488)

LIPA = low-intensity physical activity; MVPA = moderate-to-vigorous physical activity; EE = energy expenditure; MET = metabolic equivalent of task

The SpO_2 dataset contained 1.83% error values and an additional 1.49% were excluded during the first two steps of the data-cleaning algorithm (see Figure 3.3), resulting in 96.68% of valid data. Nocturnal data had 99.31% of valid data (0.45% error data and 0.24% cleaned) compared to 93.27% of valid data during the day (3.62% error data and 3.11% cleaned). This was similar when only considering daytime data during rest and LIPA (EE≤3 MET; 93.90% of valid data: 3.25% error data and 2.85% cleaned). However, during MVPA (EE>3 MET), the amount of valid data decreased to 67.86% (18.34% error data and 13.80% cleaned).

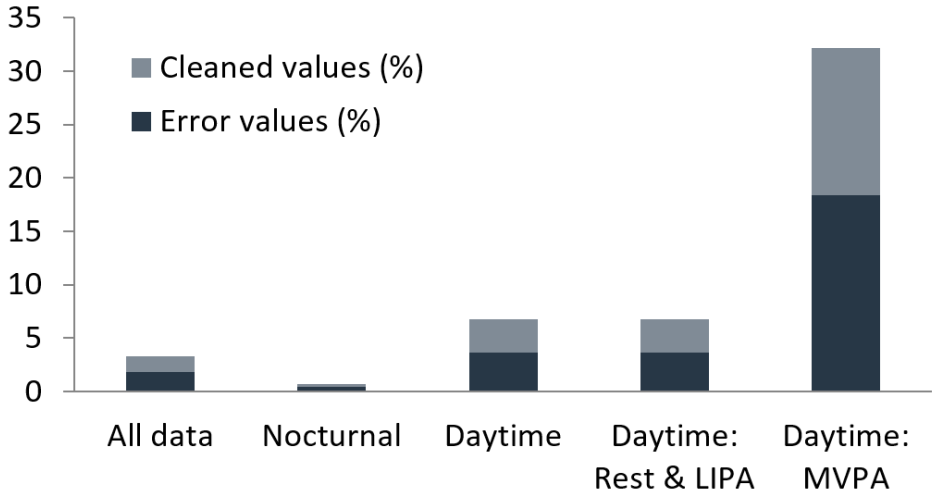


Figure 3.3: The amount of invalid data of continuous peripheral blood oxygen saturation (SpO_2) measurements for different activities. LIPA = low-intensity physical activity; MVPA = moderate-to-vigorous physical activity.

4.3. SpO_2 features and fluctuations

The weekly averages of mean SpO_2 were 89.9% (SD 3.4), 91.9% (SD 3.1), and 92.1% (SD 2.9) for nocturnal (n=20), daytime (n=17), and daytime-in-rest (n=17) measurements, respectively. Figure 3.4 shows that mean nocturnal SpO_2 was lower than mean daytime SpO_2 in rest (P<.001). Weekly averages of mean SpO_2 were between 84.7% and 96.0% for daytime SpO_2 in rest and between 80.3% and 94.3% for nocturnal SpO_2 (see Figure 3.4). The weekly averages of CT90 were 35% (SD 34), 20% (SD 29), and 18% (SD 29) for nocturnal, daytime, and daytime-in-rest measurements, respectively. No significant correlations were found between patient characteristics and weekly averages of the SpO_2 features.

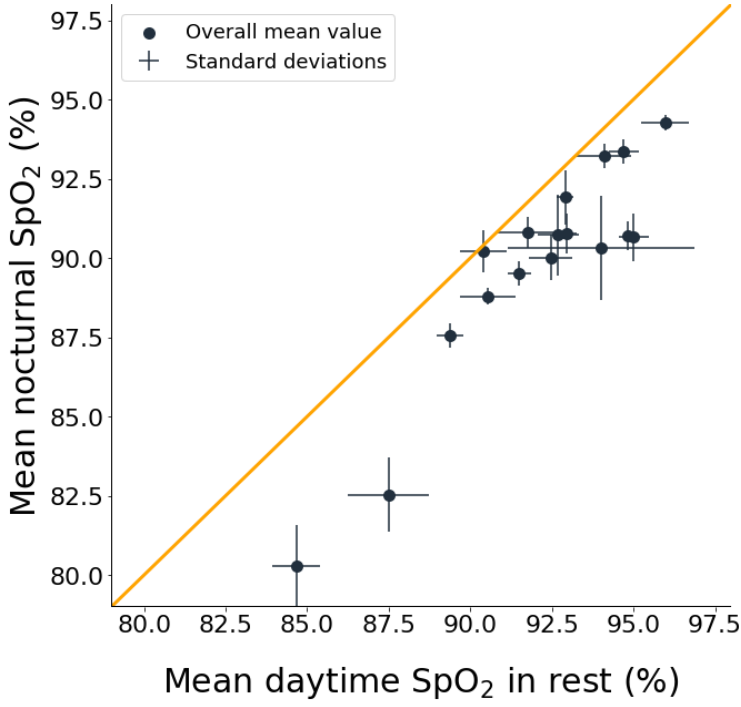


Figure 3.4: Mean nocturnal peripheral blood oxygen saturation (SpO_2) compared to mean daytime SpO_2 in rest. The dots indicate weekly averages of mean SpO_2 for every patient, lines indicate the standard deviation of the mean SpO_2 values over different days and nights, and the orange line is the line of equality.

Intraday and intranight SpO_2 fluctuations were quantified as the weekly average of SpO_2 SD for nocturnal (1.6%, SD 0.6), daytime (1.8%, SD 0.7), and daytime-in-rest (1.6%, SD 0.6) measurements. Nocturnal, daytime, and daytime-in-rest SpO_2 SD values were inversely correlated with nocturnal, daytime, and daytime-in-rest mean SpO_2 values (all: $P<.001$, $R^2>0.4$), respectively. On average, SpO_2 in rest values ranged over 10.8% (SD 4.4) within one day. There was a significant difference between mean SpO_2 in the afternoon and in the evening ($P<.001$) (see Supplementary Figure 3.3), with an average difference of 0.8% (SD 0.7) for those days where patients performed at least one hour of measurements during both the afternoon and evening. For this comparison, a total of 46 days from 12 different patients were used (median of 4 days per patient).

Night-to-night and day-to-day SpO_2 fluctuations were quantified as the weekly ranges of mean SpO_2 (2.0%, SD 1.1; 1.9%, SD 1.5; 1.9%, SD 1.5) and CT90 (28%, SD 25; 19%, SD 20; 18%, SD 21) for nocturnal, daytime, and daytime-in-rest measurements, respectively. A more detailed analysis of the night-to-night changes in CT90 is shown in Figure 3.5. When considering the definition of a nocturnal desaturator, three types of patients can be distinguished: consistent desaturators (5/20, 25%), consistent non-desaturators (5/20, 25%), and occasional desaturators that changed category over the 7 nights (10/20, 50%). A total of 6 occasional desaturators (6/10, 60%) were desaturators or non-desaturators in the first two nights, but changed category when SpO_2 measurements of another night were considered. The weekly average of mean SpO_2 for occasional desaturators was between 89.5% and 91.9%, compared to 80.3%-88.8% and 91.8%-94.3% for consistent desaturators and consistent non-desaturators, respectively.

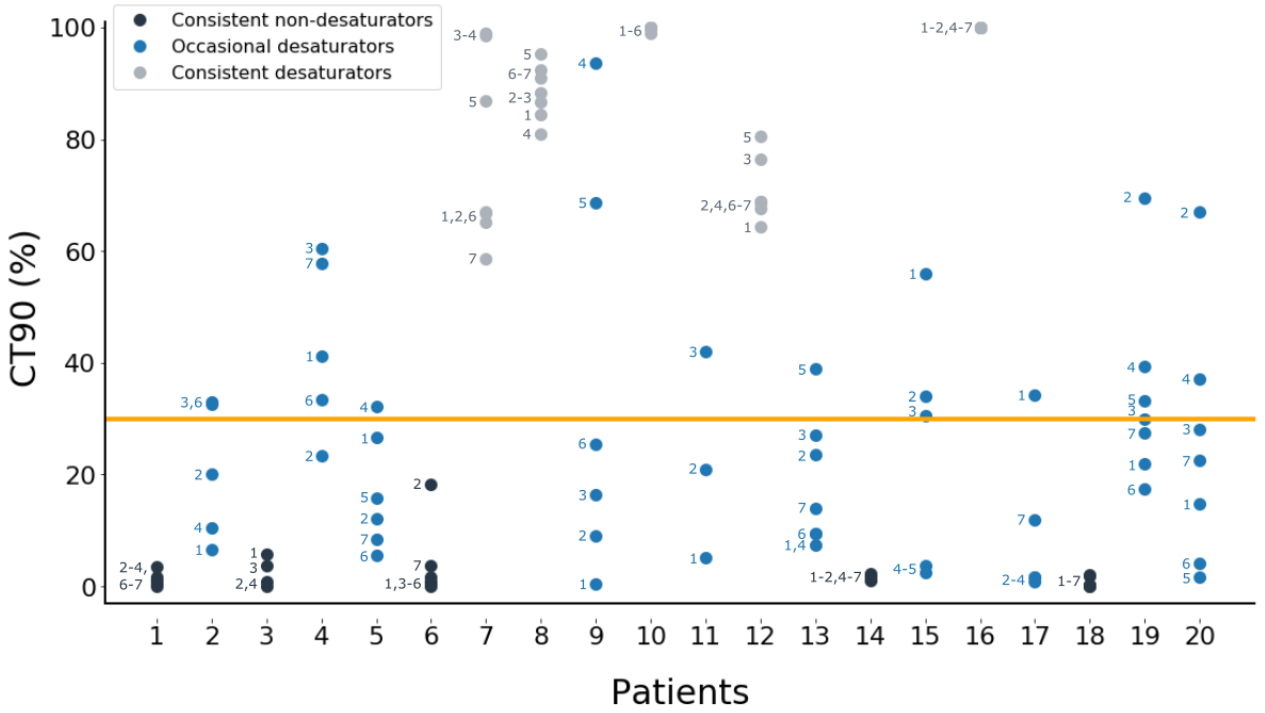


Figure 3.5: Cumulative time spent with peripheral blood oxygen saturation (SpO_2) below 90% (CT90) values for every night of every patient showed that 50% (10/20) of the included patients changed category between desaturator and non-desaturator. The number next to each dot indicates the corresponding night of the measuring week and the orange line indicates the threshold of CT90 (30%) that divides nights with and without desaturation. A missing night number indicates that no data was available for that night.

5. Discussion

Continuous SpO_2 measurements with wearable pulse oximeters identified significant SpO_2 fluctuations between and within multiple days and nights of patients with COPD. COPD patients are known to be a heterogeneous group [14, 15], which leads to large differences in mean SpO_2 values between patients. Day-to-day SpO_2 fluctuations have not yet received a lot of attention in scientific literature and night-to-night fluctuations have not yet been studied over more than two nights in patients with COPD. Some studies examined intraday fluctuations, however, these studies only examined short-term SpO_2 fluctuations (i.e. measurements of one hour or less) in healthy individuals [230] or infants [227–229]. Our results showed that significant SpO_2 fluctuations occurred between and within multiple days and nights for the included patients. This is often not taken into account in telemonitoring applications [215]. When using the current definition of nocturnal desaturation, 50% (10/20) of the included patients changed category between desaturator and non-desaturator over the course of 1 week.

Continuous SpO_2 measurements with high amounts of valid data could be obtained during a 7-day monitoring period, except during MVPA (EE>3 MET). Nocturnal measurements were well-perceived by the patients, leading to the high compliance. These measurements only had a small amount of data that was considered invalid (0.69%). This indicates that it is feasible to perform multi-night continuous SpO_2 measurements. Most patients also performed daytime measurements during rest and LIPA (i.e. 17 patients measured, on average, 7.6 hours per day). These had a limited amount of invalid data (6.10%). However, very few measurements were performed during MVPA (i.e. 0.2 hours per day) and almost one-third of these measurements produced invalid data due to motion artefacts. Therefore, it might not be recommended to analyse continuous SpO_2 measurements during periods of MVPA.

Two types of pre-processing steps for continuous SpO_2 data have been reported: (1) removing deviating samples or (2) down-sampling the data. Deviating samples have been removed visually [230, 231] by using an unspecified data-cleaning algorithm [232] or by removing samples with a sample-to-sample deviation of more than 4% [233] or 8% [234]. The latter

method, however, does not remove artefacts that last over longer periods of time (e.g. see Figure 3.2B: around 17:00-18:00). Therefore, artefacts in this study were removed by removing blocks of deviating values instead of separate samples. After sample removal, Morillo et al excluded remaining artefacts by down-sampling the data from 8 Hz to 1 Hz [234]. However, autocorrelation analyses in our study showed that a sampling time of 1 sample per second still led to oversampling of the data (see Supplementary Text 3.2). SpO_2 could be down-sampled to 1 sample per 20 seconds for improved artefact removal, without losing information about the SpO_2 dynamics.

Mean nocturnal SpO_2 was lower than mean daytime SpO_2 in rest. By taking into account the SpO_2 fluctuations over different days and nights, the results of this study generalise the findings of Soguel Schenkel et al, who only performed SpO_2 measurements during a single day and night that were up to five days apart [235]. Other studies used awake measurements of SpO_2 to predict nocturnal mean SpO_2 or CT90. They used the first 15-30 minutes of the nocturnal measurements to calculate the mean awake SpO_2 values [115, 236–238]. For these studies, it should be noted that slightly lower SpO_2 values were observed in the evening compared to the afternoon, on average a 0.8% difference, and awake SpO_2 values depend on the time of day when the measurements are performed. It is unlikely that this difference is solely due to the specified oximeter accuracy of ±2%, as no consistent bias has been reported for the $WristOx_2$ when measuring over a longer time period.

The observed patient-to-patient, day-to-day, and intraday differences can have implications for telemonitoring applications that are based on daily SpO_2 spot checks [215]. In several telemonitoring setups, alerts were raised when daily spot checks of SpO_2 dropped below a generic threshold value (e.g. 90% for all patients) [215]. However, the high patient-to-patient differences point out the shortcomings of these generic thresholds. Other telemonitoring setups used personalised thresholds, but these were still fixed on one specific threshold value for every patient [215]. For these setups, alerts can be merely a consequence of natural day-to-day and intraday fluctuations, instead of being triggered by the onset of an exacerbation. A recent paper better dealt with the day-to-day fluctuations by suggesting a day-to-day decrease of more than 4% to alert for exacerbations, however, a more thorough examination of this method is

needed [92]. Intraday SpO_2 values during rest ranged over 10.8% (SD 4.4) within one day. Moreover, statistical interpretation of weekly average of SpO_2 SD (1.6%, SD 0.6), which is a measure of intraday fluctuations, indicates that during 5% of the day in rest, SpO_2 fluctuates more than 3.2% (i.e. 2 times SpO_2 SD) beyond the mean daytime-in-rest value. In comparison, previous studies only reported a 1%-2% decrease in SpO_2 spot checks around exacerbation onset compared to stable periods [94, 126, 127]. These natural intraday fluctuations can thus easily result in false alerts for exacerbations. Patients with lower SpO_2 values might experience a higher number of false alerts as, similar to healthy individuals [230], intraday fluctuations (i.e. SpO_2 SD) increased with decreasing mean SpO_2. Altogether, personalised alerts based on intelligent algorithms will be necessary to cope with all of these natural fluctuations in daytime SpO_2 in rest. Preferably, these alerts should be based on continuous measurements over longer time periods, in contrast to the currently used daily spot checks, to account for the identified SpO_2 fluctuations and to exclude the potential effect of the ±2% oximeter accuracy. In addition, the slightly lower SpO_2 values in the evening compared to the afternoon show that the daily measurements should always be performed at the same moment of the day. A clearly defined measurement protocol, which is often not specified [215], can thus further attempt to limit the effect of natural SpO_2 fluctuations in these telemonitoring applications.

The night-to-night differences of nocturnal mean SpO_2 (i.e. average weekly range of 2.0% over the different nights) led to highly varying CT90 values over the different nights of the measurement week (i.e. average range of 28%). These high variations in CT90 resulted in 50% (10/20) of the included patients changing category between desaturator and non-desaturator, due to the fact that these occasional desaturators all had a mean SpO_2 value around the threshold of 90%. A similar finding has been reported by Lewis et al, who concluded that 35% of the included patients changed category over two consecutive nights of measurements [221]. Later studies then tackled this problem by performing measurements over two nights, categorising a patient as a desaturator if desaturation occurred in at least one of both nights [114, 116, 219, 220]. However, the results of this study indicate that even two nights are insufficient to make a consistent separation between desaturators and non-desaturators, as 6 out of 10 occasional desaturators (60%) were desaturators or non-desaturators in

the first two nights and only changed category afterward. Our results suggest that it might be impossible to consistently categorise COPD patients with a mean nocturnal SpO_2 value around 90% as desaturator or non-desaturator. Based on measurements over multiple nights, these patients could thus be referred to as occasional desaturators. Further research is needed to assess the clinical relevance of identifying these three different nocturnal desaturation profiles.

Some limitations should be taken into consideration when interpreting the results of this study. The main limitation, as is often the case in similar studies, is the small sample size. Consequently, no comparison could be made between mild, moderate, and severe hypoxemic patients. Nevertheless, the increasing SpO_2 SD with decreasing mean SpO_2 suggests an increase in SpO_2 fluctuations for more hypoxemic patients. No control group was included because this study aimed to perform continuous SpO_2 measurements in COPD patients for identification of SpO_2 fluctuations that could affect SpO_2 applications, rather than comparing SpO_2 between COPD patients and healthy controls. In addition, daily home routines can greatly differ between patients and healthy controls [239], impeding a proper comparison. As shown in Supplementary Figure 3.1, daytime measurements were only seldom performed during full days due to the impracticalities of wearing the finger clip during activities that require manual actions (e.g. during morning routines). This, in combination with the high amount of invalid data during MVPA, suggests that continuous SpO_2 measurements with a finger clip will have more profound limitations in a population that is more physically active than the target population of this study. Reliable wearable oximeters that do not require a finger clip could thus increase compliance. Moreover, the limited battery life and the inability of real-time data transmission of the used oximeter can further complicate the integration of continuous SpO_2 measurements into practice. Technological advances are thus needed to allow for long-term, continuous monitoring of SpO_2. This study, however, mainly intended to show the potential of prolonged continuous measurements to identify SpO_2 fluctuations. Therefore, a certified wearable pulse oximeter with finger clip was preferred over more user-friendly, watch-type oximeters that have not yet been proven to be accurate. The resulting, more fragmented, daytime measurements were sufficient to identify large natural fluctuations occurring within one day (i.e. SpO_2 in rest ranged over 10.8% [SD 4.4] within

one day), confirming the a priori posed hypothesis. The limited battery life was addressed by providing the patients with multiple sensors to cover the 7-day monitoring period.

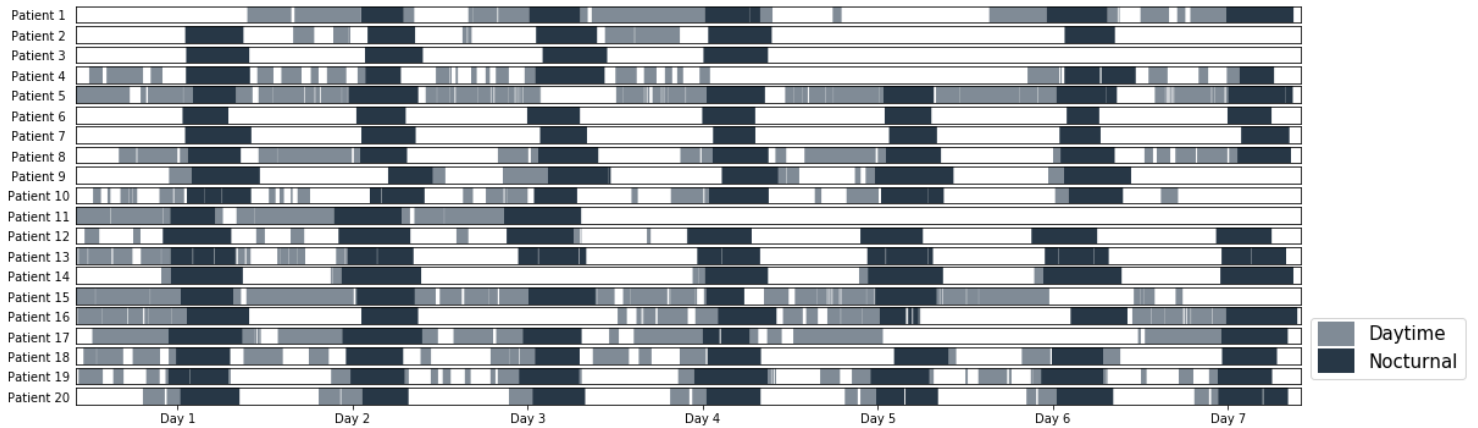
This study was the first to use wearable finger pulse oximeters for prolonged continuous SpO_2 measurements in COPD patients, as opposed to only performing spot checks or continuous measurements during one or two nights. These measurements showed that spot checks or one- or two-night measurements should be interpreted with caution, as the conclusions based on these measurements might change depending on the moment of the measurement. Measurements were performed at home during daily life routines of COPD patients, which provides a more natural SpO_2 profile compared to supervised measurements. By adding actigraphy measurements, the necessary contextual information could be gathered for more accurate analyses of the continuous SpO_2 measurements.

In conclusion, continuous SpO_2 measurements with wearable pulse oximeters identified significant SpO_2 fluctuations between and within multiple days and nights of patients with COPD. Continuous SpO_2 measurements during the daily home routine of patients with COPD generally had high amounts of valid data, except for motion artefacts during MVPA. The continuous measurements showed that mean nocturnal SpO_2 was lower than mean daytime SpO_2 in rest, and significant SpO_2 fluctuations occurred between and within multiple days and nights. The large fluctuations of daytime SpO_2 in rest indicate that clear measurement protocols and personalised alerts, based on intelligent algorithms, will be needed to increase the performance of telemonitoring applications that make use of daily SpO_2 spot checks. Lastly, it was shown that CT90 values can vary greatly from night to night in patients with a nocturnal mean SpO_2 around 90%, indicating that these patients cannot be consistently categorised as desaturators or non-desaturators. We recommend using wearable sensors for performing continuous SpO_2 measurements over longer time periods to determine the clinical relevance of the identified SpO_2 fluctuations.

6. Supplementary material

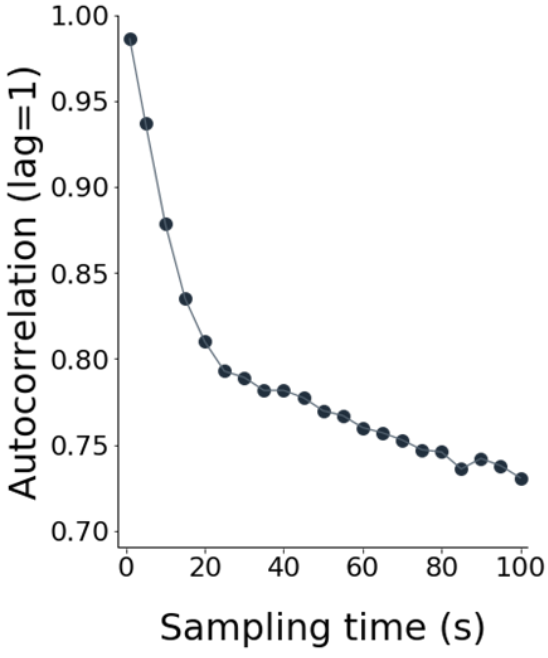
6.1. Supplementary Figure 3.1

The Figure below visualises the continuous SpO_2 measurements that were included for analyses.



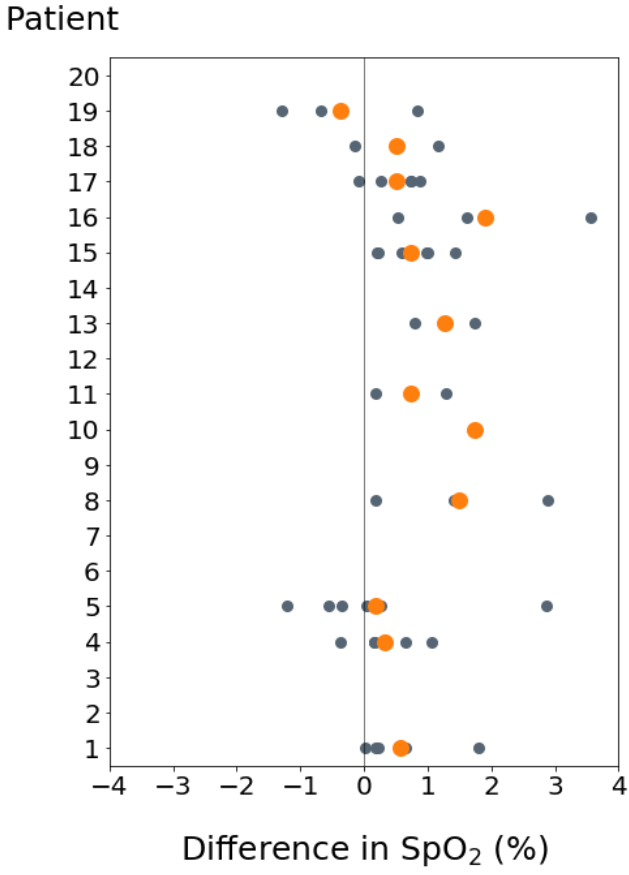
6.2. Supplementary Text 3.2

Autocorrelation analyses were performed to test whether SpO_2 data could be down-sampled without losing information about the dynamics of the SpO_2 signal. For every patient, an autocorrelation value with lag 1 (AR(1); i.e. the correlation between two consecutive values) was calculated for different sampling times ranging between 1 and 100 seconds, based on all their available SpO_2 data. Hereafter, the average AR(1) value of all patients was calculated for every sampling time (see figure below). AR(1) of the data at the original sampling time of 1 second was 0.99 (± 0.01), indicating consecutive values are highly correlated and the time series could be down-sampled without losing information about the dynamics of the data. Resampling the data with increasing sampling times led to a quick drop in AR(1) to 0.81 (± 0.09) at a sampling time of 20 seconds, after which AR(1) decreased more steadily to 0.73 (± 0.10) at a sampling time of 100 seconds (see figure). This initial drop in AR(1) was due to the diminished effect of oversampling. Therefore, the turning point at 20 seconds was chosen as the best suiting sampling time for improved artefact removal without losing information about the SpO_2 dynamics.



6.3. Supplementary Figure 3.3

The Figure below indicates the differences between mean peripheral oxygen saturation (SpO_2) in the afternoon and in the evening; Grey dots indicate the differences within the same day of the same patient, orange dots indicate the average of these differences for every patient. The number of grey dots per patient indicate the amount of days with measurements in both the afternoon and evening.



Chapter 4 – Box-Jenkins transfer function modelling for reliable determination of $\dot{V}O_2$ kinetics in patients with COPD

Published as: Buekers J, Theunis J, Peña Fernández A, Wouters EFM, Spruit MA, De Boever P, Aerts J-M. *Applied Sciences-Basel.* 2019; 9(9): 1822. DOI: 10.3390/app9091822

This Chapter introduces and evaluates an alternative data analysis technique, which is less influenced by low signal-to-noise ratios compared to conventional techniques, for analysing physiological exercise responses in patients with COPD. The focus of this evaluation is on the ability of this alternative technique to account for low signal-to-noise ratios that can be observed in patients with COPD. The results of this Chapter address the second objective of this dissertation.

1. Abstract

Background: Oxygen uptake ($\dot{V}O_2$) kinetics provide information about the ability to respond to the increased physical load during a constant work rate test (CWRT). Box-Jenkins transfer function (BJ-TF) models can extract kinetic features from the phase II $\dot{V}O_2$ response during a CWRT, without being affected by unwanted noise contributions (e.g. phase I contribution or measurement noise).

Methods: CWRT data of 18 COPD patients were used to compare model fits and kinetic feature values between BJ-TF models and three conventional exponential modelling methods.

Results and conclusion: Autocorrelation tests and normalised root-mean-squared error values (BJ-TF: 2.8 ± 1.3%; exponential methods A, B and C: 10.5 ± 5.8%, 11.3 ± 5.2% and 12.1 ± 7.0%; $p < 0.05$) showed that BJ-TF models, in contrast to exponential models, could account for the most important noise contributions. This led to more reliable kinetic feature values compared to methods A and B (e.g. mean response time (MRT), BJ-TF: 74 ± 20 s; methods A-B: 100 ± 56 s - 88 ± 52 s; $p < 0.05$). Only exponential modelling method C provided kinetic feature values comparable to BJ-TF features values (e.g. MRT: 75 ± 20 s). Based on theoretical considerations, we recommend using BJ-TF models, rather than exponential models, for reliable determinations of $\dot{V}O_2$ kinetics.

2. Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease characterised by persistent airflow limitations due to a combination of airway and alveolar abnormalities. COPD is associated with high morbidity and mortality rates, posing a high economical and societal burden [1]. The most important symptom of COPD is dyspnoea during daily activities, but later also at rest. As a result, patients become physically less active, which is the start of a vicious circle of physical deconditioning [10]. Physical capacities can be assessed using standard exercise tests like a cardiopulmonary exercise test (CPET, incremental cycling work rate (WR)) or a constant work rate test (CWRT, constant cycling WR) [120]. During a CPET, oxygen uptake ($\dot{V}O_2$, $ml.min^{-1}$) increases linearly until the maximal or peak $\dot{V}O_2$ value is reached. This maximal (or peak) $\dot{V}O_2$ value, the maximal

WR reached during CPET and the endurance time during CWRT are the most frequently used metrics for evaluating physical capacities. However, there is additional information, besides these maximal values, that can be extracted from the breath-by-breath $\dot{V}O_2$ time series that are generated during these tests.

During a CWRT, there is typically a 3-phase $\dot{V}O_2$ response towards the step increase of cycling WR. During phase I, the cardiodynamic phase, $\dot{V}O_2$ shows an instant response driven by an increased cardiac output and pulmonary blood flow (Figure 4.1). In phase II, the fundamental component of the response, $\dot{V}O_2$ increases exponentially, similar to the working muscle oxygen uptake. In phase III, $\dot{V}O_2$ can reach a steady-state or can steadily keep increasing, i.e. $\dot{V}O_2$ slow component (Figure 4.1), depending on the exercise intensity [128]. Kinetic analyses of the $\dot{V}O_2$ response aim to quantify the speed and amplitude of the primary (phase II) response using a combination of kinetic features. Time delay (TD), time constant (TC) and mean response time (MRT = TD + TC) assess the speed of the response. Response amplitude (Amp) and gain (= $Amp.\Delta WR^{-1}$) assess the magnitude of the response, with ΔWR indicating the step increase of cycling WR at the start of the exercise test (Figure 4.1). These features quantify the ability to respond to the increased physical load during a CWRT [128]. Generally, COPD patients exhibit a slower $\dot{V}O_2$ response than healthy subjects [129, 130], but supplemental oxygen [132], medication use [131, 133] and exercise training [57], can speed up the $\dot{V}O_2$ response to the step increase in WR.

Typically, exponential models are used to extract these kinetic features from the $\dot{V}O_2$ time series. Three mono-exponential modelling methods have been described in COPD literature, which will be referred to as method A [130, 131], B [57, 240] and C [133, 241]. Method A assumes there is no delay in the $\dot{V}O_2$ response (TD = 0 s), whereas methods B and C estimate a TD value as one of the model parameters. Method B uses data starting from t = 0 s (WR onset), while method C aims to exclude the contribution of the cardiodynamic phase by only using data starting from t = 20 s. Nevertheless, these exponential models are all still influenced by other unwanted noise contributions, such as measurement noise or cardiac output dynamics, that are not related to the increased working muscle oxygen uptake.

In contrast to the generally applied exponential models, Box-Jenkins transfer function (BJ-TF) models can extract the same kinetic features [138]

without being affected by these unwanted noise contributions. BJ-TF models are able to separate the unwanted contributions from the noise-free primary $\dot{V}O_2$ response (i.e. phase II). Therefore, extraction of the kinetic features will not be influenced by the unwanted contribution of these additional components. To the authors' knowledge, BJ-TF models have not yet been used to extract kinetic features from CWRT data. Therefore, the aim of this study was to compare model fits and kinetic feature values between BJ-TF models and the three different exponential modelling methods that were identified in COPD literature.

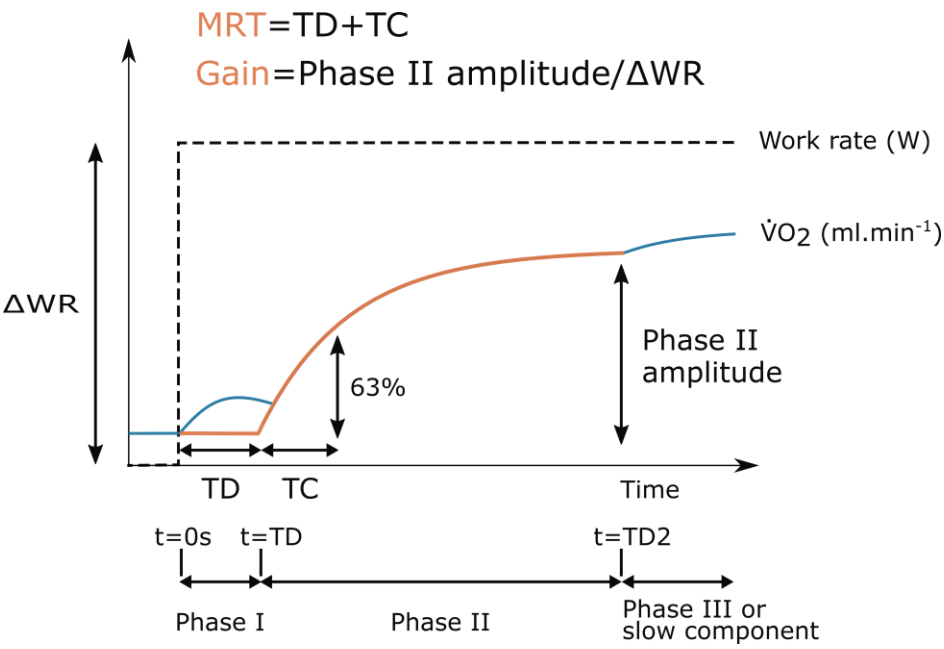


Figure 4.1: Graphical representation of the kinetic features that quantify the phase II response. The blue line represents the theoretical oxygen uptake ($\dot{V}O_2$) response, the orange line shows the phase II contribution that should be modelled, the black dashed line visualises the WR increase at t = 0 s. The blue and orange lines coincide during phase II. TD = Time delay; TC = time constant; MRT = mean response time; Amp = response amplitude; ΔWR = the step increase in work rate at t = 0 s; TD2 = time delay of phase III or the slow component, variable between 100-200 s [277].

3. Material and methods

3.1. Study design and participants

Twenty COPD patients (GOLD II-IV) were recruited at CIRO (Horn, the Netherlands) during a standard baseline assessment prior to pulmonary rehabilitation [222]. Two patients were excluded from analyses because they failed to perform a CWRT during the baseline assessment. Demographics, partial pressure of oxygen and carbon dioxide, post-bronchodilator pulmonary function data (e.g. forced expiratory volume in 1 second, forced vital capacity and transfer factor for carbon monoxide) and modified Medical Research Council dyspnoea scores were collected during the standard baseline assessment at CIRO. The study was approved by the Medical Research Ethics Committees United (NL58079.100.16, MEC-U, the Netherlands) and all patients provided written informed consent.

3.2. Exercise testing

Patients performed a CPET during the first day and a CWRT during the second day of the baseline assessment. The tests were performed on an electrically braked cycle ergometer and $\dot{V}O_2$ data were collected breath-by-breath (Oxycon Pro, Carefusion, Houten, the Netherlands). Both tests started with 3 minutes of rest, followed by 3 minutes of unloaded cycling (WR = 0). During CPET, WR then increased 1 Watt per 4, 6 or 12 seconds, depending on the relative fitness of the patient. During CWRT, WR remained constant at 75% of the maximal WR obtained during the CPET. In both tests, patients were asked to keep their cycling speed constant between 60 and 70 rotations per minute and to cycle until limitation (exhaustion and/or severe dyspnoea). The tests ended with a 3-minute recovery period. CWRT time series data were used for the analyses described below.

3.3. Data pre-processing

Deviating breath values, identified as data samples deviating more than 3 standard deviations from the local mean (i.e. 31 s centred moving average), were deleted. An integrated random walk smoothing algorithm (CAPTAIN toolbox [242]) was used to converse the non-equidistant breath-by-breath $\dot{V}O_2$ data into a smoothed 1 Hz time series, while still preserving the

dynamics of the time series. Data after 180 s of loaded cycling were discarded to diminish the potential contribution of the $\dot{V}O_2$ slow component.

3.4. Kinetic analyses

The dynamic response of physiological variables towards an increase in physical load can be described by a number of features (Figure 4.1). These features were extracted using both exponential models and BJ-TF models. The following first order model was used as a basis for exponential modelling:

$$\begin{aligned} 0 \le t \le TD: &\qquad \Delta VO_2(t) = 0, \\ TD < t \le 180: &\qquad \Delta VO_2(t) = Amp \cdot \left(1 - e^{-\left(\frac{t-TD}{TC}\right)}\right), \end{aligned} \tag{1}$$

where $\Delta\dot{V}O_2(t)$ is the difference between the pre-processed $\dot{V}O_2$ time series and the unloaded $\dot{V}O_2$ level ($\dot{V}O_{2,unloaded}$), i.e. $\Delta\dot{V}O_2(t) = \dot{V}O_2(t) - \dot{V}O_{2,unloaded}$. $\dot{V}O_{2,unloaded}$ is calculated as the mean $\dot{V}O_2$ value of the last 30 s of unloaded cycling. The model parameters (*Amp*, *TD* and *TC*) were estimated using non-linear least squares (Matlab 2015b, MathWorks Inc., Natick, Massachusetts, USA). Three mono-exponential modelling methods have been described in COPD literature. They will be referred to as method A [130, 131], B [57, 240] and C [133, 241]. Method A assumes there is no *TD* in the $\dot{V}O_2$ response (*TD* = 0 s). Method B estimates the three model parameters using data from t = 0 s (WR onset) until t = 180 s, whereas method C only uses data between t = 20 s and t = 180 s to diminish the contribution of the cardiodynamic phase (phase I).

Time evolutions and autocorrelation tests of the model residuals were checked to assess whether the model residuals retained any meaningful structure. Remaining structure in the model residuals indicates that the residuals contain information that is not captured by the model. The relative amplitude of these residuals was assessed by the normalised root-mean-squared error (*NRMSE*), defined as the root-mean-squared error divided by the amplitude of the $\dot{V}O_2$ response:

$$NRMSE = \sqrt{\frac{\sum_{t=1}^{n} residuals(t)^2}{n}} \cdot Amp^{-1}. \tag{2}$$

A discrete-time, single-input, single-output BJ-TF model with time-invariant parameters can generally be written as follows:

$$y(t) = \frac{B(z^{-1})}{A(z^{-1})}u(t - TD) + \frac{C(z^{-1})}{D(z^{-1})}e(t), \quad (3)$$

where *y(t)* is the model output at time t, *u(t)* is the model input at time t, z^{-1} is the backwards shift operator (i.e. z^{-s} y(t) = y(t−s)), *e(t)* is zero mean white noise and $A(z^{-1})$, $B(z^{-1})$, $C(z^{-1})$ and $D(z^{-1})$ are polynomials containing the model parameters:

$$\begin{aligned} A(z^{-1}) &= 1 + a_1 z^{-1} + \cdots + a_m z^{-m}, \\ B(z^{-1}) &= b_0 + b_1 z^{-1} + \cdots + b_n z^{-n}, \\ C(z^{-1}) &= 1 + c_1 z^{-1} + \cdots + c_p z^{-p}, \\ D(z^{-1}) &= 1 + d_1 z^{-1} + \cdots + d_q z^{-q}. \end{aligned} \quad (4)$$

Thus, the full BJ-TF model (3) is a combination of a 'noise-free' system model (first term) and a noise model (second term). As phase II is known to follow a first-order exponential response, the system model was defined as a first order model with one gain parameter. This transformed the full model (3) as follows:

$$\Delta VO_2(t) = \frac{b_0}{1 + a_1 z^{-1}} WR(t - TD) + \frac{C(z^{-1})}{D(z^{-1})}e(t), \quad (5)$$

where the input variable *WR(t)* was defined as:

$t \leq 0$: $WR = 0\ Watt$,
$t > 0$: $WR = 75\%\ of\ the\ maximal\ WR\ reached\ during\ CPET$.

The order of the noise model, given by the order of polynomial $D(z^{-1})$, was unknown and was therefore identified by comparing the performances of models with noise models up to order three in $C(z^{-1})$ and/or $D(z^{-1})$. Full model fits were inspected visually and the residuals were checked using autocorrelation tests and NRMSE values. In addition, the full models with different noise structures were compared by their Young Identification Criterion (YIC) value [137]. YIC combines goodness of fit and reliability of the parameter estimations, while penalising for over-parameterisation. A more negative YIC value indicates a better model performance. The noise model structure will be referred to as [p q], where p and q are the orders of polynomials $D(z^{-1})$ and $C(z^{-1})$, respectively.

The parameters of the full model were estimated using the refined instrumental variable approach of the CAPTAIN toolbox in Matlab [137, 243]. From the system model parameters a_1 and b_0, TC and $Gain$ were calculated as follows:

$$TC = \frac{-\Delta t}{\log(-a_1)}, \tag{6}$$

$$Gain = \frac{b_0}{1+a_1}. \tag{7}$$

where Δt is the sampling time (= 1 s). MRT was calculated as the sum of TD and TC, Amp was calculated by multiplying $Gain$ with the WR increase (ΔWR).

3.5. Statistical analysis

Patient characteristics were summarised for all patients as mean and standard deviation (SD). NRMSE and kinetic feature values were summarised as median and interquartile range (IQR). Wilcoxon signed-rank tests were used to look for differences in NRMSE and kinetic feature values as calculated with the different exponential modelling methods and BJ-TF modelling. A p-value lower than 0.05 was considered to provide statistical significance. All analyses were performed using Matlab 2015b (MathWorks Inc., Natick, Massachusetts, USA).

4. Results

Eighteen patients (14 male and 4 female) performed a CWRT. Table 4.1 summarises the clinical characteristics of the participants. On average, the elderly patients had a moderate-to-severe degree of airflow limitation, an impaired diffusing capacity and a slightly overweight body mass index. None of the patients were on long-term oxygen therapy. A median of 1.5 (± 2) deviating breath values were deleted per patient.

Table 4.1: Patient characteristics.

	Value mean (SD)
Age (years)	63 (7)
Body mass index (kg/m^2)	26 (5)
Forced expiratory volume in 1 second (FEV_1; % predicted)	48 (14)
Forced vital capacity (FVC; % predicted)	105 (18)
FEV_1/FVC (%)	37 (13)
Transfer factor for carbon monoxide (% predicted)	55 (15)
Partial pressure of oxygen (kPa)	8.8 (1.8)
Partial pressure of carbon dioxide (kPa)	5.3 (0.7)
Modified Medical Research Council dyspnoea scores (scores 1-2-3)	2-14-2
CPET maximal cycling work rate (% predicted)	50 (23)
CPET maximal oxygen uptake (ml/min)	1133 (231)
CPET maximal oxygen uptake (% predicted)	55 (21)
CWRT cycling work rate (W)	57 (16)
CWRT endurance time (s)	243 (81)

CPET = cardiopulmonary exercise test; CWRT = constant work rate test.

4.1. Exponential modelling

Figure 4.2 shows an example of the three exponential modelling methods fitted to data of the same patient. NRMSE values differed between the three methods (method A: 10.5 ± 5.8; method B: 11.3 ± 5.2; method C: 12.1 ± 7.0; $p < 0.05$ for all pairwise comparisons). As shown in Figure 4.2, method C is the only method that can completely surpass the cardiodynamic phase.

The exponential model residuals contained remaining structure, as can be seen by plotting the relative residual values in function of time and the autocorrelation coefficients from lag 1 to 10 (example shown in 4.3a). The same behaviour was obtained for all patients for all three methods.

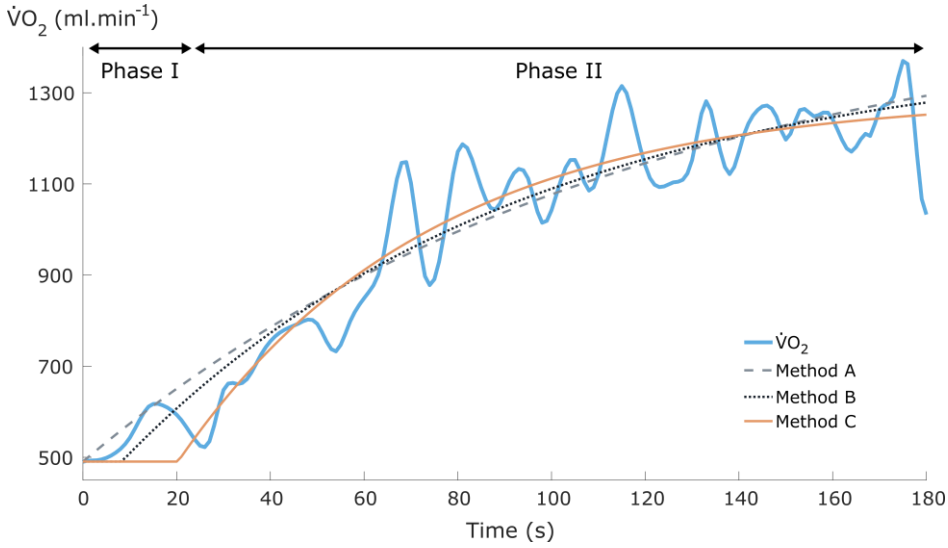


Figure 4.2: Example plot of oxygen uptake ($\dot{V}O_2$) data and the three different exponential modelling methods. The estimated time delay values for methods B and C were 8.3 s and 20.3 s, respectively

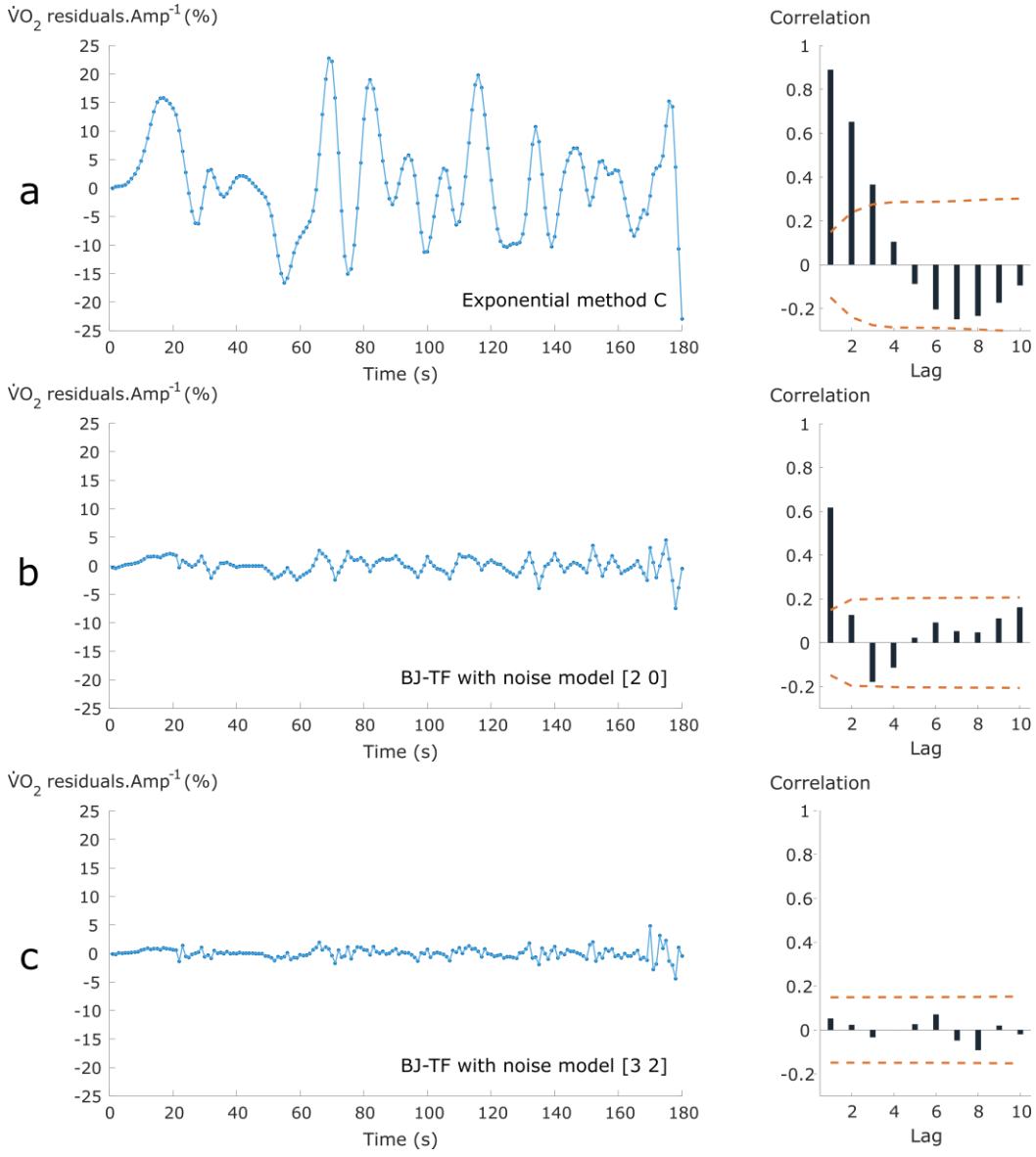


Figure 4.3: Residual analyses of the residuals from (a) exponential method C (representative for methods A and B) and Box-Jenkins transfer function (BJ-TF) models with noise model orders (b) [2 0] and (c) [3 2]. Left: residual values divided by the response amplitude (Amp), plotted in function of time. Right: autocorrelation coefficients up to lag 10.

4.2. Box-Jenkins transfer function modelling

Based on the full model fits, YIC values and NRMSE values (see below and Discussion), a first order system model with a [2 0] noise model order was selected and used for comparing kinetic feature values between exponential and BJ-TF models in the next section. An example of applying this BJ-TF model is shown in Figure 4.4.

BJ-TF models with first order noise models (i.e. first order in $D(z^{-1})$) resulted in visually inappropriate model fits. Noise models of order [1 0] and [1 1] led to the full model (i.e. system + noise model) lagging behind the measured $\dot{V}O_2$ data. This lag was solved in the noise models of order [1 2] and [1 3]. However, for both these noise model structures the full model fits were completely off for some patients. Similarly, noise model orders [2 3] and [3 3] led to bad fits for some patients. YIC and NRMSE values of the remaining noise model orders are summarised in Table 4.2. Second order noise models had more negative (i.e. better) YIC values, but slightly higher residual values compared to third order models. Example residual and autocorrelation plots for [2 0] and [3 2] noise models are shown in Figure 4.3b,c, respectively. These noise model orders were chosen as examples because they had the lowest YIC value of all second and third order noise models, respectively. All second order noise models exhibited similar residual and autocorrelation plots, whereas some third order noise models still had a significant autocorrelation coefficient at lag 1, opposite to the example in Figure 4.3c.

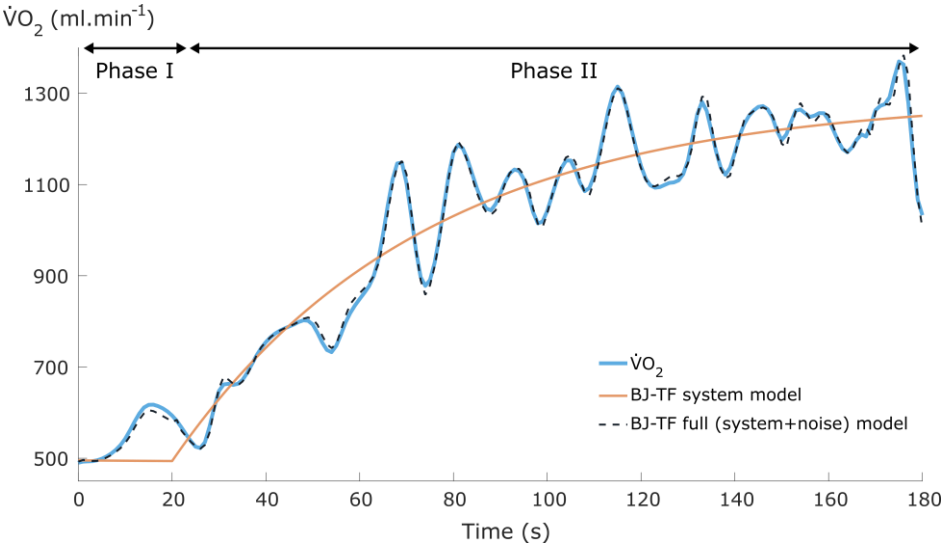


Figure 4.4: Example plot of oxygen uptake ($\dot{V}O_2$) data and the Box-Jenkins transfer function (BJ-TF) system and full (system + noise) model. The estimated time delay value was 20 s.

Table 4.2: Model performance characteristics for identification of the noise model order. Dark squares show noise model orders that resulted in visually inappropriate full model fits. Upper values for every noise model structure are Young Identification Criterion (YIC) values, and lower values are normalised root-mean-squared error values (NRMSE) (%).

		Order D(z^{-1})		
		1	**2**	**3**
Order C(z^{-1})	**0**		−6.94 (2.31) 2.8 (1.3)	−5.69 (2.12) 2.1 (1.1)
	1		−6.82 (2.91) 2.5 (1.7)	−6.20 (2.11) 2.0 (2.6)
	2		−6.75 (2.63) 2.1 (1.6)	−6.21 (2.69) 2.0 (1.6)
	3			

4.3. Kinetic features

Figure 4.5 provides an overview of the $\dot{V}O_2$ kinetic feature values as calculated with the different exponential (methods A, B and C) and full BJ-TF models. Methods A and B resulted in a smaller TD and a higher TC, MRT, Amp and Gain compared to method C and the BJ-TF full model (Figure 4.5). On a group level, method C and BJ-TF did not show significant differences between the kinetic feature values of the included patients (Figure 4.5). On an individual level, the median (± IQR) of the absolute differences between the feature values as calculated with method C and BJ-TF were 4 ± 13 s, 11 ± 17 s, 7 ± 8 s, 27 ± 43 ml·min^{-1} and 0.5 ± 0.7 ml·min^{-1}·W^{-1} for TD, TC, MRT, Amp and Gain, respectively. These absolute differences were respectively 24%, 20%, 9%, 4% and 4% of the respective median feature values as extracted from BJ-TF models. MRT values varied less than TC values between the different methods (Figure 4.5).

Two patients had extremely large kinetic feature values in all applied models (e.g. TC > 200 s and/or Gain > 20 ml·min^{-1}·W^{-1}). One of these patients cycled at a very low WR during CWRT (22 W), the other patient showed a $\dot{V}O_2$ response that increased almost linearly. When applying method A, one additional patient had extremely large kinetic feature values.

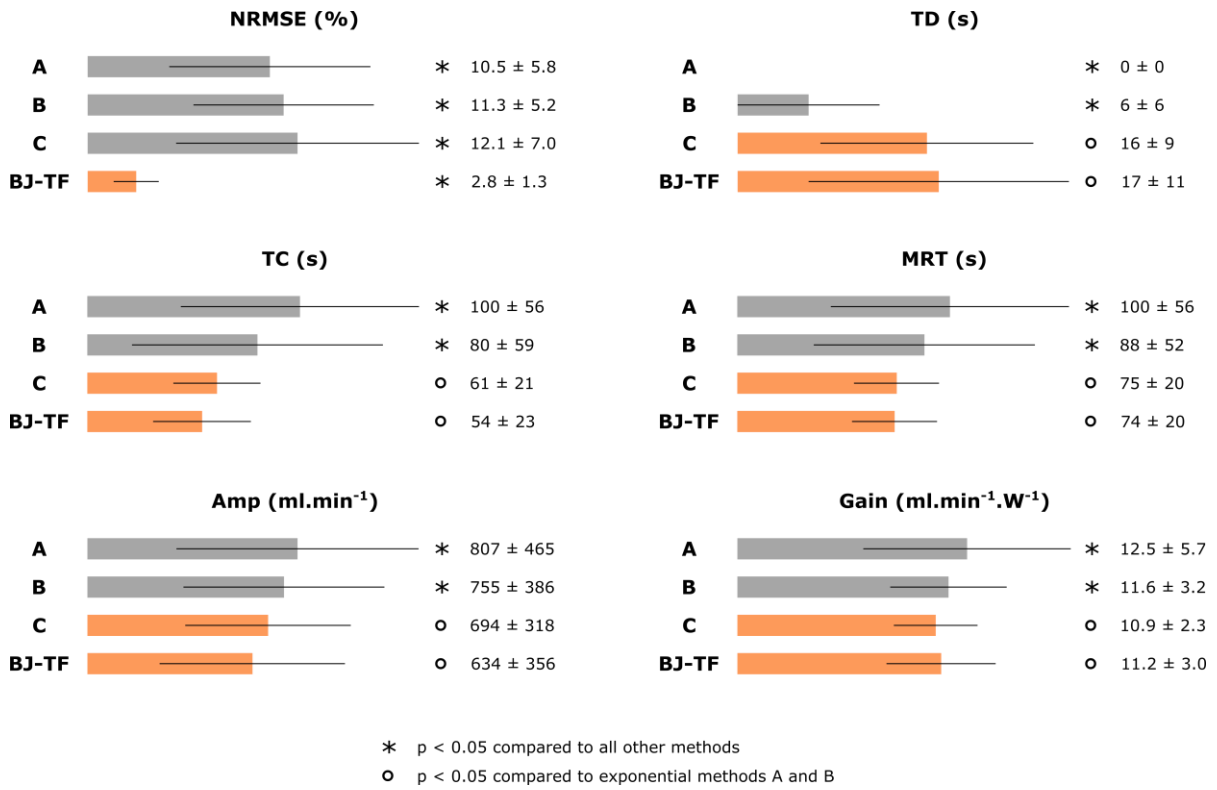


Figure 4.5: Normalised root-mean-squared error (NRMSE) and kinetic feature values summarised as median (bar) and interquartile range (line) for exponential modelling methods A, B, C and the Box-Jenkins transfer function (BJ-TF) model with noise model order [2 0]. TD = Time delay; TC = time constant; MRT = mean response time; Amp = response amplitude.

5. Discussion

This is the first study to apply BJ-TF models to determine $\dot{V}O_2$ kinetics during a CWRT. BJ-TF models provided better fits than the typically applied exponential models and were able to account for unwanted contributions (e.g. phase I contribution or measurement noise). When applying exponential models, method C succeeded best at surpassing the phase I contribution and most closely resembled the "noise-free" system model of BJ-TF models.

Exponential models are most commonly used to examine $\dot{V}O_2$ kinetics [128]. However, none of the applied exponential modelling methods were able to account for the noise components in the $\dot{V}O_2$ time series, as could be seen in the $\dot{V}O_2$ time series, residual and autocorrelation plots (Figures 4.2 and 4.3). NRMSE values showed that the residuals acted on a magnitude of 10–12% of the total response amplitude, indicating that these noise components should not be neglected. Methods B and C had higher NRMSE values because they tried to surpass the contribution of the cardiodynamic phase (phase I), leading to higher residual values at the start of the test when the cardiodynamic phase plays an important role (Figures 4.2 and 4.3). However, method A is mechanistically unrealistic, as it does not assume any transit delays between muscle oxygen uptake and oxygen uptake at the mouth [244]. Only method C was able to discard the phase I contribution by removing the first 20 s of data. The ability to (partly) surpass the cardiodynamic phase was mainly reflected in the TD values, which in turn greatly affected all other feature values (Figure 4.5). This shows that for COPD patients, similar to healthy subjects [244, 245], the applied exponential modelling method had a significant effect on the kinetic feature values.

Another strategy to exclude the phase I contribution might be applying a second-order exponential model, which aims to separately model the phase I and phase II contributions [128, 245]. However, a second-order exponential model is based on the unproven assumption that the phase I response is exponential of nature [245]. Furthermore, the phase I contribution was not the only unwanted noise component in the data, as can be seen in Figure 4.3a. These other noise contributions acted at a similar level as phase I, making it difficult to distinguish phase I from other noise

contributions (Figure 4.3a). The relatively small phase I contributions, compared to the other noise contributions, might be a result of the patients suffering from COPD [129] or because the test was preceded by unloaded cycling [244]. Averaging the $\dot{V}O_2$ response of several repetitions of the same exercise can cancel out the noise contributions that are not related to the phase I contribution [134, 246], but this requires unnecessarily strenuous exercise sessions. Therefore, BJ-TF models were preferred because of their ability to account for all unwanted components at once.

A [2 0] noise model structure was considered the most suitable for BJ-TF modelling. When considering all second order noise models, NRMSE values were all at the same magnitude, and a [2 0] structure had the best YIC values. This indicates that increasing the order of $C(z^{-1})$ above zero induced unnecessary complexity. Some structure remained in the residuals when applying a second order noise model, but at a very low magnitude (Figure 4.3b and Table 4.2). When increasing the noise model dynamics to order three, this low-magnitude structure in the residuals disappeared in most patients (Figure 4.3c) and NRMSE values became slightly lower, but were still at a similar magnitude as second order models (Table 4.2). The improvements of increasing the noise model order were thus minimal compared to the cost of the increased complexity (i.e. more difficult to interpret, greater risk of overfitting and more computationally expensive), resulting in higher YIC values for third order noise models (Table 4.2). A [2 0] noise model showed the best balance between model fit and model complexity.

BJ-TF models provided better fits than the exponential modelling methods. Whereas exponential models only provided an estimate of the general trend of the $\dot{V}O_2$ response (Figure 4.2), BJ-TF models were able to account for the unwanted noise contributions around the general trend (Figure 4.5), without having to average $\dot{V}O_2$ responses over several repetitions [134, 246]. These noise contributions are especially important for COPD patients, as the reduced $\dot{V}O_2$ responses, due to the lower workloads that are feasible for COPD patients [120], increase the relative magnitude of the noise contributions (i.e. lower signal to noise ratio). Residual and autocorrelation plots confirmed that the noise models accounted for the most important noise contributions (Figure 4.3), and the remaining residuals were four times smaller than residuals from exponential models (Figure 4.5). Whereas exponential modelling models A

and B failed to provide satisfying estimates of TD, BJ-TF models with a [2 0] noise model always provided satisfactory results without having to manipulate the data manually (cf. method C).

The ability of BJ-TF models to separate the phase II contribution from other unwanted noise contributions ensured that these noise contributions could not influence the extracted kinetic feature values, which is a key advantage compared to exponential modelling. The influence of the unwanted contributions, mostly phase I, led to lower TD and higher TC, MRT, Amp and Gain values when applying methods A and B. Only method C produced similar feature values as BJ-TF models on a group level, pointing out that this method should be preferred over methods A and B when exponential models are applied on CWRT data from COPD patients. Nevertheless, median absolute differences between the feature values of individual patients, as calculated with method C and BJ-TF models, were up to 24%, showing that different feature values were obtained for individual patients when the two different methods were applied. Unfortunately, due to the unwanted noise components in $\dot{V}O_2$ responses, the true $\dot{V}O_2$ kinetic feature values are not exactly known. As a result, no quantitative evidence could be provided that indicates which model (method C or BJ-TF) was mainly responsible for these differences in feature values on an individual level. Nevertheless, some theoretical considerations favour BJ-TF models over exponential models, as discussed below.

Unwanted noise contributions influencing $\dot{V}O_2$ kinetic features values are a general concern when applying exponential models [134, 247, 248]. In contrast, BJ-TF models explicitly account for the unwanted contributions and the extracted feature values will thus be less influenced by these contributions. Furthermore, parameters in the exponential models were estimated using the generally applied method of least squares, which can be influenced by unwanted noise contributions in the data, in contrast to the more robust refined instrumental variable approach that was used to estimate the model parameters in BJ-TF models [136, 137]. In addition, BJ-TF models do not require data manipulation by removing the first 20 s of data after the WR onset. Although this method has been proven robust for changes in the amount of removed data under specific conditions, e.g. using the averaged data of four repetitions of the test and a sampling time of 10 s [249], the effect of changing the amount of removed data under less strict conditions, e.g. when only a single test is available, is still unclear and could

thus influence the extracted feature values. Based on these elements, BJ-TF models are believed to be more reliable than exponential method C for the determination of kinetic feature values.

MRT varied less than TC over the different modelling methods for quantifying the speed of the primary $\dot{V}O_2$ response (Figure 4.5). This confirms the findings from test–retest reliability studies that determine $\dot{V}O_2$ kinetics from healthy subjects using a treadmill [250] or step test [251]. Inaccurate TD estimates will directly affect TC estimates in the opposite direction. These opposing effects are balanced in the calculation of MRT, making MRT more robust towards inaccurate TD estimations. This study also confirms earlier findings that not all CWRT datasets of COPD patients are well-suited for kinetic analyses [252]. One patient showed no meaningful $\dot{V}O_2$ response due to a very low WR (22 W). More interestingly, another patient had an almost linear primary $\dot{V}O_2$ response that was not due to a low WR. Limited oxygen delivery to the working muscles might have led to this alteration of the $\dot{V}O_2$ response [128]. Analyses of larger COPD populations will be required to confirm this hypothesis.

In addition to the more reliable determination of kinetic feature values compared to exponential methods A and B, BJ-TF models can also be applied more broadly than exponential models. Exponential models do not explicitly include an input variable in their model, limiting their use to experiments with a single input transition (e.g. non-active to active or unloaded to loaded cycling). BJ-TF, however, are able to estimate kinetic feature values with multiple input transitions, e.g. for time-domain analyses of pseudo-random binary sequences of the cycling WR [253], or during unsupervised physical activities. As physical activity and $\dot{V}O_2$ can nowadays be measured with wearable devices [224, 254], combining these measurements with BJ-TF modelling can produce frequent estimates of kinetic feature values during standard unsupervised training sessions, without the need for elaborate testing procedures. Similar models have already been successfully used to model heart rate responses during road cycling [255].

Although this study showed the advantages of applying BJ-TF models, some considerations should be taken into account. We only examined a specific population, which exhibits a reduced signal to noise ratio (due to the reduced $\dot{V}O_2$ response amplitudes [120]) and phase I contribution [129]. It would thus be interesting to test the performance of BJ-TF models in other

population types (e.g. athletes or other disease states). Furthermore, other exercise modalities (e.g. treadmill walking) and exercise intensities should be examined to test the general applicability of BJ-TF models for analysing $\dot{V}O_2$ kinetics.

In conclusion, low residual values showed that BJ-TF models accurately model the $\dot{V}O_2$ response of COPD patients during a CWRT. These models, in contrast to the typically used exponential models, were able to account for unwanted noise contributions (e.g. the phase I contribution), leading to more reliable determinations of kinetic feature values compared to methods A and B. Only exponential modelling method C, which excludes the data during the cardiodynamic phase, led to comparable kinetic feature values as extracted from BJ-TF models. Based on theoretical considerations, we recommend using BJ-TF, rather than exponential models, for reliable determinations of $\dot{V}O_2$ kinetics.

Chapter 5 – Kinetic analyses as a tool to examine physiological exercise responses in a large sample of patients with COPD

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In this Chapter, the Box-Jenkins transfer function models that were developed in Chapter 4 are applied on an extended dataset of patients with COPD (n=265) in order to establish simple guidelines that can identify patients for whom kinetic analyses are (un)likely to be reliable, and to examine whether impaired physiological exercise responses are associated with ventilatory, cardiovascular and/or physical impairments. The results of this Chapter, combined with the results of Chapter 6, address the third objective of this dissertation.

1. Abstract

Background: Kinetic features such as oxygen uptake ($\dot{V}O_2$) mean response time (MRT) and gains of $\dot{V}O_2$, carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) can describe ventilatory and gas exchange responses during a constant work rate test of patients with chronic obstructive pulmonary disease (COPD). This study aimed to establish simple guidelines that can identify COPD patients for whom kinetic analyses are (un)likely to be reliable, and examined whether slow $\dot{V}O_2$ responses and gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ are associated with ventilatory, cardiovascular and/or physical impairments.

Methods: Kinetic features were examined for 265 COPD patients (FEV_1: 54±19%predicted) that performed a constant work rate test (duration>180 s) with breath-by-breath measurements of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$. Negative/positive predictive values were used to define cut-off values of relevant clinical variables below/above which kinetic analyses are (un)likely to be reliable.

Results: Kinetic feature values were unreliable for 21% (=56/265) of the patients and for 79% (=19/24) of the patients with a peak work rate (WR_{peak})<45 W. Kinetic feature values were considered reliable for 94% (=133/142) of the patients with an FEV_1>1.3 L. For patients exhibiting reliable kinetic feature values, $\dot{V}O_2$ MRT was associated with ventilatory (e.g. FEV_1%predicted: p<0.001; r=-0.35) and physical (e.g. $\dot{V}O_{2,peak}$%predicted: p=0.009; r=-0.18) impairments. Gains were mainly associated with cardiac function and ventilatory constraints, representing both response efficiency and limitation.

Conclusions: Kinetic analyses are likely to be unreliable for patients with a WR_{peak}<45 W. While gains enrich analyses of ventilatory and gas exchange responses, $\dot{V}O_2$ MRT shows potential to serve as a motivation-independent, physiological indicator of physical performance.

2. Introduction

Dynamic responses of pulmonary oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) during a constant work rate cycling test (CWRT) depend on adequate pulmonary, cardiovascular and muscle functioning [256]. During a CWRT, $\dot{V}O_2$ responses are characterised by a rapid cardio-dynamic phase (phase I; Figure 5.1), followed by an exponential $\dot{V}O_2$ increase (phase II, the primary component of the response) towards an anticipated steady state (phase III) [244]. An additional slow component, superimposed on the primary component of the response (Figure 5.1), can delay or prevent reaching this steady state [257, 258]. Kinetic features such as mean response time (MRT) and gain describe the primary component of the $\dot{V}O_2$ response [259]. $\dot{V}O_2$ MRT indicates the rate of the $\dot{V}O_2$ increase above unloaded cycling. It represents the time to reach 63% of the anticipated steady state while excluding the potential contribution of the slow component (Figure 5.1). A slow $\dot{V}O_2$ response, indicated by a high MRT, leads to higher dependencies on anaerobic energy sources and contributes to exercise intolerance [256]. $\dot{V}O_2$ gain quantifies the $\dot{V}O_2$ increase (related to the primary component of the response) per unit increase in external work rate (WR). Equivalent gains can be calculated for $\dot{V}CO_2$ and $\dot{V}_E$. These gains thus quantify the magnitude of the primary component of the $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ responses above unloaded cycling, corrected for external WR.

Patients with chronic obstructive pulmonary disease (COPD) suffer from decreased exercise tolerance, characterised by slow $\dot{V}O_2$ responses, compared to healthy peers [129, 130, 132, 241, 260]. These slow $\dot{V}O_2$ responses in patients with COPD have been attributed to slow muscle O_2 utilisation [130, 132, 260] and/or ventilatory and cardiovascular restrictions that reduce oxygen delivery to the working muscles [129, 131, 133, 240, 241, 261]. When a $\dot{V}O_2$ response is severely slowed, the $\dot{V}O_2$ increase is rather linear in nature, making MRT calculations unreliable [259]. Low response amplitudes during CWRT can additionally lead to unreliable kinetic feature values for patients with COPD [58]. Nevertheless, the issue of unreliable kinetic feature values has not yet been properly addressed. Additionally, $\dot{V}O_2$ kinetics of patients with COPD have only been examined in small study samples including at most 45 patients [57, 58, 252, 260–265, 129–133, 240, 241, 247]. Lastly, the impact of COPD-related

ventilatory and cardiovascular impairments on gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ remains unclear. We hypothesised that these gains could be an informative tool to examine ventilatory and gas exchange responses at exercise onset of patients with COPD.

To address these issues, this study used a large sample of patients with COPD (n=265): i) to establish simple guidelines that can identify patients for whom kinetic analyses are (un)likely to be reliable; ii) to determine whether slow $\dot{V}O_2$ responses during a standard CWRT are associated with ventilatory, cardiovascular and/or physical impairment; and iii) to determine whether gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ during a standard CWRT are associated with ventilatory, cardiovascular and/or physical impairment.

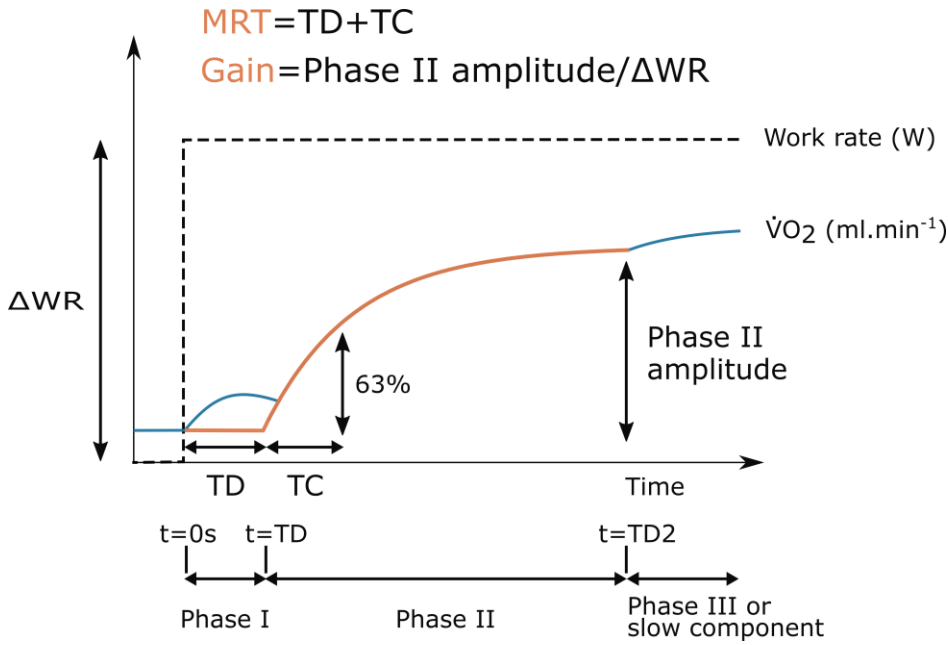


Figure 5.1: Representation of a typical oxygen uptake ($\dot{V}O_2$) response at the onset of a constant work rate test (blue line) and the specific phase II contribution (orange line). Both lines coincide during phase II. The black dashed line visualises the WR increase at t = 0 s. MRT = mean response time; TD = time delay; TC = time constant; WR = work rate; TD2 = time delay of phase III or the slow component, variable between 100-200 s [277].

3. Material and methods

3.1. Study design and participants

The investigated dataset is part of the COPD, health status and comorbidities (CHANCE) study, an observational, cross-sectional, single-centre study examining health status and comorbidities in patients with COPD [266]. The CHANCE study was approved by the Medical Ethical Committee of the Maastricht University Medical Centre (METC 11-3-070) and registered at the Dutch Trial Register (NTR 3416). All patients provided written informed consent. The Medical Ethical Committee of the Maastricht University Medical Centre (METC 2018-0546) confirmed that the Medical Research Involving Human Subjects Act did not apply for additional analyses of ventilatory and gas exchange responses, and thus additional official approval by the Committee was not required for the current study.

Patients with COPD, referred to CIRO (Horn, the Netherlands) for clinical assessment and pulmonary rehabilitation [222], were recruited during their pre-rehabilitation assessment [266]. CIRO provides an interdisciplinary pulmonary rehabilitation program in accordance with the latest international American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation [63]. Demographics, resting post-bronchodilator spirometry, whole-body plethysmography, lung diffusion capacity, the modified Medical Research Council (mMRC) dyspnea grading, resting arterial blood gas analyses (i.e. arterial oxygen saturation, pH and partial pressure of oxygen and carbon dioxide), fat-free mass index using dual-energy X-ray absorptiometry and physical performance (i.e. six-minute walking distance, $\dot{V}O_{2,peak}$, WR_{peak}, CWRT endurance time and quadriceps isokinetic peak torque) data were collected during the pre-rehabilitation assessment as described before [222, 266]. Maximal voluntary ventilation (MVV) was estimated by multiplying FEV_1 by 40. Resting echocardiography was added to these standard tests to assess left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter, left atrium diameter, right ventricle diameter and interventricular septum thickness [266]. A symptom-limited incremental cardiopulmonary exercise test was performed on an electrically braked cycle ergometer (Oxycon Pro, Carefusion, Houten, the Netherlands) to assess peak $\dot{V}O_2$ and WR values. The day after, a symptom-limited CWRT was performed to assess CWRT

endurance time. In accordance to standard practice, the CWRT started with a period of rest (3 minutes) and unloaded cycling (3 minutes), after which the WR increased instantaneously to 75% of the WR_{peak} achieved during the prior incremental cardiopulmonary exercise test [63]. $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ responses were determined breath-by-breath (Oxycon Pro, Carefusion, Houten, the Netherlands).

3.2. Kinetic analyses

Breath-by-breath data during CWRT were pre-processed and resampled to a 1 Hz time series as explained by Buekers and colleagues [259]. A Box-Jenkins transfer function with a first order system model and a second order noise model was fitted to the $\dot{V}O_2$ time series from 30 s before the increase in WR until 180 s after this step increase in WR to calculate $\dot{V}O_2$ MRT (= time delay + time constant; Figure 5.1) [259]. This 180 s cut-off has generally been used to diminish the potential contribution of the slow component [257, 258]. Gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ were estimated as follows:

$$Gain = \frac{Variable_{[150s-180s]} - Variable_{unloaded}}{\Delta WR}$$

where $Variable_{[150s-180s]}$ was calculated as the mean of the last 30 s of the $\dot{V}O_2$, $\dot{V}CO_2$ or $\dot{V}_E$ responses that were used for kinetic modelling (i.e. 150s to 180 s); $Variable_{unloaded}$ as the mean of the last 30 s of $\dot{V}O_2$, $\dot{V}CO_2$ or $\dot{V}_E$ during unloaded cycling before the increase in WR; and ΔWR as the WR increase. The system model fit was assessed by the normalised root-mean-squared error value (NRMSE), calculated as the root-mean-square of the system model errors (i.e. difference between the modelled value and the pre-processed time series) divided by the difference between $Variable_{[150s-180s]}$ and $Variable_{unloaded}$.

Patients were excluded from analyses if they did not perform breath-by-breath measurements of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ during the CWRT or if they had a CWRT endurance time lower than 180 s. In addition, patients exhibiting unreliable kinetic feature values were excluded for kinetic analyses. Kinetic feature values could not reliably be calculated due to: 1) a low increase above unloaded cycling of $\dot{V}O_2$ (<200 $ml.min^{-1}$), $\dot{V}CO_2$ (<200 $ml.min^{-1}$) or $\dot{V}_E$ (<7 $L.min^{-1}$) after 180 s (being lower than 2.5 standard deviations of the

breath-by-breath fluctuations [134, 247]); 2) a poor $\dot{V}O_2$ system model fit, defined as NRMSE >25%; 3) a severely slowed $\dot{V}O_2$ response ($\dot{V}O_2$ MRT > 150 s; see Supplementary Text 5.1). MRT values of patients with a severely slowed $\dot{V}O_2$ response were considered unreliable because these responses were rather linear in nature, leading to extremely high MRT values [259].

3.3. Statistical analyses

Results are presented as mean and standard deviation or median and interquartile range for respectively normally or non-normally distributed variables. Normality was tested using the Kolmogorov-Smirnov test. Patients with missing data were only excluded for statistical testing of the specific variable where data was missing. Patient characteristics were compared between patients exhibiting unreliable and reliable kinetic feature values, using Student's t-tests, Wilcoxon rank-sum tests and chi-squared tests, as appropriate.

In addition, this comparison between patients that exhibited unreliable and reliable kinetic feature values was used to highlight the variables of interest that could identify patients for whom kinetic analyses are (un)likely to be reliable. A range of cut-off values for these variables of interest were then tested as a prediction method, where kinetic feature values were predicted to be unreliable (or reliable) for patients below (or above) the cut-off value. For each cut-off value, patients were then classified as a true negative (patients exhibiting unreliable kinetic feature values for whom kinetic feature values were also predicted to be unreliable), true positive (exhibiting reliable and predicted to be reliable), false negatives (exhibiting reliable, but predicted to be unreliable) or false positives (exhibiting unreliable, but predicted to be reliable). Negative predictive values (i.e. the amount of true negatives divided by the total amount of predicted negatives) were examined to determine cut-off values below which kinetic analyses are unlikely to be reliable. These negative predictive values indicated the percentage of patients below the selected cut-off values who indeed exhibited unreliable kinetic feature values. Equivalently, positive predictive values (i.e. the amount of true positives divided by the total amount of predicted positives, which indicated the percentage of patients above the selected cut-off value who indeed exhibited reliable kinetic feature values) were examined to determine cut-off values above which

kinetic analyses are likely to be reliable. In addition, the group of patients that would be identified as "(un)likely to exhibit reliable kinetic feature values" should be sufficiently large. Therefore, the amount of patients with values below or above the selected cut-off values were simultaneously assessed.

For the patients that were included for kinetic analyses, correlations between kinetic feature values and patient demographics, resting pulmonary function, resting arterial blood gases, resting echocardiography and physical performances were assessed using Pearson and Spearman correlation coefficients, as appropriate. In addition, patient demographics, resting pulmonary function and resting echocardiography were used as independent variables in a multiple linear regression model to identify which patient characteristics were independently related to the kinetic feature values. Statistical significance was accepted at the $p<0.05$ level.

4. Results

4.1. Patient characteristics

One hundred and forty-three of the 518 recruited COPD patients did not perform breath-by-breath measurements of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ during CWRT (Figure 5.2). For 70% of these patients (=100/143), this was because they received long-term oxygen therapy (Supplementary Text 5.2). An additional 110 patients with severe ventilatory and physical impairments were excluded for analyses because of an insufficient (<180 s) CWRT endurance time (Figure 5.2; Supplementary Text 5.2). The 265 remaining patients had an average age of 63±9 years, suffered from moderate to very severe COPD, had an impaired diffusion capacity and experienced physical impairments (Table 5.1). There were slightly more men (156/265=59%) and 28 (28/265=11%) of the patients suffered from reduced LVEF (<50%). There were missing data points for fat-free mass index (n=12), transfer factor for carbon monoxide (TLCO; n=10), residual volume (RV; n=8), mMRC dyspnoea grading (n=2), echocardiography (n=3), quadriceps isokinetic peak torque (n=23) and six-minute walking distance (n=1).

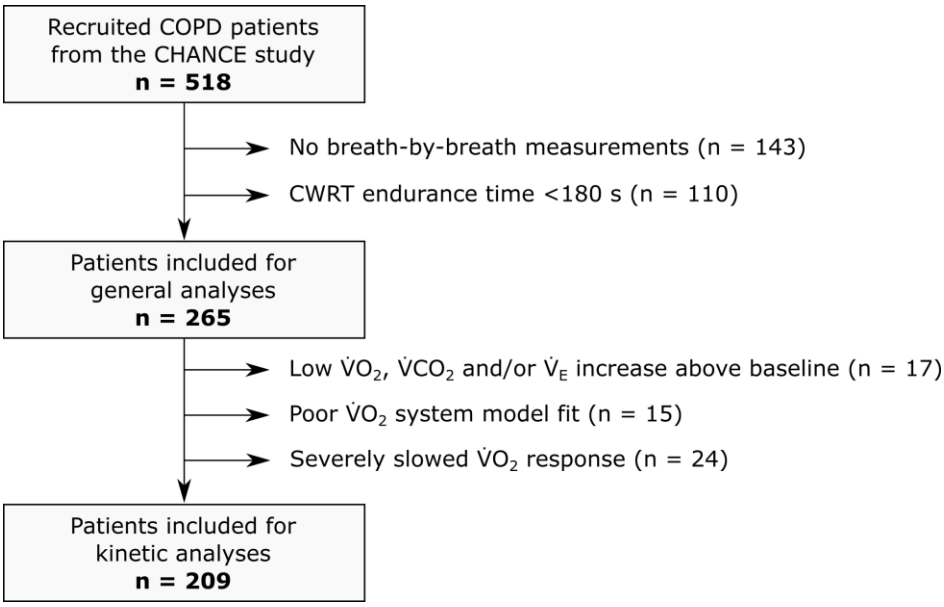


Figure 5.2: Overview of patients included for general and kinetic analyses. CWRT = constant work rate test; $\dot{V}O_2$ = oxygen uptake; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}_E$ = minute ventilation.

Table 5.1: Characteristics of patients included for general analyses (first column), divided as patients exhibiting unreliable (second column; excluded for kinetic analyses) and reliable (third column; included for kinetic analyses) kinetic feature values.

	Patients included for general analyses (n=265)	Patients with unreliable kinetic feature values (n=56)	Patients with reliable kinetic feature values (n=209)
Demographics			
Male – female	156 – 109	27 – 29	129 – 80
Age (years)	63 (9)	**68 (8)**	**62 (9)****
Body Mass Index (kg/m^2)	26.8 (6.0)	26.4 (5.4)	26.9 (6.2)
Fat-free mass index (kg/m^2)	17.4 (2.5)	17.0 (2.3)	17.5 (2.6)
Resting pulmonary function			
FEV_1 (%predicted)	54 (19)	**43 (15)**	**57 (19)*****
Forced vital capacity (FVC; %predicted)	104 (18)	100 (20)	105 (17)
FEV_1/FVC (%)	39 (12)	**33 (10)**	**42 (12)*****
TLCO (%predicted)	55 (16)	**47 (12)**	**56 (16)****
Residual volume (%predicted)	151 (44)	**164 (36)**	**147 (45)***
mMRC grading ≥ 2 (% patients)	72	**88**	**68****
Resting arterial blood gases			
Arterial oxygen saturation (%) #	94.8 (2.7)	94.4 (3.3)	94.9 (2.6)
Partial pressure of oxygen (kPa)	9.66 (1.36)	9.53 (1.25)	9.69 (1.38)
Partial pressure of carbon dioxide (kPa) #	5.00 (0.70)	5.20 (0.90)	5.00 (0.70)
pH #	7.42 (0.03)	7.42 (0.05)	7.42 (0.03)
Resting echocardiogram			
Left ventricular ejection fraction (%) #	61 (7)	**59 (8)**	**62 (7)***
Left ventricular end-diastolic diameter (mm)	44 (6)	43 (6)	44 (6)
Left atrium diameter (mm)	36 (6)	35 (6)	36 (6)
Right ventricle diameter (mm)	35 (5)	35 (4)	34 (5)
Interventricular septum thickness (mm) #	9 (2)	9 (2)	9 (2)

Values are represented as mean (standard deviation). # Indicates when values are represented as median (interquartile range). Values in bold indicate significant differences between the two patient groups using Student's t-tests, Wilcoxon rank-sum tests or chi-squared tests, as appropriate (*: $p<0.05$; **: $p<0.001$; ***: $p<10^{-5}$). FEV_1 = forced expiratory volume in 1 second; TLCO = transfer factor for carbon monoxide; mMRC grading = modified medical research council grading; CWRT = constant work rate test; MVV = maximal voluntary ventilation

Table 5.1 – Continued

	Patients included for general analyses (n=265)	Patients with unreliable kinetic feature values (n=56)	Patients with reliable kinetic feature values (n=209)
Physical performance			
Six-minute walking distance (m)	477 (105)	**401 (97)**	**497 (98)*** **
Six-minute walking distance (%predicted)	74 (15)	**67 (15)**	**76 (14)** **
Peak work rate (W) #	76 (39)	**54 (29)**	**85 (37)*** **
Peak work rate (%predicted) #	58 (31)	**46 (29)**	**60 (29)** **
Peak oxygen uptake ($ml.min^{-1}$) #	1105 (495)	**911 (287)**	**1178 (505)*** **
Peak oxygen uptake (%predicted) #	63 (32)	60 (38)	64 (31)
Isokinetic peak torque (Nm)	104 (38)	**83 (30)**	**110 (38)*** **
Isokinetic peak torque (%predicted)	71 (18)	**63 (14)**	**73 (19)** **
CWRT - Endurance time (s) #	294 (184)	**242 (119)**	**305 (199)** **
CWRT - Minute ventilation$_{[150s-180s]}$ (%MVV)	78 (24)	**84 (33)**	**76 (21)***

Values are represented as mean (standard deviation). # Indicates when values are represented as median (interquartile range). Values in bold indicate significant differences between the two patient groups using Student's t-tests, Wilcoxon rank-sum tests or chi-squared tests, as appropriate (*: $p<0.05$; **: $p<0.001$; ***: $p<10^{-5}$).

4.2. Kinetic analyses

Kinetic feature values were unreliable for 56 of the patients that were included for general analyses (17+15+24=56; 56/265=21%; Figure 5.2). These patients were thus excluded for kinetic analyses. Figure 5.3 provides representative examples of $\dot{V}O_2$ responses of patients that exhibited unreliable kinetic feature values due to a low $\dot{V}O_2$ response, a poor $\dot{V}O_2$ system model fit or a severely slowed $\dot{V}O_2$ response. These 56 patients were older and suffered from more severe ventilatory and physical impairments compared to the 209 patients with reliable kinetic feature values (Table 5.1). Consequently, WR_{peak} and FEV_1 (in L) were considered as the variables of interest to identify patients for whom kinetic analyses are (un)likely to be reliable. As illustrated in Figure 5.4, kinetic feature values were unreliable for most patients with a low WR_{peak}, whereas kinetic feature values were reliable for most patients with a high FEV_1 value.

A WR_{peak} cut-off value of 45 W (corresponding to a negative predictive value of 79%) was selected to identify patients for whom kinetic analyses are unlikely to be reliable, as higher cut-off values would drastically increase the amount of patients for whom kinetic feature values would falsely be predicted to be unreliable (i.e. a drastic decrease of the negative predictive value, Figure 5.4). Twenty-four patients (24/265=9%) had a WR_{peak} value lower than this 45 W cut-off value (Figure 5.4). For FEV_1, a cut-off value of 1.3 L (corresponding to a positive predictive value of 94%) was selected to identify patients for whom kinetic analyses are likely to be reliable (Figure 5.4). One hundred and forty-two patients (142/265=53%) had a FEV_1 value higher than this 1.3 L cut-off value (Figure 5.4). Higher cut-off values could still increase the positive predictive value, however, this would drastically decrease the size of the patient group that could be identified as "likely to exhibit reliable kinetic feature values" (Figure 5.4).

Figure 5.5 illustrates representative $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ responses of a patient that could be included for kinetic analyses. The Box-Jenkins transfer function system models of the 209 patients that were included for kinetic analyses had a median NRMSE of 11.6±6.5%. No differences in NRMSE values were observed when these patients were dichotomised according to age (≥60 years: 11.8±6.8%; <60 years: 11.3±6.4%; p=0.63), gender (male: 11.4±6.4%; female: 11.7±6.1%; p=0.38) or GOLD stage (GOLD stage I-II: 11.3±7.1%; GOLD stage III-IV: 11.6±5.3%; p=0.77).

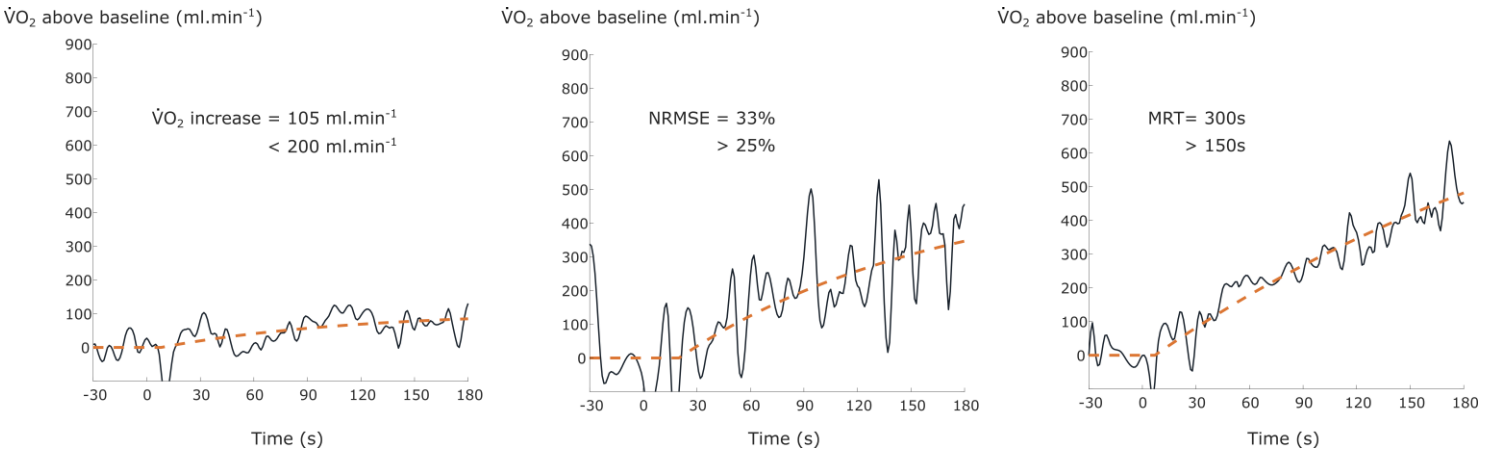


Figure 5.3: Representative examples of $\dot{V}O_2$ responses of patients exhibiting unreliable kinetic feature values due to a low $\dot{V}O_2$ increase above unloaded cycling (left), a poor $\dot{V}O_2$ system model fit (middle) or a severely slowed $\dot{V}O_2$ response. The orange dashed lines represents the Box-Jenkins transfer function system model. $\dot{V}O_2$ = oxygen uptake; NRMSE = normalised root-mean-squared error; MRT = mean response time.

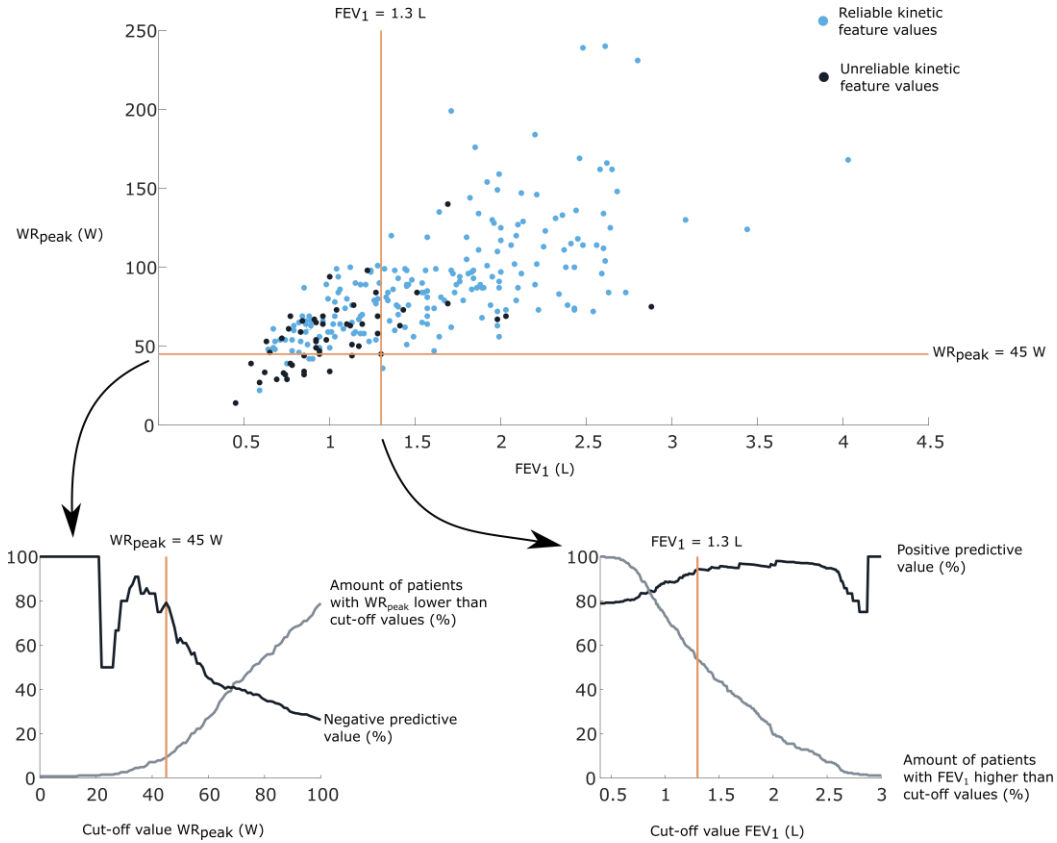


Figure 5.4: A peak work rate (WR_{peak}) cut-off value of 45 W corresponded to a negative predictive value of 79% for the prediction of patients who exhibited unreliable kinetic feature values. Twenty-four patients (24/265=9%) had a WR_{peak} <45 W. A forced expiratory volume in 1 s (FEV_1) cut-off value of 1.3 L corresponded to a positive predictive value of 94% for the prediction of patients who exhibited reliable kinetic feature values. One hundred and forty-two patients (142/265=53%) had a FEV_1 >1.3 L.

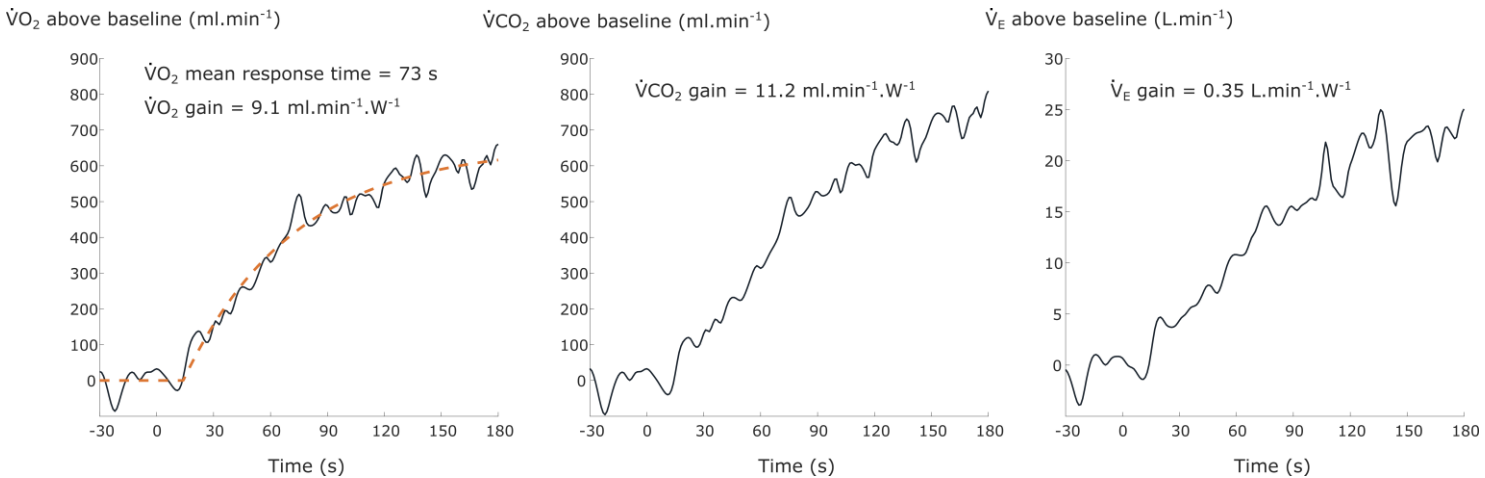


Figure 5.5: Representative example of oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) responses above unloaded cycling at exercise onset of a patient that was included for kinetic analyses. The work rate increased from 0 W to 67 W at Time = 0 s. The orange dashed lines represents the Box-Jenkins transfer function system model.

4.3. Mean response time

Patients exhibiting reliable kinetic feature values had a median $\dot{V}O_2$ MRT of 72±30 s. $\dot{V}O_2$ MRT was negatively correlated with FEV_1%predicted ($p<0.001$; $r=-0.35$), TLCO%predicted ($p=0.01$; $r=-0.18$) and partial pressure of oxygen ($p=0.02$; $r=-0.16$), while being positively correlated with age ($p=0.004$; $r=0.20$), RV%predicted ($p<0.001$; $r=0.29$) and $V_E/MVV_{[150s-180s]}$ ($p<0.001$; $r=0.26$). Multiple regression analysis generated the following model: $\dot{V}O_2$ MRT = – (0.47 × FEV_1%predicted) + (0.51 × age) + 73.7 (R^2 = 0.17). In addition, slower $\dot{V}O_2$ responses were linked with physical impairment as assessed by six-minute walking distance in meters ($p=0.01$; $r=-0.18$) and as %predicted ($p=0.009$; $r=-0.18$), $\dot{V}O_{2peak}$ in $ml.min^{-1}$ ($p=0.002$; $r=-0.22$) and as %predicted ($p<0.001$; $r=-0.24$). No significant correlations were observed between $\dot{V}O_2$ MRT and gains of $\dot{V}O_2$, $\dot{V}CO_2$ or $\dot{V}_E$.

4.4. Gains

Patients exhibiting reliable kinetic feature values had a mean $\dot{V}O_2$ gain of 9.4±1.8 $ml.min^{-1}.W^{-1}$. $\dot{V}O_2$ gain was negatively correlated with FEV_1%predicted ($p<0.001$; $r=-0.23$), left atrium diameter ($p=0.02$; $r=-0.17$) and interventricular septum thickness ($p=0.03$; $r=-0.15$), while being positively correlated with RV%predicted ($p=0.002$; $r=0.22$), partial pressure of carbon dioxide ($p=0.03$; $r=0.15$), LVEF ($p=0.001$; $r=0.23$) and $\dot{V}_E/MVV_{[150s-180s]}$ ($p<0.001$; $r=0.38$). Multiple regression analysis generated the following model: $\dot{V}O_2$ gain = – (0.022 × FEV_1%predicted) + (0.044 × LVEF) + 8.04 (R^2 = 0.10)

Patients exhibiting reliable kinetic feature values had a mean $\dot{V}CO_2$ gain of 11.1±1.9 $ml.min^{-1}.W^{-1}$. $\dot{V}CO_2$ gain was negatively correlated with age ($p=0.002$; $r=-0.21$), BMI ($p=0.04$; $r=-0.14$), fat-free mass index ($p=0.03$; $r=-0.16$), left atrium diameter ($p=0.02$; $r=-0.16$), right ventricle diameter ($p=0.02$; $r=-0.16$) and interventricular septum thickness ($p=0.02$; $r=-0.16$), while being positively correlated with TLCO%predicted ($p=0.03$; $r=0.15$), partial pressure of oxygen ($p<0.001$; $r=0.23$), LVEF ($p=0.008$; $r=0.19$) and $\dot{V}_E/MVV_{[150s-180s]}$ ($p<0.001$; $r=0.22$). Multiple regression analysis generated the following model: $\dot{V}CO_2$ gain = – (0.032 × age) – (0.17 × fat-free mass index) + (0.028 × TLCO%predicted) + 14.56 (R^2 = 0.11). In addition, a weak

positive association was found between $\dot{V}CO_2$ gain and $\dot{V}O_{2peak}$%predicted (p=0.03; r=0.14).

Patients exhibiting reliable kinetic feature values had a median $\dot{V}_E$ gain of 0.36±0.14 $L.min^{-1}.W^{-1}$. $\dot{V}_E$ gain was negatively correlated with TLCO%predicted (p=0.005; r=-0.20), BMI (p<0.001; r=-0.27), fat-free mass index (p=0.007; r=-0.19), partial pressure of carbon dioxide (p<0.001; r=-0.26), left ventricular end-diastolic diameter (p=0.02; r=-0.16), left atrium diameter (p=0.04; r=-0.14), right ventricle diameter (p=0.004; r=-0.20) and interventricular septum thickness (p=0.04; r=-0.15), while being positively correlated with FEV_1%predicted (p=0.04; r=0.14) and $\dot{V}_E/MVV_{[150s-180s]}$ (p=0.004; r=0.20). Multiple regression analysis generated the following model: $\dot{V}_E$ gain = – (0.0017 × TLCO%predicted) – (0.0051 × BMI) + (0.0017 × FEV_1%predicted) + (0.0084 × left atrium diameter) + 0.48 (R^2 = 0.20). In addition, V_E gain was negatively correlated with isokinetic peak torque as %predicted (p=0.01; r=-0.18) and CWRT endurance time (p<0.001; r=-0.24).

5. Discussion

This study examined kinetic feature values of ventilatory and gas exchange responses at the onset of a standard CWRT in a large sample of COPD patients with moderate to very severe COPD. Kinetic feature values were unreliable for 21% of the patients in the examined sample. The results showed that patients with a WR_{peak} value below 45 W can be expected to exhibit unreliable kinetic feature values, whereas patients with a FEV_1 value above 1.3 L can be expected to exhibit reliable kinetic feature values. For patients that exhibited reliable kinetic feature values, slow $\dot{V}O_2$ responses were associated with ventilatory and physical impairments. Gains were mainly associated with cardiac function and ventilatory constraints.

Although 15% (6 out of 41) and 48% (12 out of 25) of COPD patients were excluded for kinetic analyses in previous studies [58, 252], this patient group has not yet been further examined. The current study showed that COPD patients with unreliable kinetic feature values during a standard CWRT represented a group of older patients with very severe ventilatory and physical impairments. More than three-quarters (79%) of patients with a WR_{peak} value below 45 W exhibited unreliable kinetic feature values. These severely reduced absolute WRs led to very low response amplitudes or

reduced signal to noise ratios [259, 267], making kinetic feature values unreliable [134, 135]. Consequently, kinetic analyses are likely to be unreliable for patients with a WR_{peak} lower than 45 W. In contrast, kinetic feature values can be expected to be reliable for patients with a FEV_1 value above 1.3 L, as 94% of the included patients with an FEV_1 value above 1.3 L exhibited reliable kinetic feature values.

When ventilatory restrictions did not result in unreliable kinetic feature values, they were still associated with higher $\dot{V}O_2$ MRT values. Slow $\dot{V}O_2$ responses in patients with COPD have mainly been attributed to slow central cardiovascular responses, resulting from increased intrathoracic pressure swings due to airflow obstruction and dynamic hyperinflation, ultimately impairing convective O_2 transport to the working muscles [129, 131, 133, 240, 241, 261]. The observed associations between slow $\dot{V}O_2$ responses and airflow limitation, RV and $V_E/MVV_{[150s-180s]}$ support this reasoning. Also impaired peripheral cardiovascular responses [241, 263] and slow muscle O_2 utilisation [130, 132, 260] have been suggested to slow $\dot{V}O_2$ responses of COPD patients. Most likely, the slow $\dot{V}O_2$ responses observed in patients with COPD cannot be attributed to a single mechanism, but are the result of a combination of ventilatory, cardiovascular and/or muscular malfunctioning. Nevertheless, the results of the current study are in line with the notion that ventilatory and associated cardiovascular restrictions could be the main factor in slowing $\dot{V}O_2$ responses of COPD patients at higher exercise intensities.

The associations between $\dot{V}O_2$ MRT and physical performances indicates that $\dot{V}O_2$ MRT, extracted from a standard CWRT, could be an important physiological indicator of physical performance. This has previously also been observed in healthy men [268]. Slow $\dot{V}O_2$ responses at exercise onset introduce higher dependencies on anaerobic energy sources [256], lead to faster muscle deoxygenation in patients with COPD [241] and are thus shown to be related to impaired physical performances. Bronchodilator therapy or heliox breathing have been reported to decrease $\dot{V}O_2$ MRT by improving breathing mechanics, subsequently slowing muscle deoxygenation and ultimately leading to increased physical performances [133, 261]. Strategies decreasing $\dot{V}O_2$ MRT, e.g. due to improved breathing mechanics related to exercise training [57, 58], heliox breathing [261], bronchodilator therapy [131, 133] or bronchoscopic lung volume reduction [240], are therefore likely to improve physical performances.

Response gains have been considerably less examined than $\dot{V}O_2$ MRT. They are generally assumed to be a measure of (in)efficiency [256]. Therefore, the association of a higher $\dot{V}O_2$ gain with more severe airflow obstruction, a higher RV and a higher $\dot{V}_E/MVV_{[150s-180s]}$ suggests that these ventilatory impairments lead to $\dot{V}O_2$ inefficiency, which is most likely related to the increased O_2 cost of breathing for COPD patients with more severe airflow obstruction [269, 270]. Aliverti and colleagues calculated that O_2 cost of breathing in COPD patients might be as high as 48% of the total O_2 uptake [271]. In a similar way, $\dot{V}_E$ gain can be used as a measure of ventilatory (in)efficiency, for which generally the $\dot{V}_E/\dot{V}CO_2$ relationship during incremental exercise testing has been used [272]. The current study also confirmed that $\dot{V}_E$ gain, similar to the $\dot{V}_E/\dot{V}CO_2$ relationship [272], was negatively correlated with diffusion capacity and physical performance. Nevertheless, as a standard CWRT at 75% WR_{peak} can be considered as a test of maximal physical performance for patients with COPD [273], response gains can also represent physiological limitations. In this regard, decreased cardiorespiratory functioning at older age could explain the limited $\dot{V}CO_2$ gain for older patients [274]. Also a decreased diffusion capacity was associated with limited $\dot{V}CO_2$ gains, while increased airflow limitation was associated with limited $\dot{V}_E$ gains. Similarly, reduced LVEF and enlarged left atrium, right ventricle and interventricular septum were related to limited $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ increases per unit of WR, similar to the observed association between reduced $\dot{V}O_{2peak}$ and enlarged ventricular and atrial cavities in patients with heart failure [275]. A recent study reported a similar association between a higher left ventricular end-diastolic diameter and a decreased $\dot{V}O_2$ response per unit of WR during an incremental exercise test of patients with coexisting COPD and systolic heart failure [276]. Gains can therefore represent both response efficiency and limitation.

The kinetic features extracted from a standard CWRT ($\dot{V}O_2$ MRT and $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ gains) can thus shed light on ventilatory and gas exchanges responses at exercise onset, as discussed above. An important asset of these kinetic features is that they can be considered as motivation-independent, in contrast to generally accepted indicators of physical performance like WR_{peak}, $\dot{V}O_{2,peak}$ and CWRT endurance time [63]. This also makes kinetic features insightful for quantifying physiological adaptations after interventions like exercise training or bronchoscopic lung volume

reduction. Especially $\dot{V}O_2$ MRT shows potential to serve as a motivation-independent, physiological indicator of physical performance.

In addition, extracting kinetic features from a CWRT that is standardly performed during a pre-rehabilitation assessment does not require any additional testing, offering an easy approach to enhance clinical patient assessments. Whereas current clinical assessments are mainly based on outcomes that assess patients under 'steady-state' (resting) conditions, kinetic features quantify the dynamic, physiological responses during the 'transition-state' from unloaded cycling to cycling at 75% of WR_{peak}. This difference might also be one of the main reasons why the 'steady-state' patients characteristics in this study could only explain a relatively small proportion of the variance in kinetic feature values. Furthermore, including intramuscular variables could still increase the explanatory power of 'steady-state' (resting) patient characteristics.

Some limitations should be taken into account for proper interpretation of the results of the current study. Firstly, kinetics analyses were based on a single transition from rest to exercise, as the data were collected during a standard pre-rehabilitation CWRT [266]. This approach has been used before [58, 240, 241, 263], because performing multiple CWRTs during a pre-rehabilitation assessment might not be practically feasible for this patient population. Furthermore, a more complex type of models was used to account for breath-by-breath fluctuations [259]. Secondly, kinetic analyses of physiological responses during high intensity exercise might be affected by the presence of a slow component that can delay or prevent reaching a steady state [257, 258]. The onset of this slow component can occur around 100 – 200 s after exercise onset [277], which can add uncertainty to the extracted kinetic feature values. The slowed physiological responses of patients with COPD might also prevent that a steady state is fully reached at the 180 s cut-off value. Nevertheless, the applied 180 s cut-off has often been used to account for the potential contribution of the slow component in patients with COPD, as this slow component might not yet be discernible during the first 180 s of high-intensity exercise [131, 133, 241, 261, 263]. Thirdly, gains were estimated using the presented formula, as the very slow $\dot{V}CO_2$ and $\dot{V}_E$ responses did not allow for the development of accurate models from which $\dot{V}CO_2$ and $\dot{V}_E$ gains could be extracted. Therefore, gain values were approximations of the true underlying gains. Also the fact that exercising at 75% WR_{peak} might not correspond to the

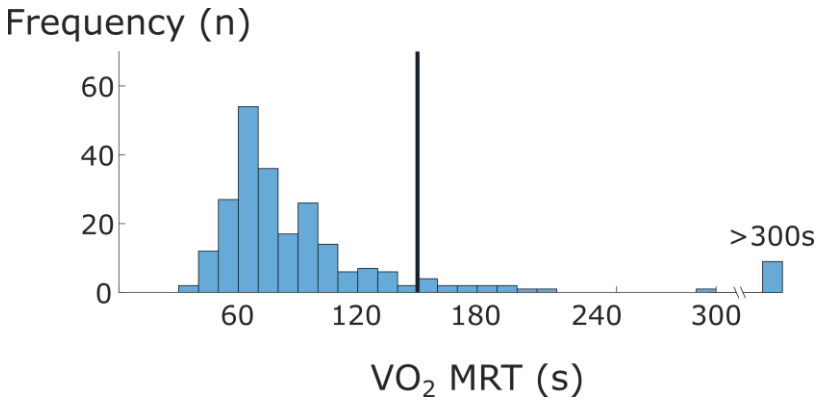
same point on the power duration curve for different patients, could add uncertainty to the estimated gains. Due to these sources of uncertainty and the cross-sectional nature of the current study, future studies will still be needed to determine the exact clinical value of kinetic features that are extracted from a standard CWRT at 75% of WR_{peak}. Nevertheless, the results of the current study show that these features capture valuable information about ventilatory and gas exchanges responses at exercise onset.

In conclusion, this study is the first to perform kinetic analyses on a large sample of COPD patients that were subjected to an elaborate clinical assessment. The results showed that patients with a WR_{peak} lower than 45 W are likely to exhibit unreliable kinetic feature values, while kinetic analyses can be considered reliable for most patients with an FEV_1 value above 1.3 L. For patients with reliable kinetic feature values, $\dot{V}O_2$ MRT during a standard CWRT could serve as a motivation-independent, physiological indicator of physical performance. Gains further enriched analyses of ventilatory and gas exchange responses at exercise onset, representing both response efficiency and limitation.

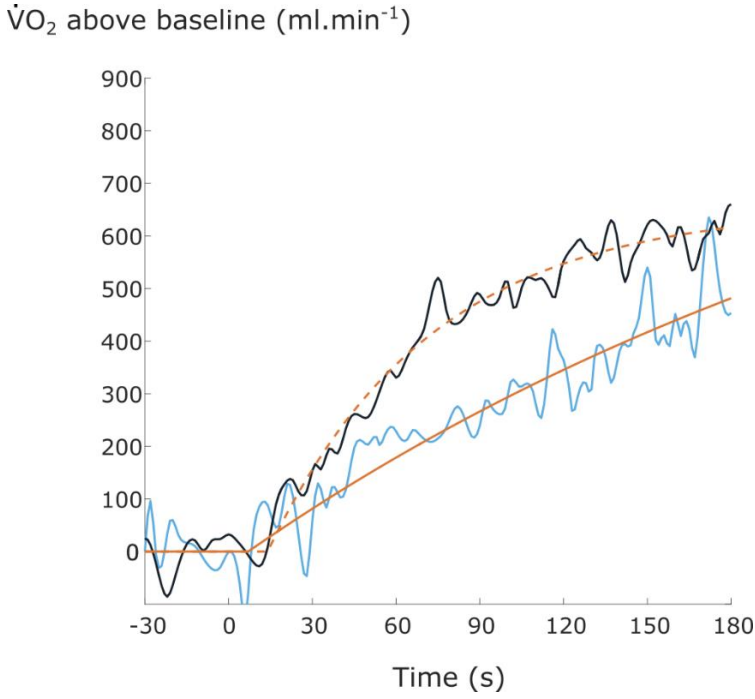
6. Supplementary material

6.1. Supplementary Text 5.1

$\dot{V}O_2$ MRT could be calculated for 233 patients (=265–17–15, see Figure 5.2). The skewed $\dot{V}O_2$ MRT distribution of these 233 patients is shown in the histogram below. $\dot{V}O_2$ MRT values were higher than 300 s for 9 patients. A $\dot{V}O_2$ response was considered to be severely slowed if the corresponding MRT value was higher than two times the interquartile range above the median of the shown $\dot{V}O_2$ MRT distribution (= 75 s + 2·39 s ≈150 s; represented by the black line in the histogram below).



Severely slowed $\dot{V}O_2$ responses, having a $\dot{V}O_2$ MRT value higher than 150 s, were rather linear in nature, as shown in the representative example on the next page. The black line visualises the $\dot{V}O_2$ response of a patient that exhibited reliable kinetic feature values ($\dot{V}O_2$ MRT = 73 s), the blue line visualises a severely slowed $\dot{V}O_2$ response ($\dot{V}O_2$ MRT > 150 s). The orange lines represent the corresponding Box-Jenkins transfer function system models.



6.2. Supplementary Text 5.2

More patients who did not perform breath-by-breath measurements during CWRT received long-term oxygen therapy, compared to patients with breath-by-breath measurements (100/143=70% vs. 11/375=3%). These patients had a lower TLCO%predicted (49±17 %predicted vs. 52±16 %predicted; p=0.02), higher partial pressure of carbon dioxide (5.3±0.8 kPa vs. 5.1±0.6 kPa; p=0.009) and lower six-minute walking distance in m (436±115m vs. 456 ± 107m; p=0.008) and as % predicted (68±17 %predicted vs. 71±15 %predicted; p=0.01) values compared to patients with breath-by-breath measurements during CWRT. No significant differences were found for other demographic, pulmonary function, resting arterial blood gas, resting echocardiography or physical performance variables.

Patients with a CWRT endurance time below 180 s (n=110) were more ventilatory and physically impaired compared to patients that could be included for general analyses (n=265; Figure 5.2), as indicated in the table below.

Table: Characteristics of patients with a sufficient (first column) and insufficient (second column) constant work rate test (CWRT) endurance time (first column).

	Patients with a CWRT endurance time < 180 s (n=110)	Patients included for general analyses (n=265)
Demographics		
Body Mass Index (kg/m^2)	**25.3 (5.4)**	**26.8 (6.0)***
Fat-free mass index (kg/m^2)	**16.5 (2.3)**	**17.4 (2.5)***
Resting pulmonary function		
FEV_1 (%predicted)	**44 (19)**	**54 (19)*****
Forced vital capacity (FVC; %predicted)	**95 (22)**	**104 (18)****
FEV_1/FVC (%)	**36 (12)**	**39 (12)****
Transfer factor for carbon monoxide (%predicted)	**46 (12)**	**55 (16)*****
Residual volume (%predicted)	**171 (49)**	**151 (44)****
mMRC grading ≥ 2 (% patients)	**87**	**72***
Physical performance		
Six-minute walking distance (m)	**406 (96)**	**477 (105)*****
Six-minute walking distance (%predicted)	**64 (15)**	**74 (15)*****
Peak work rate (W) #	**54 (28)**	**76 (39)*****
Peak work rate (%predicted) #	**44 (31)**	**58 (31)*****
Peak oxygen uptake (ml.min^{-1}) #	**852 (405)**	**1105 (495)*****
Peak oxygen uptake (% predicted) #	**52 (37)**	**63 (32)****
Isokinetic peak torque (Nm)	**84 (30)**	**104 (38)*****
Isokinetic peak torque (%predicted)	**61 (18)**	**71 (18)*****
CWRT - Minute ventilation$_{[150s-180s]}$ (%MVV)	**84 (27)**	**78 (24)***

Values are represented as mean (standard deviation). # Indicates when values are represented as median (interquartile range). Only significant differences between the two patient groups are shown, based on Student's t-tests, Wilcoxon rank-sum tests or chi-squared tests, as appropriate (*: $p<0.05$; **: $p<0.001$; ***: $p<10^{-5}$). FEV_1 = forced expiratory volume in 1 second; mMRC grading = modified medical research council grading; CWRT = constant work rate test; MVV = maximal voluntary ventilation.

Chapter 6 – Physiological changes differ between responders and non-responders to pulmonary rehabilitation in COPD

Manuscript under review

Most of the patients that were examined in Chapter 5 furthermore completed a pulmonary rehabilitation (PR) program. In this Chapter, physiological exercise responses before and after PR are compared in order to determine whether PR-induced changes of physiological exercise responses differ between patients that do or do not improve physical endurance following PR. The results of this Chapter, combined with the results of Chapter 5, address the third objective of this dissertation.

1. Abstract

Background: Not all patients with chronic obstructive pulmonary disease (COPD) experience the same benefits following pulmonary rehabilitation (PR). This pre-post study used a large sample of COPD patients to determine whether PR-induced changes of oxygen uptake ($\dot{V}O_2$) kinetics and exercise responses of $\dot{V}O_2$, carbon dioxide output ($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$), $\dot{V}_E/\dot{V}CO_2$, breathing frequency and tidal volume differed between responders and non-responders to PR.

Methods: Responders to PR were defined as patients with a minimal clinically important increase in endurance time of 105 s. Isotime (=180 s) values of $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$, breathing frequency and tidal volume; gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$; and $\dot{V}O_2$ mean response time of 183 patients with COPD (forced expiratory volume in 1 second: 56±19%predicted) were compared between pre- and post-PR constant work rate tests.

Results: Only responders, in contrast to non-responders, decreased $\dot{V}O_2$ mean response time (75±21 to 70±17 s; $p<0.05$), $\dot{V}CO_2$ gain, $\dot{V}_E$ gain and isotime values of $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ following PR (all $p<0.001$), while also improving their breathing pattern (e.g. breathing frequency isotime value: 28.8±6.2 to 25.0±5.4 breaths·min^{-1}; $p<0.0001$). These changes were correlated with changes in physical performance (e.g. correlation between changes in $\dot{V}O_2$ mean response time and endurance time: $p<0.001$, $r=-0.32$).

Conclusion: PR-induced changes in physiological exercise responses differed between responders and non-responders. Physiological changes are important in explaining the variable improvements of physical performance following PR in patients with COPD.

2. Introduction

Pulmonary rehabilitation (PR) is a comprehensive intervention, combining patient-tailored therapies such as exercise training, education and behavioural changes. It aims to increase physical performance and quality of life of patients with chronic obstructive pulmonary disease (COPD) [63]. A constant work rate test (CWRT) at 75% of the individual peak work rate (WR) can be used to assess improvements of physical performance following PR [63, 120, 121, 278]. An increase in the lower-limb physiological ability can explain, at least in part, improvements in physical

performance. Indeed, vastus lateralis muscle oxidative enzyme activity increased in patients with COPD following 10-12 weeks of exercise training [53, 54].

A number of studies with sample sizes ranging from 11 to 35 patients with COPD showed that exercise training also speeds oxygen uptake ($\dot{V}O_2$) kinetics at exercise onset, as quantified by a decreased $\dot{V}O_2$ mean response time (MRT) [57, 58, 262]. In patients with COPD, an elevated $\dot{V}O_2$ MRT is associated with both ventilatory and physical impairments [279]. Therefore, a PR-induced decrease of $\dot{V}O_2$ MRT (which reduces ventilatory and cardiovascular demands [256]) can help improve physical performance. In addition, PR has been shown to decrease carbon dioxide output ($\dot{V}CO_2$), decrease minute ventilation ($\dot{V}_E$) and alter breathing patterns during exercise in patients with COPD [57–59, 262].

Nevertheless, not all patients with COPD experience the same benefits from PR programs [278]. Although improvements of physical performance can vary between patients, the previously mentioned studies that observed physiological changes following PR did not make a distinction between patients with COPD that increased endurance time more than the minimal clinically important difference of 105 s [280] (responders) and patients who did not (non-responders). We hypothesised that the earlier described physiological changes following PR, such as speeded $\dot{V}O_2$ kinetics, might not be evident in all patients with COPD. Consequently, the objective of this study was to use a large sample of patients with COPD (n=183) to determine whether changes of $\dot{V}O_2$ MRT following PR differed between patients that did or did not respond to PR. In addition, we determined whether PR-induced changes of $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$, breathing frequency and tidal volume responses during exercise were different between responders and non-responders to PR.

3. Material and methods

3.1. Study design and participants

Clinically stable patients with COPD (no exacerbation within previous 4 weeks) were recruited at the start of an interdisciplinary PR program at CIRO (Horn, the Netherlands). Demographics, resting post-bronchodilator pulmonary function, the modified Medical Research Council dyspnoea

grading and resting arterial blood gas analyses were collected during a pre-PR assessment [266]. Physical performance was assessed by the six-minute walking distance, peak isokinetic quadriceps strength and peak values of $\dot{V}O_2$ and WR during a symptom-limited incremental cardiopulmonary exercise test [266]. Additionally, a symptom-limited CWRT was performed on an electrically braked cycle ergometer with a gas exchange analyser (Oxycon Pro, Carefusion, Houten, the Netherlands) for measuring CWRT endurance time. The CWRT consisted of a period of rest (3 minutes) and unloaded cycling (3 minutes), followed by an instantaneous WR increase to 75% of WR_{peak}. Borg scores for dyspnoea and fatigue were obtained at exercise cessation. Six-minute walking distance, peak isokinetic quadriceps strength and CWRT endurance time were measured again post-PR to quantify changes of physical performance following PR. Further details about the measurements described above can be found in Smid et al. [266].

The described data were collected as part of the COPD, Health status and Comorbidities (CHANCE) study, a single-centre study examining health status and comorbidities in patients with COPD [266]. This study was registered at the Dutch Trial Register (NTR 3416) and approved by The Medical Ethical Committee of the Maastricht University Medical Centre (METC 11-3-070). All patients provided written informed consent. The Medical Ethical Committee of the Maastricht University Medical Centre (METC 2018-0546) confirmed that additional approval by the Committee was not required for the current additional analyses. Data from the CHANCE study (i.e. the baseline kinetic feature values [279] and the effects of PR on physical performance and health status [281–284]) have already been published. The current description of the changes in physiological exercise responses following PR have not been reported before.

3.2. Pulmonary rehabilitation

Included patients underwent a PR program of 40 sessions that conforms to the latest international American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation [63, 222]. The interdisciplinary PR program consisted of physical exercise training, occupational therapy, nutritional counselling, psychosocial counselling, optimising medication use and adherence to medication, education and exacerbation management. Physical exercise training was the cornerstone

of the program, consisting of stationary cycling, treadmill walking and exercises to strengthen muscle groups in the upper and lower extremities. Exercise training was performed at moderate-to-high intensity, i.e. ≥60% of WR_{peak} (cycling), six-minute walking test speed (walking) and 1-repetition maximum (strengthening exercises). The training intensity of stationary cycling and treadmill walking was adjusted weekly based on Borg scores for dyspnoea and fatigue (target score of 4-6). The load of the strengthening exercises increased 3-5% per week. In addition, patients underwent flexibility exercises, general physical exercise for lower and upper extremities and daily supervised 30-minute outdoor walks. The program was implemented by an interdisciplinary team including a chest physician, respiratory nurse, dietician, occupational therapist, physiotherapist, psychologist and social worker.

3.3. Physiological responses during a constant work rate test

Ventilatory and gas exchange responses during CWRT were collected breath-by-breath (Oxycon Pro, Carefusion, Houten, the Netherlands) and pre-processed according to our previously described methodology [259]. Isotime values were calculated for $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$, breathing frequency and tidal volume as the mean of the last 30 s before isotime at t = 180 s. Isotime was selected at 180 s as this is the minimal target duration of a CWRT [121], while the potential contribution of the slow component is also minimal during the first 180 s of a CWRT [257, 258], see Figure 5.1.

At the onset of a CWRT, $\dot{V}O_2$ typically follows a three phase response (Figure 5.1). $\dot{V}O_2$ response kinetics, i.e. $\dot{V}O_2$ MRT and gain, quantify the fundamental component of this $\dot{V}O_2$ response [259, 279] (Figure 5.1). MRT describes the time needed to reach 63% of an anticipated steady state, indicating the speed of the $\dot{V}O_2$ increase at exercise onset. $\dot{V}O_2$ gain describes the $\dot{V}O_2$ increase of the fundamental component per unit increase in external work rate (WR) [259].

For the calculation of $\dot{V}O_2$ MRT, Box-Jenkins transfer functions with a first order system model and a second order noise model were fitted to the $\dot{V}O_2$ time series from 30 s before the WR increase until isotime at 180 s after this step WR increase [259, 279]. The system model fit was then assessed by the normalised root-mean-squared error value [279]. $\dot{V}O_2$ gain was calculated as $(\dot{V}O_{2,isotime} - \dot{V}O_{2,unloaded})/\Delta WR$ where $\dot{V}O_{2,unloaded}$ was the mean of the last

30 s of unloaded cycling and *ΔWR* was the WR increase at t=0 s (Figure 5.1). $\dot{V}CO_2$ and $\dot{V}_E$ gains were calculated in the same way. No gains were calculated for breathing frequency and tidal volume due to the variable nature of these responses at CWRT onset (Supplementary Figure 6.1).

3.4. Patient exclusion and unreliable kinetic feature values

Patients cycling until at least 105 s before the time limit pre-PR (i.e. CWRT endurance time pre-PR ≥ 1095 s) were excluded because they could not be identified as a responder (Figure 6.1). Patients not reaching the minimal target duration of a CWRT (i.e. 180 s [121]) pre- or post-PR were also excluded (Figure 6.1). Patients exhibiting unreliable kinetic feature values (i.e. unreliable $\dot{V}O_2$ MRT or gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$) pre- or post-PR were excluded for subsequent kinetic analyses (Figure 6.1) [279]. Kinetic feature values could not reliably be calculated due to (see [279]): 1) a low increase above unloaded values of $\dot{V}O_2$ (<200 ml·min^{-1}), $\dot{V}CO_2$ (<200 ml·min^{-1}) or $\dot{V}_E$ (<7 L·min^{-1}) at isotime, being lower than 2.5 standard deviations of the breath-by-breath fluctuations [134, 247]; 2) a poor $\dot{V}O_2$ system model fit, defined as normalised root-mean-squared error >25%; 3) a severely slowed $\dot{V}O_2$ response ($\dot{V}O_2$ MRT >150 s). $\dot{V}O_2$ MRT values of patients with a severely slowed $\dot{V}O_2$ response were considered unreliable because these responses were rather linear in nature, leading to extremely high MRT values [259, 279].

3.5. Statistical analyses

Results are presented as mean and standard deviation or median and interquartile range for normally or non-normally distributed variables, respectively. Normality was tested using the Kolmogorov-Smirnov test. Patients with missing data were only excluded for statistical testing of the specific variable where data was missing. Patients that increased CWRT endurance time following PR with more than 105 s, the lower bound of a minimal clinically important difference [63, 280], were classified as responders to PR, other patients as non-responders. Patient characteristics, isotime and kinetic feature values were compared between responders and non-responders using Student's t-tests, Wilcoxon rank-sum tests and chi-squared tests, as appropriate. Paired Student's t-tests and Wilcoxon signed rank tests were used to compare physical performance and physiological

exercise responses pre- and post-PR. Pearson correlations were used to correlate changes in six-minute walking distance, quadriceps isokinetic peak torque and CWRT endurance time following PR with changes in physiological exercise responses during CWRT. Statistical significance was accepted at the $p<0.05$ level. All analyses were performed using Matlab 2015b (MathWorks Inc., Natick, Massachusetts, USA).

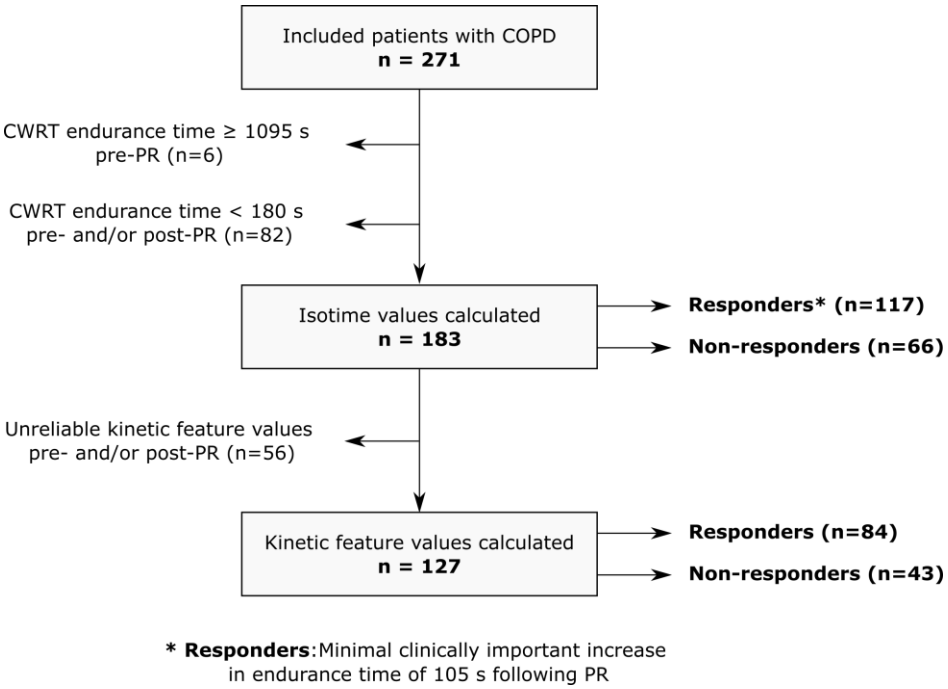


Figure 6.1: Overview of patient numbers included for analyses of isotime values (n=183) and for subsequent analyses of kinetic feature values (n=127). PR = pulmonary rehabilitation; CWRT = constant work rate test.

4. Results

4.1. Patient characteristics

Isotime values were calculated for 183 patients with COPD (Figure 6.1). These elderly patients were slightly overweight, suffered from mild to very severe COPD, impaired diffusion capacities and limited physical performances (Table 6.1). Responders (n=117), compared to non-responders (n=66), were younger, more overweight, had a higher fat-free mass index, better resting pulmonary function and less physical impairment before PR (Table 6.1).

Most patients that changed from unreliable (pre-PR) to reliable kinetic feature values (post-PR) were responders to PR (9/11=82%; Supplementary Text 6.2). Fifty six patients exhibited unreliable kinetic feature values pre- or post-PR (56/183=31%), leading to 127 patients that could be included for kinetic analyses (Figure 6.1). Patients with unreliable kinetic feature values pre- or post-PR were older and more ventilatory and physically impaired compared to patients with reliable kinetic feature values (Supplementary Text 6.2) [279]. When only considering patients with reliable kinetic feature values, similar differences between responders (n=84) and non-responders (n=43) as seen in Table 6.1 could be observed (Supplementary Tables 6.3). There were missing data points for fat-free mass index (n=7), transfer factor for carbon monoxide (n=6), residual volume (n=4), quadriceps isokinetic peak torque (n=14) and six-minute walking distance (n=1).

4.2. Physical performance and isotime values

Before PR, responders (n=117) had significantly higher values for quadriceps isokinetic peak torque, CWRT endurance time, isotime $\dot{V}O_2$, isotime $\dot{V}CO_2$ and isotime tidal volume, as well as significantly lower values for isotime $\dot{V}_E/\dot{V}CO_2$, compared to non-responders (n=66; all $p<0.05$). Only responders increased physical performance during endurance tests ($p<0.0001$ for both tests) following PR, whereas both patient groups increased quadriceps muscle strength ($p<0.0001$ for both groups; Table 6.2). Only the group of responders significantly decreased Borg scores for dyspnoea and fatigue at exercise cessation.

Table 6.1: Pre-rehabilitation characteristics, presented as mean (standard deviation), of patients with COPD that performed a constant work rate test (CWRT) pre- and post-pulmonary rehabilitation, divided as patients with (responders) and without (non-responders) clinically relevant increase of CWRT endurance time following pulmonary rehabilitation (i.e. >105 s increase).

	All patients (n=183)	Responders (n=117)	Non-responders (n=66)
Demographics			
Male – female	104 – 79	68 – 49	36 – 30
Age (years)	62 (9)	**61 (9)**	**65 (9)****
Body Mass Index (kg·m^{-2})	26.6 (6.0)	**27.6 (6.4)**	**24.9 (4.8)****
Fat-free mass index (kg·m^{-2})	17.3 (2.5)	**17.6 (2.7)**	**16.8 (2.1)***
Resting pulmonary function			
FEV_1 (%predicted)	56 (19)	**58 (19)**	**52 (18)***
Forced vital capacity (FVC; %predicted)	104 (18)	104 (18)	103 (19)
FEV_1/FVC (%)	41 (12)	**42 (12)**	**38 (12)***
TLCO (%predicted)	55 (16)	**57 (16)**	**52 (16)***
Residual volume (%predicted)	149 (44)	146 (43)	155 (47)
Intrathoracic gas volume (%predicted)	141 (33)	**137 (33)**	**148 (31)***
Total lung capacity (%predicted)	116 (17)	115 (16)	118 (19)
mMRC ≥ 2 (% patients)	72	70	76
Resting arterial blood gases			
Arterial oxygen saturation (%) #	94.9 (2.5)	94.9 (2.6)	94.9 (2.5)
Partial pressure of oxygen (kPa)	9.69 (1.33)	9.60 (1.30)	9.84 (1.38)
Partial pressure of carbon dioxide (kPa)	5.06 (0.59)	5.07 (0.61)	5.05 (0.55)
pH #	7.42 (0.03)	7.43 (0.03)	7.42 (0.03)
Physical performance			
Six-minute walking distance (m)	487 (102)	493 (103)	476 (101)
Six-minute walking distance (%predicted)	75 (14)	76 (14)	75 (15)
Peak work rate (W) #	80 (37)	**84 (46)**	**69 (36)***
Peak work rate (%predicted)	64 (25)	65 (24)	62 (28)
Peak oxygen uptake (ml·min^{-1})	1202 (410)	**1276 (428)**	**1069 (339)****
Peak oxygen uptake (%predicted) #	64 (33)	65 (33)	56 (30)
Isokinetic peak torque (Nm)	103 (37)	108 (36)	93 (37)*
Isokinetic peak torque (%predicted)	70 (18)	72 (17)	67 (21)
Constant work rate test – Endurance time (s) #	295 (184)	**310 (184)**	**267 (133)****
Constant work rate test – Borg dyspnoea score #	8 (3)	8 (2)	8 (3)
Constant work rate test – Borg fatigue score #	7 (4)	7 (5)	7 (4)

Values in bold indicate significant differences between responders and non-responders (*: $p<0.05$; **: $p<0.005$). # Variables are presented as median (interquartile range). FEV_1 = forced expiratory volume in 1 second; TLCO = transfer factor for carbon monoxide; mMRC grading = modified medical research council grading.

Only responders, in contrast to non-responders, had lower $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ isotime values following PR, accompanied by a change of breathing pattern, as indicated by the reduction of isotime breathing frequency and the increase of isotime tidal volume (all $p<0.05$; Table 6.2; Figure 6.2; Supplementary Figure 6.4). Similar results were obtained when only the 127 patients with reliable kinetic feature values were used for these analyses (Supplementary Tables 6.3).

4.3. Kinetic feature values

Before PR, no significant differences in kinetic feature values were observed between responders (n=84) and non-responders (n=43). Only for responders, $\dot{V}O_2$ MRT significantly decreased following PR ($p<0.05$). $\dot{V}O_2$ gain increased for both responders (close to significance, $p=0.05$) and non-responders ($p<0.05$; Table 6.3; Figure 6.2). In contrast, only responders experienced a decrease in $\dot{V}CO_2$ and $\dot{V}_E$ gain after PR (both $p<0.001$), which was not observed for non-responders (Table 6.3; Figure 6.2).

4.4. Correlations between changes in physiological exercise responses and physical performance

For the 183 included patients with COPD, the change in CWRT endurance time and six-minute walking distance post- compared to pre-PR was correlated with the change in isotime values of $\dot{V}CO_2$ ($p=0.002$, $r=-0.23$; $p=0.01$, $r=-0.19$, respectively), $\dot{V}_E$ ($p<0.001$, $r=-0.29$; $p<0.001$, $r=-0.27$, respectively), $\dot{V}_E/\dot{V}CO_2$ ($p=0.009$, $r=-0.19$; $p=0.05$, $r=-0.15$, respectively) and breathing frequency ($p<0.001$; $r=-0.25$; $p<0.001$; $r=-0.32$, respectively).

When only considering the 127 patients with reliable kinetic feature values, the change in CWRT endurance time and six-minute walking distance was additionally correlated with gains of $\dot{V}CO_2$ ($p=0.001$, $r=-0.29$; $p=0.04$, $r=-0.18$, respectively) and $\dot{V}_E$ ($p<0.001$, $r=-0.31$; $p=0.02$, $r=-0.21$, respectively). Changes in $\dot{V}O_2$ MRT were correlated with changes in CWRT endurance time ($p<0.001$, $r=-0.32$) and quadriceps isokinetic peak torque ($p=0.04$, $r=-0.19$).

Table 6.2: Changes in physical performance and constant work rate test (CWRT) isotime values following pulmonary rehabilitation (PR), presented as mean (standard deviation).

	Responders: Pre-PR	Responders: Post-PR	Pre-post difference (P-value)	Non-responders: Pre-PR	Non-responders: Post-PR	Pre-post difference (P-value)
Physical performance						
Six-minute walking distance (m)	493 (103)	536 (96)	**< 0.0001**	476 (101)	484 (94)	0.34
Isokinetic peak torque (Nm)	108 (36)	121 (40)	**< 0.0001**	93 (37)	101 (38)	**< 0.0001**
CWRT endurance time (s) #	310 (184)	829 (675)	**< 0.0001**	267 (133)	280 (138)	0.44
CWRT – Borg dyspnoea score #	8 (2)	6 (3)	**< 0.0001**	8 (3)	7 (3)	0.33
CWRT – Borg fatigue score #	7 (5)	4 (4)	**< 0.0001**	7 (4)	7 (4)	0.13
CWRT isotime value						
Oxygen uptake ($ml \cdot min^{-1}$)	1170 (330)	1154 (335)	0.26	1025 (246)	1029 (262)	0.74
Carbon dioxide output ($ml \cdot min^{-1}$)	1242 (401)	1136 (367)	**< 0.0001**	1069 (285)	1042 (301)	0.13
Minute ventilation ($L \cdot min^{-1}$)	45.5 (12.6)	40.1 (11.0)	**< 0.0001**	42.1 (11.0)	41.0 (11.2)	0.15
Minute ventilation·Carbon dioxide output^{-1} ($L \cdot L^{-1}$)	37.6 (6.7)	36.1 (5.8)	**< 0.0001**	39.8 (6.0)	39.9 (6.5)	0.85
Breathing frequency ($breaths \cdot min^{-1}$)	28.8 (6.2)	25.0 (5.4)	**< 0.0001**	29.6 (6.7)	28.4 (7.2)	0.05
Tidal volume ($L \cdot breath^{-1}$)	1.54 (0.48)	1.59 (0.48)	**0.04**	1.39 (0.42)	1.42 (0.46)	0.17

Patients are classified as responders (n=117) and non-responders (n=66). Displayed p-values indicate whether there were significant differences between pre- and post-PR values for responders (third column) and non-responders (sixth column). # Variables are presented as median (interquartile range).

Table 6.3: Changes in kinetic feature values following pulmonary rehabilitation (PR), presented as mean and standard deviation.

	Responders: Pre-PR	Responders: Post-PR	Pre-post difference	Non-responders: Pre-PR	Non-responders: Post-PR	Pre-post difference
$\dot{V}O_2$ mean response time (s)	75 (21)	70 (17)	**0.04**	78 (21)	83 (24)	0.11
$\dot{V}O_2$ gain ($ml \cdot min^{-1} \cdot W^{-1}$)	9.2 (1.7)	9.5 (1.5)	0.06	8.9 (1.6)	9.7 (1.7)	**0.01**
$\dot{V}CO_2$ gain ($ml \cdot min^{-1} \cdot W^{-1}$)	11.1 (1.8)	10.4 (1.5)	**< 0.001**	10.6 (1.6)	11.0 (1.8)	0.15
$\dot{V}_E$ gain ($L \cdot min^{-1} \cdot W^{-1}$)	0.38 (0.11)	0.33 (0.09)	**< 0.0001**	0.38 (0.11)	0.40 (0.11)	0.26

Patients are classified as responders (n=84) and non-responders (n=43). Displayed p-values indicate whether there were significant differences between pre- and post-PR values for responders (third column) and non-responders (sixth column).

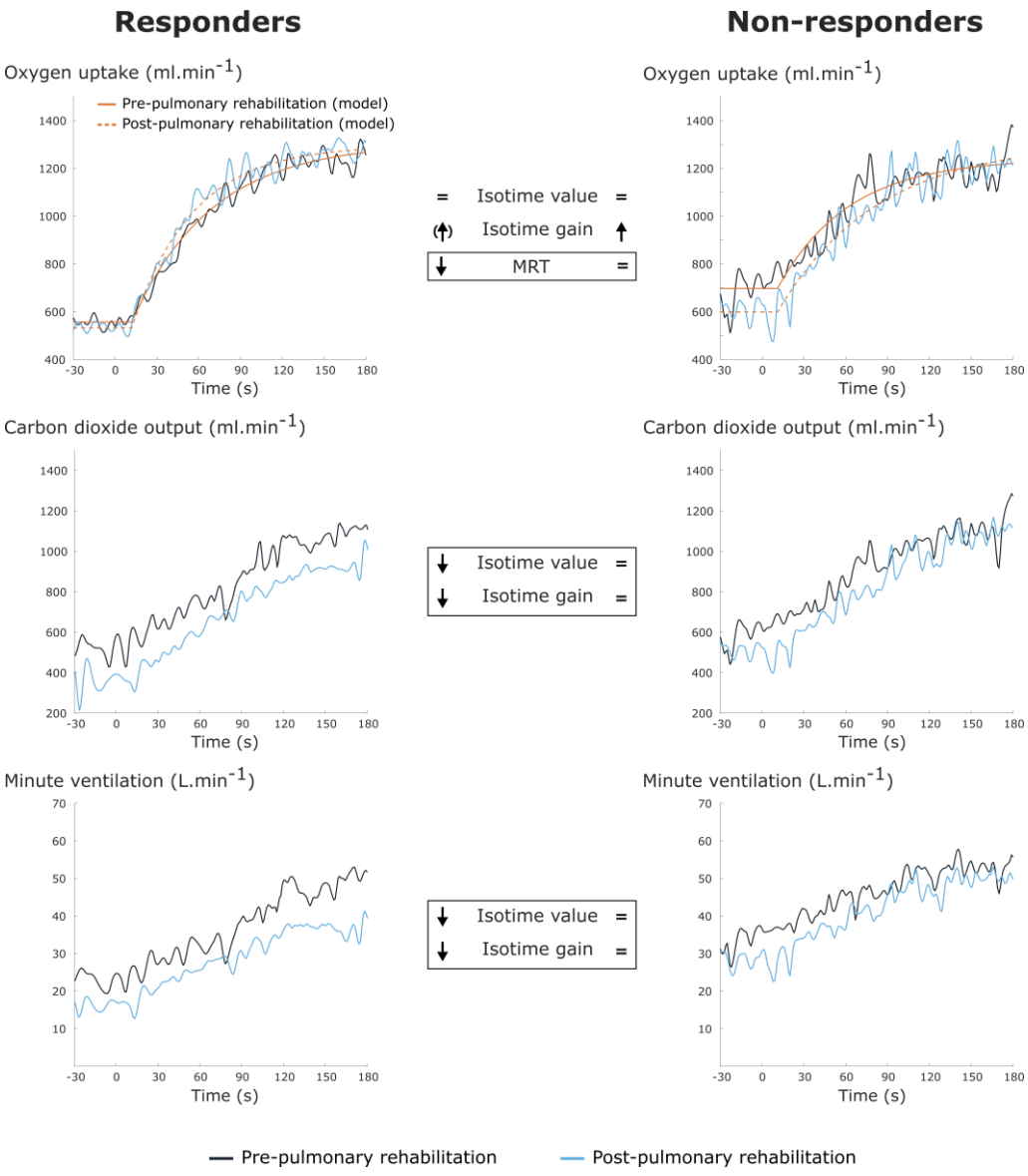


Figure 6.2: Examples of changes in physiological exercise responses following pulmonary rehabilitation for responders and non-responders. For clarity reasons, responses of different responders and non-responders are shown. Symbols in between the plotted responses indicate increased (upward arrow), decreased (downward arrow) or unchanged values (equality sign) for responders (symbols on the left side) and non-responders (symbols on the right side) following pulmonary rehabilitation. Framed symbols indicate differences between responders and non-responders for that specific variable. Similar examples of changes in minute ventilation/carbon dioxide production, breathing frequency and tidal volume are provided in Supplementary Figure 6.4.

5. Discussion

This study was the first to examine whether PR-induced changes in physiological exercise responses differ between patients with COPD who do or do not have a clinically relevant increase in CWRT endurance time following PR. Interestingly, only the group of responders showed a faster $\dot{V}O_2$ response (i.e. decreased $\dot{V}O_2$ MRT), a decrease in $\dot{V}CO_2$ and $\dot{V}_E$ gain, a decrease in isotime values of $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ and an improved breathing pattern following PR. These changes were correlated with changes in physical performance post-PR.

The results of the current study confirm that exercise training can speed $\dot{V}O_2$ kinetics, as quantified by a decreased $\dot{V}O_2$ MRT [57, 58, 262]. Interestingly however, this could not observed in the group of non-responders. This, in combination with the association between changes of $\dot{V}O_2$ MRT and changes of physical performance, highlights the importance of a swift $\dot{V}O_2$ response at exercise onset. Enhancements in peripheral oxygen delivery (related to decreased dynamic hyperinflation and subsequent faster cardiovascular responses [57–59, 279]) and consumption (related to improved muscle function and morphology [11]) most likely contribute to the faster $\dot{V}O_2$ response following PR in the group of responders. This faster response subsequently reduces lactate accumulation related to phosphocreatine breakdown and glycogenolysis, which decreases circulatory and ventilatory requirements, ultimately increasing CWRT endurance time [256, 268].

Decreased $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ responses post-PR (as indicated by the decreased gains and isotime values) were also only observed in the group of responders. For this group, the faster $\dot{V}O_2$ responses (combined with PR-induced improvements of muscle function and morphology [11]) can enhance aerobic ATP production and therefore reduce the need for anaerobic energy sources and subsequent lactate accumulation [256, 268]. As a result, the magnitude of the $\dot{V}CO_2$ response decreases and, due to the close coupling between $\dot{V}CO_2$ and $\dot{V}_E$, also the $\dot{V}_E$ response is reduced [60, 120].

Underlying the decreased $\dot{V}_E$ response in the group of responders was an improved breathing pattern, indicated by a decrease in breathing frequency and a small, but significant increase in tidal volume following PR. The decrease in breathing frequency post-PR is most likely related to a

reduction of dynamic hyperinflation [59]. Although improved breathing patterns have previously been reported after exercise training in patients with COPD [121], our study is the first to indicate that these changes cannot be observed in all patients with COPD following PR. Changes in isotime breathing frequency were furthermore associated with increases of CWRT endurance time and six-minute walking distance post-PR.

As a result of the observed $\dot{V}_E$ decrease during exercise in the group of responders (enabled by enhancements of aerobic ATP production and improved breathing patterns), the work of breathing is also reduced. This decreases the oxygen requirements of ventilatory muscles, making more oxygen available for the exercising muscles and consequently reducing lactate accumulation even further. This ultimately results in a further decrease of the $\dot{V}CO_2$ and $\dot{V}_E$ responses following PR in the group of responders [271]. The lowered isotime $\dot{V}_E/\dot{V}CO_2$ following PR indicates that the $\dot{V}_E$ decrease was more pronounced than the decrease of $\dot{V}CO_2$.

Interestingly, only the group of responders decreased Borg scores at exercise cessation following PR. Also this could be related to enhanced aerobic ATP production [256, 271] and improvements of the ventilatory demand-capacity imbalance [63]. In contrast, these changes were not observed in the group of non-responders. Therefore, they probably experienced the same exercise limitations post-PR compared to pre-PR, preventing them from increasing physical endurance.

These results show that physiological changes are important in explaining the highly variable improvements of physical performance that can be observed in patients with COPD following PR. In addition, physiological exercise responses can be considered motivation-independent, in contrast to the conventional indicators of improved physical performance following PR (e.g. CWRT endurance time or six-minute walking distance) [63, 121]. Another downside of these conventional indicators is that relatively large changes of CWRT endurance time could be induced by only a small shift of the power-duration curve [256]. Quantifications of physiological exercise responses could thus be an interesting (additional) tool to assess physical and physiological changes of patients with COPD after an intervention such as PR.

Some limitations should be taken into account. First, although there were clear physiological changes of responders on a group level, this was more variable on an individual level. Second, not all patients could be included for

these (kinetic) analyses due to an insufficient endurance time or unreliable kinetic feature values. Therefore, these physiological analyses might not be suitable for analysing the most severely ventilatory and physically impaired patients with COPD [279]. This could be expected, as it is difficult for these patients to achieve meaningful physiological changes after exercise training [285]. Third, kinetic analyses were based on a single transition from rest to exercise, as the data were collected during standard pre- and post-rehabilitation CWRTs [266]. Nevertheless, this approach has been used before [58, 240, 241, 263, 279], because performing multiple CWRTs during standard patient assessments might not be practically feasible. Moreover, a more complex type of model was used to account for breath-by-breath fluctuations [259]. Fourth, additional measurements of operating lung volumes and dynamic hyperinflation could provide more profound insights into the improved breathing pattern of responders after PR. Despite these limitations, the results of the current study clearly highlight that the (in-)ability to reach observable physiological changes following PR is an important element for explaining why some patients physically improve after PR, and others do not.

It would furthermore be insightful to investigate why some patients are able to reach these physiological changes following PR, while others do not. Previous studies showed that it seems unlikely to be related to the observed differences in age and airflow limitation between responders and non-responders [278, 286, 287]. Based on the current results, it could be argued that non-responders were unable to reach observable physiological changes (and thus neither improvements of physical performance) because their overall lower physical performance at baseline resulted in lower exercise intensities during PR. However, previous studies reported that patients with lower physical performance pre-PR were more likely to respond to PR [278, 287, 288]. These combined results highlight the fact that it is currently still difficult to predict which patients will benefit the most from a PR program [289].

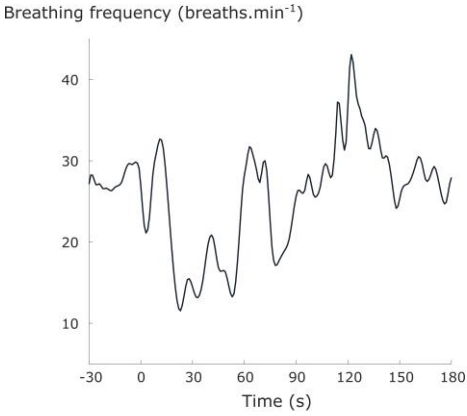
In conclusion, this study was the first to indicate that changes of physiological exercise responses following PR differed between responders and non-responders to PR. The large sample of included patients with COPD showed that only responders experienced a faster $\dot{V}O_2$ response, decreased $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ responses, and an improved breathing pattern following PR. Physiological changes are thus important in explaining the

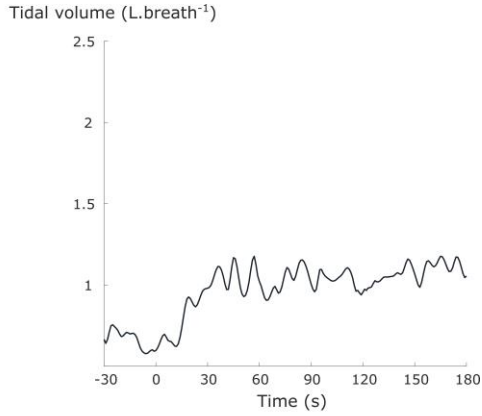
variable improvements of physical performance following PR in patients with COPD.

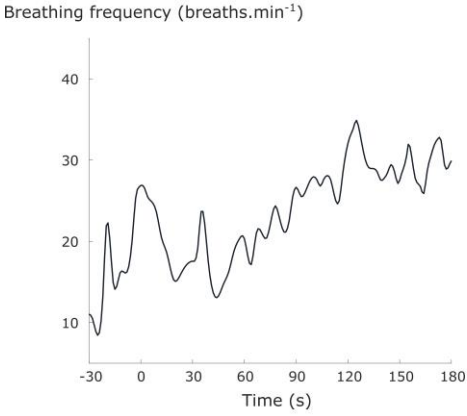
6. Supplementary material

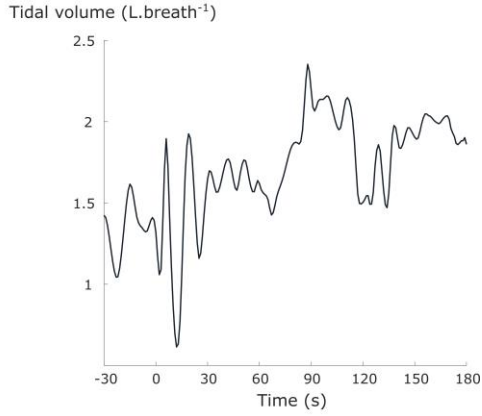
6.1. Supplementary Figure 6.1

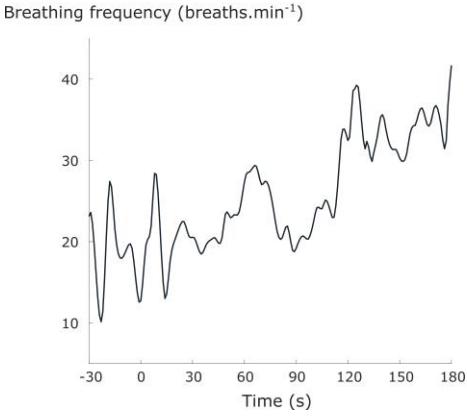
Examples of breathing frequency and tidal volume responses that show the variable nature of these responses at the onset of a constant work rate cycling test are shown on the next page. Neighbouring plots of breathing frequency and tidal volume responses originate from the same patient.

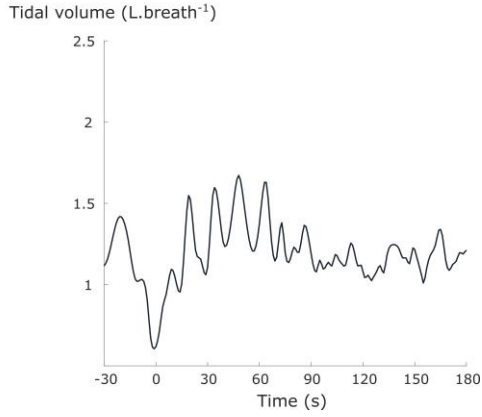

Breathing frequency (breaths.min-1)
40
30
20
10
-30
0
30
60
90
120
150
180
Time (s)


Tidal volume (L.breath-1)
2.5
2
1.5
1
-30
0
30
60
90
120
150
180
Time (s)


Breathing frequency (breaths.min-1)
40
30
20
10
-30
0
30
60
90
120
150
180
Time (s)

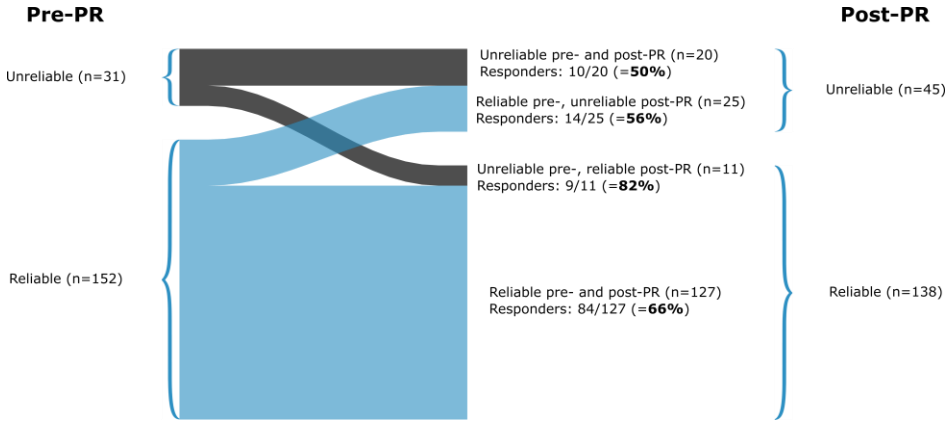

Tidal volume (L.breath-1)
2.5
2
1.5
1
-30
0
30
60
90
120
150
180
Time (s)


Breathing frequency (breaths.min-1)
40
30
20
10
-30
0
30
60
90
120
150
180
Time (s)


Tidal volume (L.breath-1)
2.5
2
1.5
1
-30
0
30
60
90
120
150
180
Time (s)

6.2. Supplementary Text 6.2

The Figure below visualises the amount of patients with COPD that exhibited unreliable or reliable kinetic feature values both pre- and post-pulmonary rehabilitation (PR), and the amount of patients that changed group post-PR. Of note, most patients that changed from unreliable (pre-PR) to reliable kinetic feature values (post-PR) were responders to PR (9/11=82%). The group of patients with unreliable kinetic features values both pre- and post-PR had the lowest relative amount of responders to PR (10/20=50%).



The Table on the next page compares patients exhibiting unreliable kinetic feature values pre- or post-PR (n=20+25+11=56; excluded for kinetic analyses) with patients exhibiting reliable kinetic feature values pre- and post-PR (n=127; included for kinetic analyses).

Table: Pre-rehabilitation characteristics, presented as mean (standard deviation) of patients with reliable and unreliable kinetic feature values pre- and/or post-pulmonary rehabilitation.

	Patients with reliable kinetic feature values (n=127)	Patients with unreliable kinetic feature values (n=56)
Demographics		
Male – female	73 – 54	31 – 25
Age (years)	**61 (10)**	**65 (3)****
Body Mass Index ($kg \cdot m^{-2}$)	26.7 (6.0)	26.4 (6.2)
Fat-free mass index ($kg \cdot m^{-2}$)	17.4 (2.5)	16.9 (2.5)
Resting pulmonary function		
FEV_1 (%predicted)	**60 (17)**	**44 (17)*****
Forced vital capacity (FVC; %predicted)	**107 (17)**	**97 (19)****
FEV_1/FVC (%)	**43 (11)**	**35 (11)*****
TLCO (%predicted)	**57 (17)**	**52 (15)***
Residual volume (%predicted)	145 (44)	158 (44)
Intrathoracic gas volume (%predicted)	138 (32)	148 (34)
Total lung capacity (%predicted)	116 (17)	116 (17)
mMRC grading ≥ 2 (% patients)	65	89
Resting arterial blood gases		
Arterial oxygen saturation (%)	94.4 (2.3)	94.2 (3.0)
Partial pressure of oxygen (kPa)	9.68 (1.34)	9.70 (1.31)
Partial pressure of carbon dioxide (kPa)	**5.00 (0.56)**	**5.19 (0.63)***
pH	7.43 (0.03)	7.42 (0.03)
Physical performance		
Six-minute walking distance (m)	**518 (90)**	**419 (95)*****
Six-minute walking distance (%predicted)	**79 (12)**	**68 (15)*****
Peak work rate (W)	**94 (34)**	**63 (22)*****
Peak work rate (%predicted)	**68 (25)**	**54 (24)****
Peak oxygen uptake ($ml \cdot min^{-1}$)	**1288 (415)**	**1008 (327)****
Peak oxygen uptake (%predicted)	70 (25)	65 (29)
Isokinetic peak torque (Nm)	**109 (37)**	**89 (34)****
Isokinetic peak torque (%predicted)	**74 (18)**	**63 (17)****
Constant work rate test – Endurance time (s) #	**311 (178)**	**241 (90)****
Constant work rate test – Borg dyspnoea score #	8 (3)	8 (3)
Constant work rate test – Borg fatigue score #	7 (4)	7 (4)

Values in bold indicate significant differences between patients with reliable and unreliable kinetic feature values (*: $p<0.05$; *: $p<0.005$; ***: $p<0.0001$). # Variables are presented as median (interquartile range). FEV_1 = forced expiratory volume in 1 second; TLCO = transfer factor for carbon monoxide; mMRC grading = modified medical research council grading.

6.3. Supplementary Tables 6.3

Table: Pre-rehabilitation characteristics, presented as mean (standard deviation), of patients with COPD that performed a constant work rate test (CWRT) and had reliable kinetic feature values pre- and post-pulmonary rehabilitation, divided as patients with (responders) and without (non-responders) clinically relevant increase of CWRT endurance time following pulmonary rehabilitation (i.e. >105 s increase).

	All patients (n=127)	Responders (n=84)	Non-responders (n=43)
Demographics			
Male – female	73 – 54	49 – 35	24 – 19
Age (years)	61 (10)	**60 (10)**	**64 (9)***
Body Mass Index ($kg \cdot m^{-2}$)	26.7 (6.0)	**27.7 (6.4)**	**24.9 (4.6)***
Fat-free mass index ($kg \cdot m^{-2}$)	17.4 (2.5)	17.7 (2.7)	17.0 (2.1)
Resting pulmonary function			
FEV_1 (%predicted)	60 (17)	**63 (17)**	**56 (18)***
Forced vital capacity (FVC; %predicted)	107 (17)	108 (16)	106 (18)
FEV_1/FVC (%)	43 (11)	**45 (11)**	**40 (12)***
TLCO (%predicted)	57 (17)	**59 (17)**	**53 (16)***
Residual volume (%predicted)	145 (44)	142 (42)	151 (47)
Intrathoracic gas volume (%predicted)	138 (32)	**135 (32)**	**145 (31)***
Total lung capacity (%predicted)	116 (17)	115 (16)	118 (18)
mMRC grading ≥ 2 (% patients)	65	63	67
Resting arterial blood gases			
Arterial oxygen saturation (%) #	94.9 (2.5)	94.9 (2.5)	94.7 (2.7)
Partial pressure of oxygen (kPa)	9.68 (1.34)	9.62 (1.35)	9.80 (1.32)
Partial pressure of carbon dioxide (kPa)	5.00 (0.56)	5.00 (0.57)	5.01 (0.56)
pH #	7.43 (0.03)	7.43 (0.03)	7.42 (0.03)
Physical performance			
Six-minute walking distance (m)	518 (90)	522 (88)	508 (94)
Six-minute walking distance (%predicted)	79 (12)	79 (11)	79 (15)
Peak work rate (W) #	89 (45)	**91 (50.5)**	**84 (35)***
Peak work rate (%predicted)	68 (25)	70 (25)	64 (25)
Peak oxygen uptake ($ml \cdot min^{-1}$)	1288 (415)	**1361 (430)**	**1143 (343)****
Peak oxygen uptake (%predicted) #	65 (35)	67 (31)	59 (27)
Isokinetic peak torque (Nm)	109 (37)	**113 (36)**	**99 (37)***
Isokinetic peak torque (%predicted)	74 (18)	75 (17)	71 (20)
Constant work rate test – Endurance time (s) #	311 (178)	**337 (183)**	**295 (191)***
Constant work rate test – Borg dyspnoea score #	8 (3)	8 (2)	8 (3)
Constant work rate test – Borg fatigue score #	7 (4)	7 (5)	7 (5)

Values in bold indicate significant differences between responders and non-responders (*: $p<0.05$; **: $p<0.005$). # Variables are presented as median (interquartile range). FEV_1 = forced expiratory volume in 1 second; TLCO = transfer factor for carbon monoxide; mMRC grading = modified medical research council grading

Table: Changes in physical performance and constant work rate test (CWRT) isotime values following pulmonary rehabilitation (PR) for patients with reliable kinetic feature values (n=127), presented as mean (standard deviation).

	Responders: Pre-PR	Responders: Post-PR	Pre-post difference (P-value)	Non-responders: Pre-PR	Non-responders: Post-PR	Pre-post difference (P-value)
Physical performance						
Six-minute walking distance (m)	522 (88)	562 (90)	**< 0.0001**	508 (94)	515 (87)	0.41
Isokinetic peak torque (Nm)	113 (36)	128 (41)	**< 0.0001**	99 (37)	107 (39)	**< 0.0001**
CWRT endurance time (s) #	337 (183)	952 (591)	**< 0.0001**	295 (191)	309 (164)	0.31
CWRT – Borg dyspnoea score #	8 (2)	6 (4)	**< 0.0001**	8 (3)	9 (4)	0.64
CWRT – Borg fatigue score #	7 (5)	4 (4)	**< 0.0001**	7 (5)	7 (4)	0.25
CWRT isotime value						
Oxygen uptake ($ml \cdot min^{-1}$)	1231 (323)	1218 (335)	0.32	1070 (260)	1080 (269)	0.54
Carbon dioxide output ($ml \cdot min^{-1}$)	1326 (397)	1217 (365)	**< 0.0001**	1126 (287)	1110 (313)	0.47
Minute ventilation ($L \cdot min^{-1}$)	48.0 (11.8)	42.7 (10.7)	**< 0.0001**	44.5 (11.5)	43.8 (11.8)	0.47
Minute ventilation·Carbon dioxide output^{-1} ($L \cdot L^{-1}$)	37.2 (7.0)	35.9 (6.1)	**< 0.001**	40.0 (6.1)	39.9 (5.6)	0.88
Breathing frequency ($breaths \cdot min^{-1}$)	29.0 (5.8)	25.5 (5.5)	**< 0.0001**	29.6 (5.9)	29.0 (6.9)	0.34
Tidal volume ($L \cdot breath^{-1}$)	1.65 (0.46)	1.68 (0.47)	0.22	1.48 (0.41)	1.52 (0.48)	0.29

Patients are classified as responders (n=84) and non-responders (n=43). Displayed p-values indicate whether there were significant differences between pre- and post-PR values for responders (third column) and non-responders (sixth column). # Variables are presented as median (interquartile range).

6.4. Supplementary Figure 6.4

Examples of changes in physiological exercise responses following pulmonary rehabilitation for responders and non-responders (see next page). For clarity reasons, responses of different responders and non-responders are shown. Symbols in between the plotted responses indicate increased (upward arrow), decreased (downward arrow) or unchanged values (equality sign) for responders (symbols on the left side) and non-responders (symbols on the right side) following pulmonary rehabilitation. Framed symbols indicate differences between responders and non-responders for that specific variable.


Responders
Non-responders
Minute ventilation.Carbon dioxide output-1 (L.L-1)
Minute ventilation.Carbon dioxide output-1 (L.L-1)
Isotime value =
Time (s)
Time (s)
Breathing frequency (breaths.min-1)
Breathing frequency (breaths.min-1)
Isotime value =
Time (s)
Time (s)
Tidal volume (L.breath-1)
Tidal volume (L.breath-1)
Isotime value =
Time (s)
Time (s)
Pre-pulmonary rehabilitation
Post-pulmonary rehabilitation

Chapter 7 – General discussion and conclusions

This last chapter will start with a short summary of the main findings of Chapters 2-6. Afterwards, the results of Chapters 2-6 will be used to illustrate that patients with COPD can be considered as complex, individual, time-varying and dynamic (CITD) biological systems. Consequently, appropriate data analysis and modelling techniques are required to capture and exploit this complex and variable nature, as will be discussed next. In the following sections, future perspectives of both telemonitoring and physical performance testing are considered. The last part of this Chapter will provide the general conclusions of this dissertation.

1. Summary of main findings

The results of this dissertation confirm the formulated hypothesis that current clinical assessments and interventions of patients with COPD can be enhanced by including time series analyses of continuously measured physiological variables. These improvements can be achieved in different ways.

One-week continuous measurements of peripheral oxygen saturation (SpO_2) showed that SpO_2 values of patients with COPD exhibit significant fluctuations during and between different days and nights (**Chapter 3**). Nevertheless, these fluctuations are currently often overlooked (**Chapter 2**). Consequently, **Chapter 3** showed that night-to-night SpO_2 fluctuations can lead to misclassifications of nocturnal (non-)desaturators. In addition, intraday and day-to-day SpO_2 fluctuations can decrease the performance of current telemonitoring applications that alert for exacerbations based on a combination of daily spot check measurements and simple thresholds (**Chapters 2 and 3**). Overall, continuously measuring SpO_2 over prolonged time periods, combined with suitable analyses of the resulting time series, has the potential to enhance both desaturator classifications and telemonitoring applications for patients with COPD.

In **Chapters 4 to 6**, continuously measured physiological variables during exercise were analysed to characterise physiological exercise responses of patients with COPD. These characterisations can enrich clinical assessments of physical performance. A new methodology was introduced for reliable analyses of oxygen uptake ($\dot{V}O_2$) kinetics in patients with COPD (**Chapter 4**). The introduced Box-Jenkins transfer function (BJ-TF) models were able to account for natural fluctuations in the data, in contrast to generally applied exponential models. Applying these models on a large sample of patients with COPD (n=265) showed that $\dot{V}O_2$ mean response time (MRT) shows potential to serve as a motivation-independent, physiological indicator of physical performance. Gains of $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) can further enrich analyses of physiological exercise responses in patients with COPD, as they represent both response efficiency and limitation (**Chapter 5**). It should furthermore be noted that kinetic analyses are likely to be unreliable for COPD patients with a peak work rate (WR) below 45 W. Lastly, PR-induced changes in physiological exercise responses of $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$,

breathing frequency and tidal volume were found to differ between responders and non-responders to PR, indicating that physiological improvements are important in explaining the variable improvements of physical performance following PR in patients with COPD (**Chapter 6**).

2. COPD patients are complex, individual, time-varying and dynamic biological systems

The results of this dissertation perfectly fit the framework of COPD patients being complex, individual, time-varying and dynamic (CITD) systems [290], as will be clarified below.

2.1. Complex

The complexity of COPD has been extensively discussed in **Chapter 1**. It was illustrated that COPD is a heterogeneous and multicomponent chronic condition that is manifested through a variety of respiratory and non-respiratory pathologies. This complexity can make it difficult to provide conclusive explanations for all the observed results in this dissertation. It is therefore important to note that the discussion sections of the different chapters (especially **Chapter 5 and 6**) aim to explain the observed results, whereas alternative or additional explanations can be valid as well. For example, the observed physiological changes of responders following PR (**Chapter 6**) can also be explained in the light of an improved mechanical efficiency [270]. Mechanical efficiency quantifies the ratio between the external work rate (1 W = 0.014 kcal.min^{-1}) and the total energy expenditure (in kcal.min^{-1}) during a CWRT. Improvements of mechanical efficiency following PR thus correspond to a decrease of the energy that is required to perform the post-PR CWRT. The reduced energy requirements are thought to be related to a decrease in the energy requirements for breathing [270], which is in line with the results and explanations provided in **Chapter 6**. Most likely the observed physiological changes of responders following PR are related to a combination of different and interrelated mechanisms. Additional measurements (e.g. operating lung volumes and dynamic hyperinflation in **Chapters 5 and 6**) would furthermore be insightful to obtain more conclusive explanations about all the observed results.

2.2. Individually different

The described heterogeneity between patients with COPD furthermore shows that they are all individually different. This is nicely illustrated by the results of **Chapter 3**, which observed a mean daytime SpO_2 difference of more than 11% between different patients with COPD, indicating that baseline SpO_2 values can vary vastly between different patients. Naturally, this urges telemonitoring applications to use individualised approaches. Nevertheless, multiple studies that were summarised in **Chapter 2** did not consider this individuality and merely used generic thresholds for the whole study sample to alert for exacerbations [152–154, 161–166]. Similar generic thresholds have also been used for other variables [77, 102]. As argued before, it is unlikely that these generic approaches will accurately predict exacerbations in patients with COPD.

Physiological exercise responses can also greatly differ between patients, as illustrated in **Chapters 4 and 5**. Most of the included patients exhibited an exponential $\dot{V}O_2$ response, while the response was almost linear for others. For other patients, ventilatory and physical impairments resulted in response amplitudes or signal-to-noise ratios that were too low to allow for reliable examinations of physiological exercise responses. Moreover, **Chapter 6** showed that also changes of physiological exercise responses following PR were very variable for different patients. It should be noted that the individualised WR of the examined constant work rate test (CWRT; i.e. 75% of WR_{peak}) already aimed to account for individual differences in physical performance [121]. In addition, the generally used exponential models examine response kinetics of individual patients. Nevertheless, visual examination of physiological exercise responses shows that not only the overall physiological responses (accounted for by the exponential models), but also physiological fluctuations around these responses can exhibit different characteristics for different patients, as illustrated for three different patients in Figure 7.1. The generally applied exponential models do not consider the effects of these fluctuations. In contrast, the introduced BJ-TF models estimate 'noise model' parameters for every patient separately to account for these individually different physiological fluctuations (**Chapter 4**). It can furthermore be assumed that current understandings of physiological exercise responses can still be enhanced by

unravelling the causes of the individually different dynamics of these physiological fluctuations.

2.3. Time-varying and dynamic

Besides differences between individual patients with COPD, physiological variables from individual patients can also differ depending on the exact moment when these variables are measured. One the one hand, gradual changes of internal factors (e.g. physical fitness or mood) or external factors (e.g. ambient temperature or air pollution) can induce *time-varying* behaviour. Due to this time-varying behaviour, recent studies argued that a single pulmonary function test may not be reliable for diagnosing patients with COPD [291, 292]. On the other hand, acute changes of internal factors (e.g. physical activity or sleep) or external factors (e.g. rapid temperature shifts) can induce *dynamic* behaviour. This dynamic behaviour is most clearly illustrated by the constant adaptations of physiological variables after acute changes in internal or external factors (e.g. dynamic physiological responses after changes of exercise intensity).

In this dissertation, the effects of time-varying and dynamic behaviour can be observed most clearly in **Chapter 3**. One-week continuous SpO_2 measurements during daily life routines revealed high variabilities of SpO_2 within and between multiple days and nights of patients with COPD. This natural variability is induced by a combination of time-varying behaviour and dynamic responses towards acute contextual changes (e.g. changes in levels of physical activity or sleep).

The sigmoidal shape of the oxygen dissociation curve (Chapter 1 and Figure 1.2) could explain the large SpO_2 fluctuations within a single day that were observed in Chapter 3. The reduced oxygen partial pressure of the included patients (i.e. 8.7±1.7 kPa) positions them closer to the steep portion of the oxygen dissociation curve (Figure 1.2). Limited fluctuations of oxygen partial pressure, e.g. due to small changes of physical activity or merely changing posture [293], could therefore induce significant fluctuations of oxygen saturation (measured as SpO_2). Also factors that shift the oxygen dissociation curve, such as changes of body temperature, can induce SpO_2 fluctuations without a change of oxygen partial pressure. Measuring oxygen partial pressure during the initiation phase of a



Figure 7.1: Oxygen uptake ($\dot{V}O_2$) responses and corresponding fluctuations at the onset of a constant work rate test (CWRT) for three different patients with COPD. Fluctuations (lower plots) are calculated as the difference between the $\dot{V}O_2$ response (black line) and Box-Jenkins transfer function system model (orange dashed line). The fluctuations of the first two patients differ greatly in amplitude, while the fluctuations of the third patient exhibit a peculiar, spiked behaviour.

telemonitoring application could therefore be a crucial aid for proper interpretations of SpO_2 measurements and fluctuations during follow-up. Especially for patients experiencing low oxygen partial pressures, low SpO_2 values and large SpO_2 fluctuations might not be the result of a deteriorating health status.

Due to these large fluctuations of SpO_2 within a single day (**Chapter 3**), spot check measurements can highly depend on the exact moment of the measurement. Still, **Chapter 2** showed that the examined telemonitoring applications nearly always performed SpO_2 spot check measurements to raise alerts for exacerbations. This is especially problematic considering the lack of standardised moments or protocols for performing these spot check measurements, subjecting them to an even larger degree of variability. Although standardised measuring protocols can already reduce this high variability, complementary measurements of the main influencing factors (e.g. actigraphic measurements of physical activity, sleep and posture) will be required to accurately interpret measurements of SpO_2.

On top of these intraday SpO_2 fluctuations, also day-to-day variations of SpO_2 were observed in stable patients with COPD (**Chapter 3**). The inability to distinguish these natural fluctuations from exacerbation-induced changes in SpO_2 will result in many false alerts for exacerbations. Furthermore, in addition to these short-term intraday or day-to-day differences, Clarke and colleagues showed that a long-term trend could be discernible when measuring patients over prolonged time periods [175]. This long-term trend will further complicate exacerbation predictions, as most studies that were reviewed in **Chapter 2** used fixed SpO_2 thresholds to alert for exacerbations, which are unable to cope with changing SpO_2 baseline values. The amount of false alerts in telemonitoring applications can thus be reduced even further by accounting for this long-term trend in daily SpO_2 measurements. Closely monitoring this trend can furthermore provide valuable information about the general, long-term progression of the disease [175]. Nevertheless, the exact clinical relevance of intraday and day-to-day SpO_2 fluctuations is yet to be determined.

In addition to the discussed implications of time-varying and dynamic behaviour on telemonitoring applications, **Chapter 3** also showed that night-to-night differences of mean SpO_2 and the cumulative time spent with SpO_2 below 90% (CT90) values complicate the binary classifications of patients as nocturnal desaturator (CT90 > 30%) or non-desaturator (CT90 ≤ 30%), based on measurements of one or two nights. One-week nocturnal SpO_2 measurements indicated that patients with a mean nocturnal SpO_2 level around 90% will, based on the current classification of nocturnal desaturators, frequently switch class. Still, the presence of nocturnal desaturation (CT90 > 30%) during a single night is one of the requirements for receiving long-term oxygen therapy in Belgium [294]. Although measurements over multiple nights can already enhance the assessment of desaturation severity, the results of **Chapter 3** also raise questions about the current classification method for nocturnal desaturators. As visible in Figure 3.4, patients with low daytime mean SpO_2 are likely to have nocturnal mean SpO_2 values lower than 90%. These patients will therefore be classified as nocturnal desaturators, even without the presence of a significant drop in SpO_2. However, the concept of desaturation implies that low SpO_2 values are the result of an SpO_2 drop, rather than of constant low SpO_2 values. Therefore, we suggest to improve nocturnal desaturator classification by including the requirement of an SpO_2 drop during the night. Some definitions of exercise-induced desaturation also state that low SpO_2 levels (below 88-90%) should be accompanied by an SpO_2 drop of at least 4% to identify exercise-induced desaturation [295, 296]. Still, regardless of the definition of nocturnal or exercise-induced desaturators, measurements should be performed during multiple nights or exercise tests to account for day-to-day or night-to-night SpO_2 variabilities.

Chapters 4-6 entirely focussed on the dynamics of physiological exercise responses, examined through dynamic transfer function modelling. As previously mentioned, also the physiological fluctuations around the main exercise responses exhibited interesting dynamic behaviour that should further be explored. Overall, the dynamics of continuously measured physiological variables can reveal a wealth of information.

Time-varying behaviour should also be considered when analysing physical performance tests in patients with COPD [297]. Although test-retest reliability of CWRT endurance time is generally assumed to be high,

learning effects have been observed to significantly increase endurance time during a repeated CWRT [273]. It can furthermore be argued that also differences in patient motivation can influence values of WR_{peak}, $\dot{V}O_{2,peak}$ or CWRT endurance time [120]. Although physiological exercise responses are less influenced by learning effect or patient motivation, they can still be subjected to variations over time, e.g. due to diurnal patterns [298] or disease progression [120]. It is therefore crucial to perform the CWRT around the same time of day pre- and post-PR. Therefore, CWRTs in **Chapter 6** were performed in the afternoon both pre- (13h00 or 13h45) and post-PR (13h45 or 14h30). Nevertheless, the 'average' later time post-PR might result in lower energy requirements of the digestive system, leading to a decrease of unloaded values of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ following PR.

Physiological adaptations towards exercise training (e.g. improved muscle function [11]) can also influence physiological exercise responses (**Chapter 6**). In this regard, assessing physiological exercise responses more frequently over prolonged time periods (e.g. daily during standard exercise training sessions of a PR program) could shed light on the overall progression of the disease. This could help to monitor patients more closely, e.g. over the course of a PR program.

3. Data analysis and modelling techniques

The discussed CITD framework emphasises the complex and variable nature of patients with COPD. Consequently, patients with COPD require individualised interventions, based on extensive clinical assessments [299, 300]. These interventions and assessments should furthermore try to account for the complex and variable nature of patients with COPD, e.g. by performing continuous measurements over prolonged time periods. Besides merely accounting for the identified CITD characteristics of patients with COPD, these characteristics can also serve as an additional source of information. Data analysis and modelling techniques that can exploit this information could thus further enhance current clinical assessments and interventions of patients with COPD. This section will discuss some explanatory and predictive data analysis and modelling techniques that are currently available.

3.1. Explanatory models

Explanatory models aim to describe the system under study in order to reach a deeper understanding of its functioning. In this regard, mechanistic models can explain the behaviour of complex (biological) systems by examining the coupling of different components and their underlying mechanisms. Due to the high explanatory power of mechanistic models, they have played a major role in the development of medical practices [301] and the understanding of biological systems [302]. In the light of this dissertation, Barstow and Molé developed a simple mechanistic model that helped the interpretation of $\dot{V}O_2$ kinetics [303]. The model was developed to examine the influence of the cardiovascular system on $\dot{V}O_2$ responses at exercise onset. It considered two distinct compartments, the muscular and pulmonary system, linked by the cardiovascular system that enables gas exchange between the two compartments (Figure 7.2).

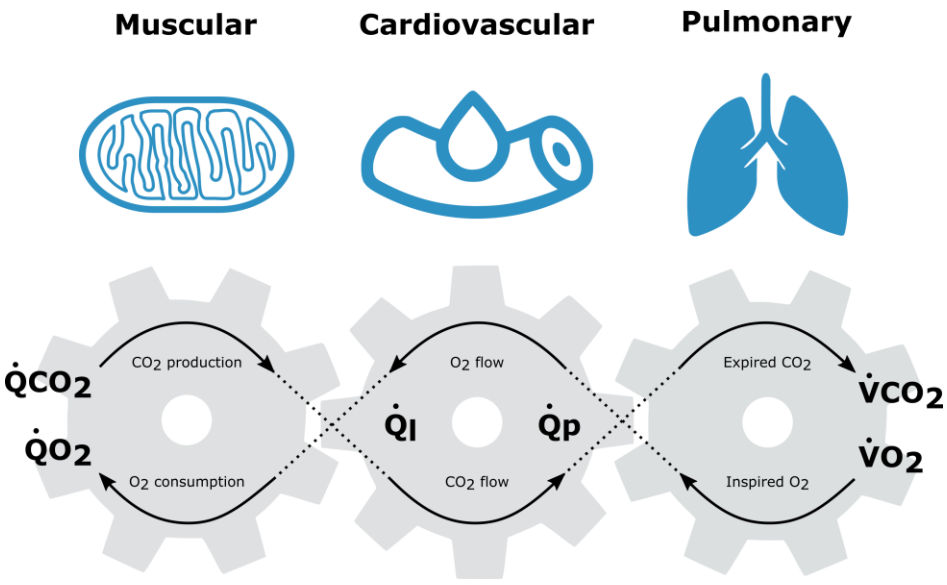


Figure 7.2: Illustration of how the cardiovascular system enables gas exchange between the ventilatory and muscular system. The figure is inspired by Figure 1 in the work of Wasserman [122]. O_2 = oxygen; CO_2 = carbon dioxide; $\dot{V}O_2$ = oxygen uptake (ml.min^{-1}); $\dot{V}CO_2$ = carbon dioxide output (ml.min^{-1}); $\dot{Q}O_2$ = muscle oxygen consumption (ml.min^{-1}); $\dot{Q}CO_2$ = muscle carbon dioxide production (ml.min^{-1}); $\dot{Q}_l$ = leg blood flow (dl.min^{-1}); $\dot{Q}_p$ = pulmonary blood flow (dl.min^{-1}).

The muscle oxygen consumption ($\dot{Q}O_2$; ml.min^{-1}; left part of Figure 7.2) and leg blood flow ($\dot{Q}_l$; dl.min^{-1}; middle part of Figure 7.2) responses at exercise onset were modelled as a mono-exponential increase with no time delay:

$$\dot{Q}O_2(t) = \dot{Q}O_{2,r} + \left(\dot{Q}O_{2,ss} - \dot{Q}O_{2,r}\right) \cdot \left(1 - e^{-t/TC,\dot{Q}O_2}\right)$$

$$\dot{Q}_l(t) = \dot{Q}_{l,r} + \left(\dot{Q}_{l,ss} - \dot{Q}_{l,r}\right) \cdot \left(1 - e^{-t/TC,\dot{Q}_l}\right)$$

where subscripts *r* and *ss* indicate values at rest or steady state, respectively. TC,$\dot{Q}O_2$ (s) and TC,$\dot{Q}_l$ (s) represent the time constant of the $\dot{Q}O_2$ and $\dot{Q}_l$ response, respectively. Pulmonary blood flow ($\dot{Q}_p$; dl.min^{-1}) was assumed to be equal to $\dot{Q}_l$. The venous oxygen content (Cv_{O_2}; ml.dl^{-1}) response was described as the difference between arterial oxygen content

(Ca_{O_2}; ml.dl^{-1}) and the oxygen extracted from arterial leg blood to the exercising muscle:

$$C_{v_{O_2}}(t) = C_{a_{O_2}} - \left(\frac{\dot{Q}O_2(t)}{\dot{Q}_l(t)}\right)$$

Ca_{O_2} was assumed to remain constant. Lastly, the $\dot{V}O_2$ (ml.min^{-1}; right part of Figure 7.2) response was described by the Fick equation:

$$\dot{V}O_2(t) = \dot{Q}_p(t) \cdot \left(C_{v_{O_2}}(t) - C_{a_{O_2}}\right)$$

Estimated values for the different variables were based on a healthy male of 70 kg with a $\dot{V}O_{2,max}$ of 4200 ml.min^{-1}. Further details about the introduced equations and values can be found in the work of Barstow and Molé [303].

Curve 1 in Figure 7.3 illustrates the simulated $\dot{V}O_2$ response, based on increases of $\dot{Q}_l$ and $\dot{Q}O_2$ at CWRT onset. Similar to observations in experimental data, the onset of the $\dot{V}O_2$ response is made up of two distinct phases: phase I and phase II. Curve 2 in Figure 7.3 represents the simulated $\dot{V}O_2$ response when only $\dot{Q}_l$ increased at CWRT onset, while $\dot{Q}O_2$ was kept constant. Area A in Figure 7.3, corresponding to phase I, was thus exclusively related to the increased blood flow at exercise onset. Changing the rate of the $\dot{Q}_l$ response, by changing the time constant of the $\dot{Q}_l$ response (TC,$\dot{Q}_l$), also mainly affected phase I only (i.e. area A) [303]. These results confirmed that phase I can be considered as the cardiodynamic phase of the response, during which the $\dot{V}O_2$ response is related to an increased blood flow.

The remaining part of the total $\dot{V}O_2$ response in curve 1, corresponding to phase II, was the result of a $\dot{Q}O_2$ increase. Moreover, the rate of the simulated phase II $\dot{V}O_2$ increase very closely resembled the rate of the $\dot{Q}O_2$ increase, as indicated by the close resemblance between the TCs of $\dot{V}O_2$ and $\dot{Q}O_2$ [303]. This has been experimentally confirmed by Rossiter and colleagues, who found a close association between kinetics of $\dot{V}O_2$ and working muscle phosphocreatine concentrations. The latter, measured using a whole-body nuclear magnetic resonance spectrometer, can be considered as an estimate for $\dot{Q}O_2$, therefore corroborating the findings from the mechanistic model of Barstow and Molé [303, 304].

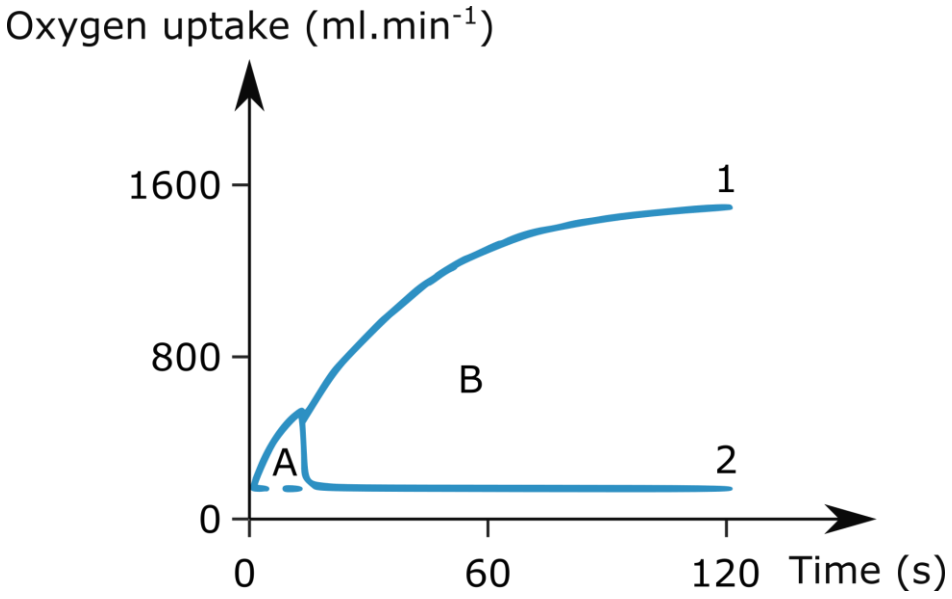


Figure 7.3: Curve 1 represents the simulated oxygen uptake response based on the mechanistic model created by Barstow and Molé [303]. Curve 2 represents the simulated oxygen uptake response when only blood flow increased at CWRT onset, while muscle oxygen consumption was kept constant. Figure adapted from the work of Barstow and Molé.

A simple mechanistic model can thus already contain high explanatory power about the mechanisms that underlie a typical $\dot{V}O_2$ responses at the onset of a CWRT. It should be noted, however, that gaining specific insights into $\dot{V}O_2$ responses of other, non-healthy populations will require adaptations to this model. As an example, the assumption of stable Ca_{O_2} values might not be valid in a non-healthy population. Also oxygen delivery limitations were not considered in the discussed mechanistic model, because it can be assumed that oxygen delivery does not affect $\dot{V}O_2$ kinetics in a healthy subject [128]. In patients with COPD, however, oxygen delivery to the working muscles can be limited due to an impaired cardiovascular response, induced by the characteristic ventilatory limitations of this population (**Chapter 5**, [131, 133, 240, 241, 261]). Therefore, the $\dot{V}O_2$ TC will not exclusively represent the rate of the $\dot{Q}O_2$ response in patients with COPD, but rather quantify a combined slowness of the pulmonary, cardiovascular and muscular system. Developing a mechanistic model that

includes these COPD-specific characteristics would therefore be insightful to determine how the muscular, cardiovascular and pulmonary system each contribute to the slow $\dot{V}O_2$ responses that are generally observed in patients with COPD. In addition, exercise training has been associated with muscular improvements (e.g. enhancements of muscle oxidative enzyme activity [53], increased capillary-to-fibre ratios [54] and enlarged muscle mass [55]), cardiovascular improvements (e.g. faster heart rate kinetics [57, 58]) and ventilatory improvements (e.g. reduced ventilatory requirements and hyperventilation [58–60]). A COPD-specific mechanistic model of physiological exercise responses would thus also be insightful to clarify how these muscular, cardiovascular and ventilatory improvements after PR each contribute to the decreased $\dot{V}O_2$ MRT that was observed in the group of responders in **Chapter 6**.

Despite the clear benefits of mechanistic models, they are sometimes too complex for the task at hand. For some applications, finding an equilibrium between explanatory power and computational efficiency can be optimal. The analyses in this dissertation were based on this philosophy. As argued before, it is important to account for, and potentially exploit, the CITD characteristics of patients with COPD. Collecting time series of physiological variables, generated through continuous measurements (*dynamic* behaviour) and/or repeated measurements (*time-varying* behaviour) of *individual* patients, can account for these characteristics. However, continuously measuring physiological variables of individual patients generates large amounts of data. Consequently, computationally efficient modelling techniques are required to enable the extraction of relevant information from the generated time series of each individual patient. Mechanistic interpretations of the extracted information can then be an important asset to expand the performance and utility of these computationally efficient models.

These considerations led to the selection of BJ-TF models for the analyses of physiological exercise responses in **Chapters 4-6**. BJ-TF models are simple, computationally efficient data-based models that are able to describe physiological exercise responses. The features that can be extracted from these models (e.g. TC, MRT or gain) can easily be interpreted physiologically. Moreover, insights from mechanistic models, such as the model from Barstow and Molé [303], can guide the interpretation of the

extracted features. This mechanistic model showed that extracting TCs from non-invasive measurements of $\dot{V}O_2$, as done with BJ-TF models in **Chapter 4-6**, can indicate the rate of the underlying $\dot{Q}O_2$ response in healthy subjects. For patients with COPD, however, the $\dot{V}O_2$ TC will rather quantify a combined slowness of the pulmonary, cardiovascular and muscular system, as discussed above. Consequently, the use of $\dot{V}O_2$ MRT might be more appropriate to indicate the rate of the $\dot{V}O_2$ response in patients with COPD, because the interpretation of $\dot{V}O_2$ MRT, in contrast to $\dot{V}O_2$ TC, does not imply a strong association with $\dot{Q}O_2$ TC. Furthermore, the low signal-to-noise ratio of the $\dot{V}O_2$ response in patients with COPD makes that $\dot{V}O_2$ MRT can be calculated more reliably than $\dot{V}O_2$ TC (**Chapter 4**). $\dot{V}O_2$ MRT was therefore used to quantify the rate of the $\dot{V}O_2$ response in **Chapters 5 and 6**, representing the combined slowness of the pulmonary, cardiovascular and muscular system. Consequently, the observed $\dot{V}O_2$ MRTs in **Chapters 4-6** were higher than the introduced $\dot{Q}O_2$ TC of 30 s in the described mechanistic model [303].

Dynamic BJ-TF models were thus able to extract clinically relevant information from continuously measured physiological variables at exercise onset of *individual* patients with COPD. Repeated measurements provided insights into PR-induced changes of these physiological exercise responses (*time-varying* behaviour). Similarly, physical activity-induced *dynamic* heart rate responses of *individual* elderly people, repeatedly measured over time (*time-varying*) and modelled with comparable transfer function models, have shown promise to serve as an indicator of physical performance for elderly in a home care setting [305]. In **Chapter 3**, the *dynamics* of SpO_2 time series furthermore revealed the appropriate sampling time for continuous SpO_2 measurements to be around 20 seconds. The *dynamics* of continuously measured SpO_2 have also been used to improve diagnosis of obstructive sleep apnoea [232, 233, 306, 307]. All combined, these examples nicely illustrate that the *dynamics* of continuously measured physiological variables of *individual* patients, preferably assessed repeatedly (*time-varying*), can exploit the CITD characteristics of patients with COPD as a valuable source of novel clinical insights.

3.2. Predictive models

The discussed explanatory models and descriptive features (e.g. $\dot{V}O_2$ MRT and gain) are not necessarily the endpoint of the analyses. In a next step, the information that is extracted from continuously measured physiological variables can be used as input for predictive models. These predictive models can be applied for a variety of applications, such as predicting the outcome of a PR program, the onset of exacerbations or mortality rates. This will further increase the performance and clinical value of the applied modelling techniques.

Nowadays, the predictive power of machine learning and artificial intelligence algorithms is extensively studied. Also healthcare applications can make use of artificial intelligence, e.g. for automatic detection of glaucoma [308] or accurate interpretations of pulmonary function tests [309]. Moreover, machine learning techniques have been proposed to improve performance of telemonitoring applications [124, 310]. Nevertheless, it is of paramount importance to be aware of the potential pitfalls of these promising, efficient and powerful techniques. False results can be obtained when the input data is in some aspects different from the training dataset [311]. These false results can remain unnoticed, as most machine learning and artificial intelligence techniques act as a black-box. Generally, this makes it difficult to interpret how the results of these techniques are obtained. As a result, explainable artificial intelligence, which aims to improve model transparency, is currently gaining more interest [312]. Nevertheless, these risk factors will have to be fully covered before machine learning and artificial intelligence will be accepted in clinical practice.

Also time series that are generated through repeated measurements over multiple days can have predictive power. In this regard, some studies that were reviewed in **Chapter 2** combined present day SpO_2 measurements with measurements from past 5-30 days to calculate simple features (e.g. mean value of past 5-30 days, deviation of present day value from this mean value or linear fit gradient) that were used to predict exacerbations [95, 97, 98, 126, 173, 174]. Still, only the study of Clarke and colleagues actually approached the daily measurements as a time series by decomposing it in a long-term trend, a short-term trend, and a residual signal [175]. The residual signal then showed potential for the prediction of exacerbations

[175]. Similar approaches can also be applied to other types of repeated measurements, e.g. repeated assessments of physiological exercise responses and related descriptive features, to closely monitor the progression of the disease. Combining the strengths of explanatory and predictive models thus seems especially beneficial.

4. Future perspectives - Telemonitoring

A frequently recurring remark on telemonitoring applications for patients with COPD is the lack of compelling evidence about their benefits [83–86]. The combination of the results of the systematic review (**Chapter 2**) and continuous SpO_2 measurements (**Chapter 3**) in this dissertation identified multiple potential causes why telemonitoring does not yet live up to the high expectations for patients with COPD. These results can furthermore be translated to other chronic disease states that can suffer from impairments of oxygen homeostasis, such as asthma or chronic heart failure. Telemonitoring of chronic disease states that relate to other key variables (e.g. blood pressure in hypertension) or the use of wearables in large populations of healthy individuals can also be affected by the same limitations that were identified in this dissertation. Potential ways of improving current telemonitoring applications are listed and discussed below. These elements are applicable for telemonitoring of a wide variety of chronic disease states.

- Increase transparency and standardisation of SpO_2 measurements
- Implement continuous SpO_2 measurements over prolonged time periods
- Combine multiple variables
- Technological advancements of measuring devices
- Explore data analysis techniques and predictive modelling
- Perform well-designed large-scale studies
- Examine patient subpopulations

4.1. Increase transparency and standardisation of SpO_2 measurements

A striking observation from **Chapter 2** is the seeming lack of profound know-how about the optimal implementation of SpO_2 measurements in telemonitoring applications and by extension telemonitoring applications as a whole [77, 82, 85], in patients with COPD. This is illustrated by the absence of standardisation and transparency concerning how or at which time of the day SpO_2 measurements should be performed, how to predict exacerbations and implement corresponding alerts, which action to take after an alert or how to evaluate telemonitoring applications and its different components (**Chapter 2**). Despite these shortcomings, some studies indicated that SpO_2-based alerts have potential to detect or predict exacerbations [94, 127, 169]. Generally, a measuring frequency of one spot check measurements per day seems to be the only common ground between different telemonitoring studies of patients with COPD [77, 82, 102, 215]. There is, however, no evidence to support this selection of daily spot check as the preferred measuring frequency. Overall, future studies should aim for higher levels of transparency and standardisation to improve telemonitoring applications of patients with COPD.

4.2. Implement continuous SpO_2 measurements over prolonged time periods

The results of **Chapter 3** highlight the pitfalls of using daily spot check measurements of SpO_2 to detect exacerbations of patients with COPD, as has already been extensively argued in this dissertation. If variables are only assessed through spot check measurements, that furthermore lack clear guidelines about how to perform the measurements (**Chapter 2**), even the most powerful algorithms will struggle to accurately predict exacerbations. This risk of using SpO_2 values that significantly deviate from baseline SpO_2 can be greatly reduced by performing continuous SpO_2 measurements over prolonged time periods (see also section 4.4). Besides merely accounting for natural physiological fluctuations, the time series generated through continuous measurements can additionally contain a wealth of information that could further increase performance of telemonitoring applications.

4.3. Combine multiple variables

Continuous SpO_2 measurements should furthermore be combined with other variables. Oximeters measuring SpO_2 will automatically be able to also measure heart rate. Including heart rate, in addition to SpO_2, has already been shown to increase the performance of telemonitoring applications in patients with COPD [95, 97, 126, 173]. Inclusion of other physiological variables, such as temperature or breathing frequency, are likely to further improve telemonitoring applications [95, 97, 126]. Actigraphy measurements can additionally provide contextual information about physical activity levels and moments of wake and sleep, which can help to correctly interpret (fluctuating) values of physiological variables, as shown for SpO_2 in **Chapter 3**. These physiological and actigraphy measurements can furthermore be combined with the often used daily symptom questionnaires [77, 79, 82, 102, 186] or monthly anxiety and depression questionnaires [313]. Measuring environmental variables (e.g. air pollution, ambient temperature or rainfall) can increase performance even further by providing additional contextual information. Future studies should therefore aim to simultaneously measure a combination of distinctly different variable types (e.g. physiological, actigraphic, symptomatic and environmental) to properly deal with the complex and variable nature of patients with COPD.

4.4. Technological advancements of measuring devices

Chapter 3 showed that valid continuous SpO_2 measurements can be obtained over a one-week study period using a wrist-worn oximeter with a finger clip. However, these measurements were unreliable when moderate-to-vigorous physical activities were performed (**Chapter 3**). A recent study similarly observed inaccurate SpO_2 spot check values during exercise in patients with COPD [314]. Furthermore, hands-on experience showed that continuous SpO_2 measurements by means of a finger clip are unlikely to be tolerated for long time periods. Unfortunately, however, continuous SpO_2 measurements without a finger clip have not been proven accurate yet. Also try-outs during this PhD research with novel wearable devices that measure SpO_2 on the arm or wrist were unsatisfactory. It will thus require further technological advancements to create user-friendly wearable devices,

without a finger clip, that are able to produce reliable, continuous SpO_2 measurements over long time periods. Hence, reliable 24/7 continuous measurements of SpO_2 over longer time periods might not yet be feasible in the near future. Although technological advancements towards user-friendly, reliable wearable devices (preferably measuring multiple variables at once) should be the ultimate ambition, using currently existing oximeters for prolonged measurements during rest (e.g. one hour per day before going to bed) or during the night will probably already have profound benefits over merely performing daily spot check measurements.

4.5. Explore and combine different data analysis and modelling techniques

As discussed in section 3, (combining) different types of data analysis and modelling techniques can provide distinct benefits. Explanatory models that make use of continuously measured physiological variables can provide new physiological insights and descriptive features. These features can in turn be used by predictive models for timely predictions of exacerbations in patients with COPD.

4.6. Perform well-designed large-scale studies and examine patient subpopulations

The previous examples show that there are still many ways to improve current telemonitoring applications. Consequently, no strong conclusions about the actual benefits of telemonitoring applications can be drawn before the suggested improvements are tested in long-term, well-designed telemonitoring studies with a sufficiently large population of patients with COPD (or other chronic disease states). A large amount of included patients can furthermore make it possible to examine whether certain subpopulations might benefit more from telemonitoring applications than others. In this regard, patients with more severe COPD or higher risks for hospitalisations might gain more from telemonitoring applications [82, 86], while other studies suggested that telemonitoring could be more cost-effective for patients younger than 60 years, patients with GOLD stage 3 or patients without co-morbidities [190, 315]. Nevertheless, **Chapter 2** showed that very few studies reported on subpopulations to evaluate the

value of SpO_2 measurements in telemonitoring applications for patients with COPD.

Altogether, we are convinced that long-term, well-designed, large-scale studies should be completed, which also consider the suggested improvements, before the actual value of telemonitoring applications for patients with COPD (or other chronic disease states) can be defined.

5. Future perspectives - Physical performance testing

The vast amounts of data that are standardly collected during tests of physical performance did not reveal all their secrets yet. This dissertation showed that in-depth analyses of physiological exercise responses provide valuable insights into the physiological response to exercise in patients with COPD. The presented approach can be expected to provide similar benefits in other chronic disease states, as these patients can also suffer from impaired physical performances. The crucial role of physical performance testing in recreational and professional sports implies that the presented approach can additionally be used to enhance assessments of physical performance in sport applications.

Nevertheless, there is still more information to be extracted from physiological exercise responses in a variety of populations. Multiple potential further analyses are therefore identified and discussed below. The suggested analyses are not only applicable to patients with COPD, but also other chronic disease states and sports applications.

- Compare introduced gains with comparable features extracted from a cardiopulmonary exercise test (CPET)
    - $\dot{V}O_2$ gain during CWRT vs $\Delta\dot{V}O_2/\Delta WR$ ratio during CPET
    - $\dot{V}_E$ gain during CWRT vs $\dot{V}_E/\dot{V}CO_2$ relationship during CPET
- Model and examine other physiological variables
- Model and examine physiological fluctuations
- Examine changes of physiological exercise responses over the course of a PR program
- Examine the prognostic value of physiological exercise responses

5.1. Compare $\dot{V}O_2$ gain during CWRT with $\Delta\dot{V}O_2/\Delta WR$ ratio during CPET

Chapter 5 illustrated that gains of physiological variables can represent both response efficiency and limitations during a CWRT. Similar features have been extracted from physiological exercise responses during an incremental CPET. The $\Delta\dot{V}O_2/\Delta WR$ ratio during CPET, representing the slope of the $\dot{V}O_2$ increase during the test, shows great similarities to $\dot{V}O_2$ gain during CWRT [316]. Also the $\Delta\dot{V}O_2/\Delta WR$ ratio during CPET can represent both response efficiency [120] or limitation [276]. Nevertheless, the difference between the $\Delta\dot{V}O_2/\Delta WR$ ratio during CPET and $\dot{V}O_2$ gain during CWRT becomes apparent when changes of these features following PR are examined. Whereas improved $\dot{V}O_2$ efficiency decreased the $\Delta\dot{V}O_2/\Delta WR$ ratio following PR [62], improved oxidative capacity increased $\dot{V}O_2$ gain by lifting the limitations that hamper the $\dot{V}O_2$ increase during CWRT (**Chapter 6**). This difference could be attributed to the intensity differences between both tests. The gradually increasing WR during CPET allows $\dot{V}O_2$ to increase accordingly, not reaching the physiological limitations that could hamper the $\dot{V}O_2$ increase until later in the test. However, the high WR during CWRT immediately requires very high levels of oxygen, therefore making the $\dot{V}O_2$ increase during CWRT more susceptible to these response limitations. The described similarities and differences call for a more extensive analysis of the value and clinical relevance of the $\dot{V}O_2$ gain during CWRT compared to the $\Delta\dot{V}O_2/\Delta WR$ ratio during CPET.

5.2. Compare $\dot{V}_E$ gain during CWRT with $\dot{V}_E/\dot{V}CO_2$ relationship during CPET

$\dot{V}_E$ gain during CWRT is related to the $\dot{V}_E/\dot{V}CO_2$ relationship during CPET in a similar, yet slightly different way. The $\dot{V}_E/\dot{V}CO_2$ relationship expresses the amount of ventilation that is needed to remove CO_2 from the body [272]. The slope and intercept of the $\dot{V}_E$ curve in function of $\dot{V}CO_2$, as well as the nadir of the $\dot{V}_E/\dot{V}CO_2$ curve in function of WR or $\dot{V}O_2$, have been used to express ventilatory efficiency [272, 317], similar to $\dot{V}_E$ gain. Nevertheless, the $\dot{V}_E/\dot{V}CO_2$ relationship expresses a specific form of ventilatory efficiency, solely related to the efficiency of CO_2 removal. In contrast, $\dot{V}_E$ gain provides a more general estimate (i.e. the ventilatory increase that is needed per unit increase of WR) that also accounts for other sources of ventilatory inefficiency, e.g. increased need for ventilation due to anaerobic energy

generation [120]. It would therefore be interesting to examine whether $\dot{V}_E$ gains during CWRT provide similar or complementary insights into ventilatory efficiency, compared to the currently used features from the $\dot{V}_E/\dot{V}CO_2$ relationship during CPET.

5.3. Model and examine other physiological variables

This dissertation mainly focussed on analysing exercise responses of ventilation ($\dot{V}_E$, breathing frequency and tidal volume) and gas exchange ($\dot{V}O_2$ and $\dot{V}CO_2$). Additional analyses of heart rate, stroke volume and cardiac output responses could shed more light on the cardiovascular response at exercise onset [129, 241, 261]. Moreover, combined analyses of different physiological responses in an integrative approach could even further exploit the information captured in the physiological responses at exercise onset. Principal component analyses and measures of information entropy during two consecutive CPETs already showed that cardiorespiratory coordination decreases during the second CPET [318]. Also the dynamics of combined variables, such as the respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$) or the rate of the $\dot{V}_E/\dot{V}CO_2$ decrease in function of WR during a CPET, can provide interesting insights into the integrated physiological response at exercise onset and should further be explored.

5.4. Model and examine physiological fluctuations

As discussed in sections 2 and 3 of this chapter, and illustrated in Figure 7.1, fluctuations around the overall physiological responses at exercise onset exhibit distinctly different characteristics for different patients. It would therefore be interesting to explore whether the dynamics of these physiological fluctuations can reveal new information, in addition to the information extracted from the main exercise responses, that can enhance current understandings of physiological exercise responses.

5.5. Examine changes of physiological exercise responses over the course of a PR program

It has been argued in section 2 of this chapter that frequent assessments of physiological exercise responses can help to closely monitor the overall progression of a patient's health status. Frequent assessments of physiological exercise responses can also make it possible to monitor the progression of a patient over the course of a PR program. This seems especially interesting, as physiological exercise responses can easily be assessed during standard exercise trainings of a PR program. Ideally, different rest to exercise transitions (towards less strenuous exercise intensities) should be included during a single test in order to account for potential sources of variability.

5.6. Examine the prognostic value of physiological exercise responses

Lastly, the prognostic value of the physiological exercise responses should be explored. It has already been shown that $\dot{V}O_{2,peak}$ and the $\dot{V}_E/\dot{V}CO_2$ relationship have a high prognostic value for mortality in patients with COPD [319, 320]. It would therefore be interesting to also assess the prognostic value of $\dot{V}O_2$ MRT and gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ to predict morbidity and mortality rates in patients with COPD. Furthermore, extensive characterisation of physiological exercise responses before the start of a PR program could help to predict which patients can benefit the most from the program.

6. General conclusions

Three objectives were formulated in **Chapter 1** that could enhance clinical assessments and interventions of patients with COPD. This last section will discuss how these objectives were addressed over the different chapters. At the present moment, **Chapters 2-5** have been published, while **Chapter 6** is under review. As first author in these publications, I performed all the analyses that are described in this dissertation. In addition, I collected the data of the telemonitoring study in **Chapter 3**. My team of supervisors provided the necessary feedback and support to be able to accomplish the different objectives of this PhD research.

The *first objective* of this dissertation was to evaluate whether the accuracy of telemonitoring applications and desaturator classifications of patients with COPD could be affected by natural SpO_2 fluctuations. Therefore, **Chapter 2** first summarised the scientific literature on the use of SpO_2 measurements in telemonitoring applications of patients with COPD. The results indicated that alerts were raised for exacerbations when SpO_2 spot check values were below fixed thresholds. These thresholds could be generic or individualised. However, multiple problems of these approaches were identified by combining the findings of **Chapter 2** with the results from **Chapter 3**:

(i) The large differences between mean daytime SpO_2 values in rest (between 84.7% and 96.0%) that were observed for different patients with COPD showed that generic thresholds will not result in accurate alerts for exacerbations. Individualised approaches should thus be preferred.

(ii) The large SpO_2 fluctuations over the course of a single day (SpO_2 values during rest ranged on average over 10.8±4.4% within one day) indicated that spot check measurements can lead to a large range of measured SpO_2 values. These natural SpO_2 fluctuations can easily trigger false alerts for exacerbations when alerts are based on a combination of spot check measurements and simple thresholds.

(iii) The observed day-to-day SpO_2 differences of individual patients (mean SpO_2 in rest ranged on average over 1.9±1.5% over the course of one week) shows that also fixed thresholds, which do not change over time, can cause false alerts for exacerbations.

These different sources of SpO_2 variability will surely reduce performances of SpO_2-based telemonitoring applications in patients with COPD. Continuous SpO_2 measurements over prolonged time periods can therefore enhance current telemonitoring applications by accounting for the identified SpO_2 fluctuations. It was furthermore argued that the dynamics of these continuous measurements can serve as an additional source of clinically relevant information.

Similarly, large night-to-night differences of CT90 were observed for the included patients (nocturnal CT90 ranged on average over 28±25% over the course of one week). As a result, 50% of the patients changed category between desaturator and non-desaturator over the course of one week. This

variability could contribute to the controversy about the actual benefits of nocturnal oxygen administration. Classifications of nocturnal desaturation should thus be based on measurements over multiple nights, possibly in combination with the requirement of a nocturnal SpO_2 drop.

In conclusion, the results in this dissertation confirm that *natural SpO_2 fluctuations can indeed affect telemonitoring applications and desaturator classifications in patients with COPD*. Continuously measuring SpO_2 over prolonged time periods, combined with suitable analyses of the resulting time series, can enhance desaturator classifications and telemonitoring applications for patients with COPD. Similar results and recommendations can be expected for other chronic disease states that can suffer from impaired oxygen homeostasis.

The *second objective* of this dissertation was to examine whether physiological exercise responses during CWRT can reliably be analysed using an alternative data analysis technique that is able to account for natural physiological fluctuations. In this regard, BJ-TF models were tested (**Chapter 4**). Autocorrelation tests and normalised root-mean-squared error values (BJ-TF: 2.8±1.3%; exponential methods A, B and C: 10.5±5.8%, 11.3±5.2% and 12.1±7.0%; $p<0.05$) confirmed that BJ-TF models were indeed able to account for the most important physiological fluctuations, in contrast to the generally applied exponential models. As a result, BJ-TF models provided more reliable kinetic feature values compared to exponential methods A and B (e.g. for MRT: BJ-TF, 74±20 s; method A, 100±56 s; and method B, 88±52 s; $p<0.05$). Only the kinetic feature values of exponential method C were comparable to feature values from BJ-TF models (e.g. MRT method C: 75±20 s). Nevertheless, on an individual level, kinetic feature values still differed between BJ-TF models and exponential method C (e.g. an average difference of 7±8 s for MRT). It can therefore be argued that, based on theoretical considerations, *BJ-TF models generate more reliable kinetic feature values than generally applied exponential models*.

The *third objective* of this dissertation was to characterise physiological exercise responses during CWRT of patients with COPD to enrich clinical assessments of physical performance. Therefore, physiological exercise responses of a large sample of patients with COPD were examined (n=265;

Chapter 5). The previously developed BJ-TF models were used to extract $\dot{V}O_2$ MRT values. Gains of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ were additionally calculated. Kinetic feature values were unreliable for 21% (=56/265) of the patients. Analyses showed that kinetic analyses are likely to be unreliable for patients that are severely physically impaired (i.e. patients exhibiting a WR_{peak} < 45 W). For patients that exhibited reliable kinetic feature values (n=209), gains were mainly associated with cardiac function and ventilatory constraints, representing both response efficiency and limitation. Furthermore, $\dot{V}O_2$ MRT showed potential to serve as a motivation-independent, physiological indicator of physical performance, as it was associated with both ventilatory (e.g. FEV_1%predicted: $p<0.001$; $r=-0.35$) and physical (e.g. $VO_{2,peak}$%predicted: $p=0.009$; $r=-0.18$) impairments.

Most of these patients furthermore completed a PR program, of which 183 patients could be used to examine whether changes in physiological exercise responses following PR differed between responders and non-responders to PR (n=66) (**Chapter 6**). Patients that improved CWRT endurance time following PR with more than 105 s, the lower bound of a minimal clinically important difference [63, 280], were classified as responders to PR, other patients as non-responders. Only the group of responders, in contrast to non-responders, decreased $\dot{V}O_2$ mean response time (75±21 to 70±17 s; $p<0.05$), $\dot{V}CO_2$ gain, $\dot{V}_E$ gain and isotime values of $\dot{V}CO_2$, $\dot{V}_E$ and $\dot{V}_E/\dot{V}CO_2$ following PR (all $p<0.001$), while also improving their breathing pattern (e.g. breathing frequency isotime value: 28.8±6.2 to 25.0±5.4 breaths·min^{-1}; $p<0.0001$). These changes were furthermore correlated with changes in physical performance (e.g. correlation between changes in $\dot{V}O_2$ mean response time and endurance time: $p<0.001$, $r=-0.32$). These results indicate that PR-induced changes in physiological exercise responses differ between responders and non-responders to PR, and that physiological improvements are important in explaining the variable improvements of physical performance following PR in patients with COPD.

Overall, the results of **Chapter 5 and 6** show that the continuously measured physiological variables during a CWRT did not reveal all their secrets yet. Consequently, not only characterisations of physiological exercise responses during CPET, but also during CWRT, *can enrich clinical assessments of physical performance in patients with COPD*. Similar enhancements can be expected for other chronic disease states or sports applications.

In conclusion, the results of this dissertation demonstrate that (i) telemonitoring applications and desaturator classifications can be affected by natural SpO_2 fluctuations. Therefore, continuous SpO_2 measurements over prolonged time periods, combined with suitable analyses of the resulting time series, can enhance desaturator classifications and telemonitoring applications for patients with COPD; (ii) BJ-TF models generate more reliable kinetic feature values than generally applied exponential models; and (iii) characterising physiological exercise responses during CWRT can enrich clinical assessments of physical performance in patients with COPD.

Altogether, these results show that, indeed, clinical assessments and interventions of patients with COPD can still be enhanced by including time series analyses of physiological variables. Many of the obtained results can furthermore be translated to other chronic diseases states or healthy populations.

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Journal articles

Buekers J, De Boever P, Vaes AW, Aerts J-M, Wouters EFM, Spruit MA, Theunis J. Oxygen saturation measurements in telemonitoring of patients with COPD: a systematic review. *Expert Review of Respiratory Medicine.* 2018; 12(2): 113–123.

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Joosen P, Piette D, Buekers J, Taelman J, Berckmans D, De Boever P. A smartphone-based solution to monitor daily physical activity in a care home. *Journal of telemedicine and telecare.* 2019; 25(10): 611-622.

Conference abstracts, presentations and posters

Buekers J, Lutin E, Vaes AW, De Boever P, Wouters EFM, Spruit MA, Theunis J, Aerts J-M. Home monitoring of sleep and exposure to black carbon in patients with COPD and healthy controls. Presented at the *International Conference on Chronic Diseases*, 2017, Brussels.

Buekers J, Cryns H, De Boever P, Wouters EFM, Spruit MA, Theunis J, Aerts J-M. Transfer function modeling of constant work-rate tests in patients with COPD. Presented at the *International Conference on Time Series and Forecasting (ITISE)*, 2018, Granada, Spain.

Buekers J, Aerts J-M, Theunis J, Vaes A, Wouters E, Spruit MA, De Boever P. Multi-night continuous nocturnal oxygen saturation measurements in patients with COPD. Presented at the *European Respiratory Society (ERS) International Congress*, 2018, Paris, France.

Buekers J, De Boever P, Peña Fernández A, Theunis J, Wouters E, Spruit MA, Aerts J-M. Box-Jenkins transfer function modelling for accurate determination of VO_2 kinetics in COPD patients. Presented at the *European Respiratory Society (ERS) International Congress*, 2019, Madrid, Spain.