Physical performance measures in patients with COPD

CHAPTER 8

Summary and general discussion

Patients with chronic obstructive pulmonary disease (COPD) frequently experience limitations in their physical performance, which can be characterized by a reduction in functional performance, exercise capacity, exercise tolerance, and/or peripheral muscle function.[1-4] Timely and extensive evaluation of a patient's physical performance is essential to identify the severity and specific domain of the impairment in order to prescribe a personalized intervention. Therefore, tests that evaluate physical performance measures must be feasible, valid, reliable, and, in case of interventions, responsive. The purpose of this thesis was to expand the existing knowledge regarding the feasibility, validity, and responsiveness of physical performance outcome measures in patients with COPD. In this chapter, the main findings will be discussed in depth according to their physical performance domain.

FUNCTIONAL PERFORMANCE

The short physical performance battery (SPPB) is a functional performance measure that evaluates mobility and balance.[5] In **Chapter 2,** univariate regression analyses were performed in a large sample of patients with COPD (n=900) to assess the validity of the SPPB in regards to, amongst others, the 6-minute walk distance, maximal workload on a symptom-limited cardiopulmonary cycle exercise test, time-to-exhaustion on a constant work rate cycle test, and isotonic and isokinetic lower-limb muscle function. Our data revealed significant correlations between the SPPB summary score and patient's exercise capacity, exercise tolerance, and peripheral muscle function. This is in line with previously reported relations between the SPPB and exercise capacity and peripheral muscle function in patients with COPD.[6, 7] However, in **Chapter 2** a multivariate linear regression analysis explained only 29% of the variance in SPPB summary score, of which the largest contribution came from the 6-minute walk distance. This finding demonstrates that only a small portion of the SPPB summary score is determined by exercise capacity, exercise tolerance, and peripheral muscle function. Thus, this emphasizes the additional value of implementation of functional tests in complement to exercise tests that assess exercise capacity, exercise tolerance, or peripheral muscle function in order to obtain an extensive overview of the patient's physical performance. Furthermore, it is important to note that the standing balance, 4-meter gait speed (4MGS), and 5-repetition sit-to-stand (5STS) subtests of the SPPB contribute independently to the SPPB summary score. These 3 subtests are related to different outcome measures. The standing balance subtest is not or to a lesser extent related to exercise capacity and exercise tolerance than the other 2 subtests, as maintenance of balance requires complex integration and coordination of musculoskeletal and neural systems.[6, 8] The 4MGS is associated with exercise capacity and psychological factors and is an excellent screening measure for exercise capacity and frailty.[6, 9] The 5STS is the only subtest that correlates with health-related quality of life in patients with COPD and thus has additional value in evaluating the impact of COPD on the patient's life.[6, 10] In addition, Bernabeau-Mora et al. determined the clinical validity of the SPPB summary score and its 3 components for identifying mobility limitations in patients with COPD.[11] They revealed that only the 5STS and the SPPB summary score showed a good discriminative capability for self-reported mobility limitations. Taken together with the notion that the greatest variation in scores was reported for the 5STS in **Chapter 2** and previously by Mohan et al.,[7] it is suggested that the 5STS has the highest discriminative power among the subtests of the SPPB to identify functional limitation in patients with COPD. Furthermore, additional analyses with data from **Chapter 3** (not reported) revealed only weak correlations between balance, 4MGS, and 5STS scores at baseline (ρ=0.142-0.329, all P-values <0.001) and no significant correlations between the changes following a pulmonary rehabilitation (PR) program. Again, this substantiates that each of the 3 SPPB subtests provides distinct information regarding the patient's mobility and balance. Therefore, it is recommended to perform all 3 SPPB subtests in patients with COPD, especially considering the great feasibility due to the simplicity of the test in terms of test duration and required equipment.

To date, functional performance outcome measures such as the SPPB are often incorporated in pre- and post-intervention assessments. Therefore, it is important to ensure the responsiveness and determine minimal important differences (MIDs) of the SPPB. **Chapter 3** evaluated the effect of a comprehensive PR program on the SPPB and determined MIDs in patients with COPD. Our data reported improvements in 4MGS, 5STS, and SPPB summary scores following the PR program, but no change was observed in balance standing test scores. This is consistent with recent studies evaluating the effect of PR programs on SPPB summary scores and/or SPPB subtests.[10, 12-16] These findings might indicate that improvements in SPPB summary scores following PR are predominantly caused by changes in 4MGS and 5STS and perhaps not, or to a lesser extent, by changes in balance standing tests. The latter can be the result of a ceiling effect as 85% of the patients in **Chapter 2** obtained the maximal standing balance score of 4. Subsequently, 15% of these moderate-to-severe patients with COPD report balance impairments at the start of the PR program. An additional analysis revealed that 74% of these patients with balance impairments did show improvements of at least 1 point in balance standing score following the PR program (data not reported). Thus, it seems that the balance standing subtest is clinically relevant to perform in patients with moderate-to-severe COPD. However, the incidence of patients with balance impairments observed in **Chapter 2** is lower than the 20% to 45% described by previous studies.[17] Furthermore, 40% of patients with COPD, and with comparable baseline characteristics as the patients in **Chapter 2**, reported falls within the previous 12 months.[18] This might indicate that the balance standing subtest of the SPPB alone can perhaps only identify patients with extreme balance impairments, and is not adequately sensitive in patients with milder balance deficits. Therefore, more comprehensive tests such as the (mini-) Balance Evaluation Systems Test or Berg Balance Scale may be more useful in patients with COPD.[19]

In addition, **Chapter 3** reported a distribution-based MID estimate of 0.83-0.96 points (1 point as the SPPB summary score is reported in whole numbers) for the SPPB summary score. This indicates that an improvement of ≥1 point following a PR intervention can be considered a statistically significant improvement, which is consistent with the study of Perera et al. who reported a substantial change of 1.0 point for SPPB summary scores in older adults.[20] For the 4MGS, a MID range of 0.05-0.13 m/s was obtained using distribution- and anchor-based (6-minute walk distance as anchor) methods in **Chapter 3**. This is in line with the MID estimate of Kon et al. (0.11 m/s).[13] Finally, a distribution-based MID range of 2.19-6.33 seconds was observed for the 5STS in **Chapter 3**. These MID estimates are larger than the anchor-based MID estimate by Jones et al. of 1.7 seconds in patients with COPD after an 8-week outpatient PR program in the United Kingdom.[10] The discrepancy between both MID estimates can be explained by the different methods used to calculate the MIDs. Distribution-based MIDs indicate a statistically significant difference and anchor-based MIDs describe a clinically meaningful difference. In **Chapter 3** only distribution-based MID estimates for the 5STS could be determined because no significant moderate or strong correlations were present between the 5STS and both anchors (i.e., COPD Assessment Test and 6-minute walk test). Jones et al. used a 5-point Likert scale (ranging from 1 'feeling much better' to 5 'feeling much worse') to calculate anchor-based MIDs and did not report distribution-based MIDs.[10] With the reported standard deviation for the baseline 5STS time (SD=6.5 s),[10] 2 distribution-based calculations can be performed ($SD_{baseline}*\sqrt{(1\text{-intraclass correlation coefficient})}=1.1$ s and $0.5*SD_{baseline}=3.3$ s). The latter MID is more comparable to the MID estimates obtained in **Chapter 3**. However, it is also important to note that differences in for example study population and intervention might explain the discrepancy between the MIDs. The choice for an appropriate MID is therefore dependent on the study population, intervention, and method used to estimate the MID.

EXERCISE CAPACITY AND TOLERANCE

To date, it is still unclear whether and to what extent patient-reported outcomes (PROs) mirror the physical performance of patients with COPD, especially for exercise tests other than the 6-minute walk test.[21] Therefore, **Chapter 4** used univariate correlations to evaluate the validity of exercise capacity (6-minute walk distance and cardiopulmonary exercise test), exercise tolerance (constant work rate cycle test), functional performance (timed 'Up and Go' test), and peripheral muscle function (isokinetic peak torque and total work of the quadriceps) in comparison to patient-reported health-related quality of life, mood status, dyspnoea, and care dependency. This study revealed weak-to-moderate correlations and demonstrated that physical performance exercise tests and PROs assess different aspects in patients with COPD. These findings are recently confirmed by Quadflieg et al. who concluded that exercise tests are generally poorly related to PROs during a severe exacerbation of COPD.[22] Furthermore, recent studies in other populations demonstrated predominantly weak correlations between PROs and performance-based measures as well.[23-26] Therefore, additional assessment of health-related quality of life, anxiety, depression, and/or the level of care dependency is recommended in addition to exercise tests.

As already mentioned, exercise tests used to evaluate the effect of interventions must be able to pick up the improvements following the intervention. Therefore, **Chapter 4** assessed the responsiveness of exercise capacity (6-minute walk distance), exercise tolerance (constant work rate cycle test), functional performance (Timed 'Up and Go' test), and peripheral muscle function (isokinetic peak torque and total work of the quadriceps during a fatigue protocol) to a comprehensive PR program and reported a significant improvement for all outcome measures. In addition, univariate correlations between changes in exercise capacity, exercise tolerance, functional performance, and peripheral muscle function with changes in patient-reported health-related quality of life, mood status, dyspnoea, and care dependency were obtained. Our data revealed only very weak-to-weak correlations between changes in exercise tests and changes in PROs following a PR program. Again, this highlights that physical performance outcomes need to be supported by PROs to get a more comprehensive insight into the effectiveness of a PR program. It should be noted that the specific goals and the content of the PR program are personalized and a patient is thus not expected to improve in all aspects. Therefore, outcome measures used to evaluate the responsiveness of the intervention should match the patient's goals.

The endurance shuttle walk test (ESWT) is a feasible, valid, reliable, and responsive measure to evaluate exercise tolerance in patients with COPD.[27-36] Unfortunately, there is a large interindividual variability in tolerated duration (Tlim) of the ESWT,[33, 37-39] which was confirmed in **Chapter 5** as half of the patients had a test duration exceeding the desired 3-8 minutes. This large variability in ESWT Tlim complicates the interpretation of intervention efficacy and increases the required number of patients in clinical studies. An option to reduce the variability would be to perform a second ESWT at an adapted pace in patients with an ESWT Tlim exceeding the desired duration of 3-8 minutes. However, this is not always feasible due to logistic constraints. Thus, it is important to evaluate determinants of the ESWT Tlim in patients with COPD (i.e., validity) to better understand this large variation and possibly even adapt the ESWT pace prior to the ESWT test in order to reduce variability. Univariate regression analyses in **Chapter 5** revealed significant correlations between ESWT Tlim and pulmonary function, physical performance, physical activity, and incremental shuttle walk test (ISWT) performance measures, and not with isometric quadriceps muscle strength, in patients with moderate-to-severe COPD. This emphasizes that exercise capacity, exercise tolerance, and peripheral muscle function are not completely independent and distinctive components of physical performance but are somehow interrelated. However, it is still important to evaluate multiple, if not all, components of physical performance to obtain an extensive and complete overview of the patient's physical performance. Furthermore, a multivariate regression model showed that next to maximal ISWT speed, other ISWT performance measures as well as clinical measures of pulmonary function, exercise capacity, and physical activity were independent determinants of ESWT Tlim. Nevertheless, these determinants only explained ~30% of the variability in ESWT Tlim, indicating that the variance is predominantly related to other outcome measures than those assessed in **Chapter 5**. Furthermore, this makes it currently difficult to individualize the ESWT pace more accurately before the ESWT itself in order to reduce the large variability. To date, others have also tried to reduce the interindividual variability in ESWT Tlim. Dolmage et al. suggested the use of predetermined usual and fast walk speeds to provide a simple, quick, and inexpensive method for clinicians to set an acceptable endurance walk speed.[40] In addition, Hill et al. found that participants with milder symptoms of dyspnoea (Borg score <4) and leg fatigue (Borg score <2) on completion of baseline 6MWT and ISWT may achieve a longer ESWT Tlim. They recommended repeating the ESWT at a higher walking speed to achieve an ESWT Tlim between the desired duration.[41] Thus, no accurate prediction formula is available yet to determine the individual ESWT pace that will result in a desired pre-intervention ESWT Tlim. Therefore, the performance of a second ESWT would be preferable when the pre-intervention ESWT Tlim exceeds the desired duration of 3-8 minutes. Future studies with additional outcome measures like dynamic hyperinflation and peripheral muscle endurance are necessary in order to obtain such a prediction formula.

PERIPHERAL MUSCLE FUNCTION

Peripheral muscle endurance is more severely reduced than muscle strength in patients with COPD and requires different training strategies.[42-44] This highlights the clinical relevance of the assessment of peripheral muscle endurance in these patients. Peripheral muscle endurance is most commonly assessed using isokinetic contractions in patients with COPD.[45] Recent studies already reported good reliability and feasibility in those patients but were only performed in research settings.[42] Therefore, **Chapter 6** assessed the feasibility of isokinetic evaluation of quadriceps muscle endurance in patients with COPD in a PR centre. The findings revealed that 3 out of 4 patients with COPD performed the isokinetic quadriceps test correctly during baseline PR assessment. The main reasons for an invalid test performance were premature test termination (i.e., not completing 30 repetitions) and not reaching peak torque within the first 5 repetitions. Furthermore, **Chapter 7** reported that 4 out of 26 patients (15%) performed the isokinetic test incorrectly. Those patients with an invalid test performance at baseline in **Chapter 6** were characterized by a lower exercise capacity and a lower isotonic peripheral and respiratory muscle strength than patients with a valid test. However, it is unclear whether repeating the baseline test will improve the feasibility in those patients with an invalid test, or whether these patients are just not capable of performing the test correctly for other unknown reasons. Therefore, further research should reveal whether a second endurance test at baseline is beneficial in patients with an invalid test. As it might not always be feasible to repeat the isokinetic endurance test in research or clinical settings, a second option would be to perform a different quadriceps endurance test. Hence, it is important to determine the feasibility of isotonic and isometric quadriceps endurance tests in clinical settings as well. **Chapter 7** showed already promising results regarding the feasibility of the isometric quadriceps endurance test as all 26 patients with COPD performed the isometric endurance test correctly.

To date, it is still unknown whether isokinetic evaluation of quadriceps muscle endurance can pick up improvements following a PR program. In addition, MIDs are currently lacking, which complicates the interpretation of intervention efficacy. Therefore, **Chapter 6** evaluated the response of isokinetic quadriceps muscle endurance following PR and determined MIDs. Our data demonstrated that isokinetic muscle strength (i.e., peak torque) and total work improved following PR, but no change was observed for work fatigue index. The improvement in isokinetic total work was also observed following a low-load/high-repetition resistance training in patients with COPD.[46, 47] The lack of change in work fatigue index following PR might be explained by the low test-retest intraclass correlation coefficient[48] or the fact that the current program did not specifically focus on the fatiguability of the quadriceps muscle. Unfortunately, no other study has evaluated the effect of an exercise training intervention on work fatigue index yet. Therefore, additional studies are needed to evaluate the responsiveness of the work fatigue index following an intervention that focuses on the fatiguability of the quadriceps muscle. In addition, sex-specific MIDs were calculated as differences between peak torque, total work, and work fatigue index were observed between healthy males and females.[49] **Chapter 6** revealed distribution-based MIDs for peak torque ranging between 6-7 Nm or 8% change for males, and 4-5 Nm or 7% change for females. For total work, the distribution-based MIDs ranged between 97-135 J or 24-25% change for males, and between 62-99 J or 13-14% change for females. Furthermore, it is important to note that these MIDs only apply to patients who perform a valid baseline and post PR test. Lastly, it should be emphasized that there was a strong relation observed in **Chapter 6** between isokinetic peak torque (i.e., muscle strength) and total work at baseline and following a PR intervention. This might question whether total work is the most appropriate outcome measure to evaluate peripheral muscle endurance. In addition, it should be highlighted that a computerized dynamometer is expensive and requires trained personnel, and not all centres have a computerized dynamometer available. In these cases, isotonic protocols might be an alternative as these tests require simpler equipment like elastic bands, exercise platforms or benches, or a pully system. These protocols are performed with a constant external load and standardized range of motion and speed and have a great reliability and feasibility in patients with COPD.[48] Furthermore, isotonic peripheral muscle endurance is correlated with functional performance and exercise capacity and is better associated with daily physical activity than isokinetic and isometric peripheral muscle endurance.[50, 51]

There is still no consensus yet on the best protocol to evaluate peripheral muscle endurance in patients with COPD. Therefore, **Chapter 7** evaluated the validity of volitional isometric and isokinetic quadriceps endurance tests by assessing its relation to non-volitional electrically stimulated isometric quadriceps endurance in patients with COPD. The study reported that outcome measures of the 2 volitional endurance tests correlate significantly and strongly. So, these 2 protocols evaluate a great amount of similarity in quadriceps endurance despite the difference in contraction type. However, neither of those volitional tests showed a significant correlation with non-volitionally assessed quadriceps muscle endurance. This might imply that volitional and non-volitional tests evaluate different constructs of quadriceps muscle endurance in patients with COPD. Recent studies have already reported that volitional isometric and isokinetic endurance exercises are related to the oxidative metabolism of the active muscle.[52-54] However, the severity of dyspnoea and central fatigue (i.e., the deficient drive of motor cortical output attenuating performance or even stopping the activity)[55] is expected to intervene to a greater extent in volitional tests than non-volitional tests. Therefore, the preferred protocol for quadriceps endurance assessment is dependent on the aim of the measurement. Non-volitional tests are less influenced by the severity of dyspnoea and the motivation and cooperation of the patient and are presumably a truer reflection of fatigue mechanisms within the peripheral muscle. However, these tests are less practical because they require more time and trained personnel and are not always tolerated by patients. This latter is supported by **Chapter 7** in which 5 of the 21 patients (24%) had an invalid non-volitional endurance test. Furthermore, the purpose of muscle function tests in clinical settings is also to prescribe an individualized exercise training. Dyspnoea and central fatigue intervene in the performance of these endurance training exercises, and thus may volitional tests perhaps be more suitable in a clinical setting.

CONCLUSIONS

Taken together, this thesis underpins the evidence that functional performance, exercise capacity, exercise tolerance, and peripheral muscle function are 4 distinctive, but partly related, domains of physical performance. All 4 domains should be evaluated to identify appropriate targets for an effective and individualized exercise intervention.

The present thesis demonstrates that the SPPB is a valid and responsive outcome measure for functional performance in patients with moderate-to-severe COPD. Furthermore, the performance of all 3 SPPB subtests is advisable in current clinical practice because they provide distinct information about the patient's mobility and frailty. Nevertheless, it should be noted that the balance standing subtest might not be adequately sensitive to pick up mild balance deficits in these patients. This knowledge will help clinicians to screen for a reduced mobility and balance in patients with COPD and therefore supports them to establish an effective treatment strategy.

PROs and exercise test outcomes establish different disease-related aspects in patients with COPD. Thus, it is recommended that exercise tests are supported by PROs to obtain a comprehensive overview of the patient and provide a more detailed insight in the efficacy of interventions. Moreover, this thesis substantiates a large interindividual variability in the outcome measure of the ESWT exercise test

(Tlim), which complicates the interpretation of intervention efficacy. Unfortunately, the current findings are largely not able to explain this variability. So, until a more specific prediction formula is available, a second ESWT is recommended when Tlim exceeds 3-8 minutes.

This thesis shows that an improvement of >7% or >8% in volitional isokinetic quadriceps muscle strength following a PR program can be considered as a true effect in female and male patients with COPD respectively. The effectiveness of a PR program on volitional isokinetic quadriceps muscle endurance depends on the outcome measures of endurance that are being applied. Nevertheless, the current thesis also indicates that a great extent of similarity in quadriceps muscle endurance can be assessed using either volitional isometric or isokinetic contractions. However, volitional and non-volitional outcome measures evaluate partly different aspects of quadriceps muscle endurance in patients with COPD. Accordingly, volitional and non-volitional outcome measures of quadriceps endurance should not be used interchangeably. Finally, this thesis reports a greater feasibility, in terms of percentage patients with a valid test performance, for the volitional isometric protocol than the volitional isokinetic and non-volitional isometric protocols. A better understanding of these protocols will guide clinicians and researchers to make an informed decision about which protocol is most suitable to perform in their specific context.

FUTURE DIRECTIONS

Even though this thesis has brought new insights into the feasibility, validity, and responsiveness of physical performance measures in patients with COPD, some aspects need to be addressed in the future. Firstly, validation of the established MID for 5STS in **Chapter 3** is needed to help clinicians and researchers interpret intervention efficacy, ideally using both anchor-based and distribution-based methods. Furthermore, additional studies on determinants of ESWT Tlim are necessary to develop an accurate prediction formula for ESWT pace to reduce the ESWT Tlim variability. As previously mentioned, this will improve the interpretation of intervention efficacy and, in turn, lead to the development of more optimal endurance training programs. Lastly, the fatiguability of the quadriceps muscles is known to be greatly reduced in patients with COPD but only limited studies have focused on the effectiveness of appropriate exercise interventions on the fatiguability of peripheral muscles in these patients. Thus, future research is needed to assess the effectiveness of exercise interventions targeting the fatiguability of the quadriceps muscle in patients with COPD. Accordingly, it is important to evaluate which quadriceps muscle endurance outcomes can be used to optimize effective individualized exercise programs.

REFERENCES

1. Eisner MD, Blanc PD, Yelin EH, Sidney S, Katz PP, Ackerson L, et al. COPD as a systemic disease: impact on physical functional limitations. Am J Med. 2008;121(9):789-96.
2. Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigare R, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014;189(9):e15-62.
3. Vaes AW, Spruit MA, Koolen EH, Antons JC, de Man M, Djamin RS, et al. "Can Do, Do Do" Quadrants and 6-Year All-Cause Mortality in Patients With COPD. Chest. 2022;161(6):1494-504.
4. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8):e13-64.
5. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49(2):M85-94.
6. Bernabeu-Mora R, Gimenez-Gimenez LM, Montilla-Herrador J, Garcia-Guillamon G, Garcia-Vidal JA, Medina-Mirapeix F. Determinants of each domain of the Short Physical Performance Battery in COPD. Int J Chronic Obstr. 2017;12:2539-44.
7. Mohan D, Benson VS, Allinder M, Galwey N, Bolton CE, Cockcroft JR, et al. Short Physical Performance Battery: What Does Each Sub-Test Measure in Patients with Chronic Obstructive Pulmonary Disease? Chronic Obstr Pulm Dis. 2020;7(1):13-25.
8. Beauchamp MK, Sibley KM, Lakhani B, Romano J, Mathur S, Goldstein RS, et al. Impairments in systems underlying control of balance in COPD. Chest. 2012;141(6):1496-503.
9. Karpman C, Benzo R. Gait speed as a measure of functional status in COPD patients. Int J Chron Obstruct Pulmon Dis. 2014;9:1315-20.
10. Jones SE, Kon SS, Canavan JL, Patel MS, Clark AL, Nolan CM, et al. The five-repetition sit-to-stand test as a functional outcome measure in COPD. Thorax. 2013;68(11):1015-20.
11. Bernabeu-Mora R, Medina-Mirapeix F, Llamazares-Herran E, Garcia-Guillamon G, Gimenez-Gimenez LM, Sanchez-Nieto JM. The Short Physical Performance Battery is a discriminative tool for identifying patients with COPD at risk of disability. Int J Chron Obstruct Pulmon Dis. 2015;10:2619-26.
12. Carrington D, Jones S, Canavan J, Nolan C, Kon S, Polkey M, et al. Responsiveness of the short physical performance battery (SPPB) in severely dyspnoeic patients with COPD. Eur Respir J. 2015;46:PA4593.
13. Kon SS, Canavan JL, Nolan CM, Clark AL, Jones SE, Cullinan P, et al. The 4-metre gait speed in COPD: responsiveness and minimal clinically important difference. Eur Respir J. 2014;43(5):1298-305.
14. Larsson P, Borge CR, Nygren-Bonnier M, Lerdal A, Edvardsen A. An evaluation of the short physical performance battery following pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. BMC Res Notes. 2018;11(1):348.

15. Pancera S, Bianchi LNC, Porta R, Villafane JH, Buraschi R, Lopomo NF. Muscle function and functional performance after pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a prospective observational study. Sci Rep. 2022;12(1):16386.
16. Vitacca M, Paneroni M, Salvi B, Spanevello A, Ceriana P, Bruschi C, et al. Airflow grades, outcome measures and response to pulmonary rehabilitation in individuals after an exacerbation of severe chronic obstructive pulmonary disease. Eur J Intern Med. 2023;107:81-5.
17. Wang C, Chen H, Qian M, Shi Y, Zhang N, Shang S. Balance Function in Patients With COPD: A Systematic Review of Measurement Properties. Clin Nurs Res. 2022;31(6):1000-13.
18. Oliveira CC, Lee AL, McGinley J, Thompson M, Irving LB, Anderson GP, et al. Falls by individuals with chronic obstructive pulmonary disease: a preliminary 12-month prospective cohort study. Respirology. 2015;20(7):1096-101.
19. Beauchamp MK. Balance assessment in people with COPD: An evidence-based guide. Chron Respir Dis. 2019;16:1479973118820311.
20. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc. 2006;54(5):743-9.
21. Punekar YS, Riley JH, Lloyd E, Driessen M, Singh SJ. Systematic review of the association between exercise tests and patient-reported outcomes in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2017;12:2487-506.
22. Quadflieg K, Machado A, Haesevoets S, Daenen M, Thomeer M, Ruttens D, et al. Physical Tests Are Poorly Related to Patient-Reported Outcome Measures during Severe Acute Exacerbations of COPD. J Clin Med. 2021;11(1):150.
23. Kavanaugh K, Moore JB, Hibbett LJ, Kaczynski AT. Correlates of subjectively and objectively measured physical activity in young adolescents. J Sport Health Sci. 2015;4(3):222-7.
24. Luna IE, Kehlet H, Peterson B, Wede HR, Hoevsgaard SJ, Aasvang EK. Early patient-reported outcomes versus objective function after total hip and knee arthroplasty A PROSPECTIVE COHORT STUDY. Bone Joint J. 2017;99b(9):1167-75.
25. Paton M, Lane R, Paul E, Linke N, Shehabi Y, Hodgson CL. Correlation of patient-reported outcome measures to performance-based function in critical care survivors: PREDICTABLE. Australian Critical Care. 2022:S1036-7314(22)00070-4.
26. Shulman LM, Pretzer-Aboff I, Anderson KE, Stevenson R, Vaughan CG, Gruber-Baldini AL, et al. Subjective report versus objective measurement of activities of daily living in Parkinson's disease. Mov Disord. 2006;21(6):794-9.
27. Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. Thorax. 1999;54(3):213-22.
28. Ngai SPC, Spencer LM, Jones AYM, Alison JA. Repeatability of the endurance shuttle walk test in people with chronic obstructive pulmonary disease. Clin Respir J. 2017;11(6):875-80.
29. McKeough Z, Leung R, Neo JH, Jenkins S, Holland A, Hill K, et al. Shuttle walk tests in people with COPD who demonstrate exercise-induced oxygen desaturation: An analysis of test repeatability and cardiorespiratory responses. Chron Respir Dis. 2018;15(2):131-7.

30. McKeough ZJ, Leung RW, Alison JA. Shuttle walk tests as outcome measures: Are two incremental shuttle walk tests and two endurance shuttle walk tests necessary? Am J Phys Med Rehabil. 2011;90(1):35-9.
31. Revill SM, Williams J, Sewell L, Collier R, Singh SJ. Within-day repeatability of the endurance shuttle walk test. Physiotherapy. 2009;95(2):140-3.
32. Revill SM, Noor MZ, Butcher G, Ward MJ. The endurance shuttle walk test: an alternative to the six-minute walk test for the assessment of ambulatory oxygen. Chron Respir Dis. 2010;7(4):239-45.
33. Maltais F, O'Donnell DE, Hamilton A, Zhao Y, Casaburi R. Comparative measurement properties of constant work rate cycling and the endurance shuttle walking test in COPD: the TORRACTO(®) clinical trial. Ther Adv Respir Dis. 2020;14:1753466620926858.
34. Eaton T, Young P, Nicol K, Kolbe J. The endurance shuttle walking test: a responsive measure in pulmonary rehabilitation for COPD patients. Chron Respir Dis. 2006;3(1):3-9.
35. Greening NJ, Evans RA, Williams JE, Green RH, Singh SJ, Steiner MC. Does body mass index influence the outcomes of a Waking-based pulmonary rehabilitation programme in COPD? Chron Respir Dis. 2012;9(2):99-106.
36. Zatloukal J, Ward S, Houchen-Wolloff L, Harvey-Dunstan T, Singh S. The minimal important difference for the endurance shuttle walk test in individuals with chronic obstructive pulmonary disease following a course of pulmonary rehabilitation. Chron Resp Dis. 2019;16:1479973119853828.
37. Pepin V, Saey D, Whittom F, LeBlanc P, Maltais F. Walking versus cycling: sensitivity to bronchodilation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;172(12):1517-22.
38. Ong KC, Chong WF, Soh C, Earnest A. Comparison of different exercise tests in assessing outcomes of pulmonary rehabilitation. Respir Care. 2004;49(12):1498-503.
39. Laviolette L, Bourbeau J, Bernard S, Lacasse Y, Pepin V, Breton MJ, et al. Assessing the impact of pulmonary rehabilitation on functional status in COPD. Thorax. 2008;63(2):115-21.
40. Dolmage TE, Rozenberg D, Malek N, Evans RA, Goldstein RS. Saving Time for Patients with Moderate to Severe COPD: Endurance Test Speed Set Using Usual and Fast Walk Speeds. Chronic Obstr Pulm Dis. 2014;1(2):193-9.
41. Hill K, Chao YL, Cavalheri V, Ng LWC, Wootton SL, McKeough ZJ, et al. Increasing Walking Speed to Achieve a Pre-training Endurance Shuttle Walk Time of 5-10 min May Improve Test Responsiveness in People With Chronic Obstructive Pulmonary Disease. J Cardiopulm Rehabil Prev. 2021;41(4):264-6.
42. Nyberg A, Saey D, Maltais F. Why and How Limb Muscle Mass and Function Should Be Measured in Patients with Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc. 2015;12(9):1269-77.
43. Vaes AW, Sillen MJH, Goertz YMJ, Machado F, Van Herck M, Burtin C, et al. The correlation between quadriceps muscle strength and endurance and exercise performance in patients with COPD. J Appl Physiol (1985). 2021;131(2):589-600.
44. Hughes DC, Ellefsen S, Baar K. Adaptations to Endurance and Strength Training. Cold Spring Harb Perspect Med. 2018;8(6):a029769.

45. De Brandt J, Spruit MA, Hansen D, Franssen FM, Derave W, Sillen MJ, et al. Changes in lower limb muscle function and muscle mass following exercise-based interventions in patients with chronic obstructive pulmonary disease: A review of the English-language literature. Chron Respir Dis. 2018;15(2):182-219.
46. Nyberg A, Lindstrom B, Rickenlund A, Wadell K. Low-load/high-repetition elastic band resistance training in patients with COPD: a randomized, controlled, multicenter trial. Clin Respir J. 2015;9(3):278-88.
47. Nyberg A, Martin M, Saey D, Milad N, Patoine D, Morissette MC, et al. Effects of Low-Load/High-Repetition Resistance Training on Exercise Capacity, Health Status, and Limb Muscle Adaptation in Patients With Severe COPD: A Randomized Controlled Trial. Chest. 2021;159(5):1821-32.
48. Frykholm E, Gephine S, Saey D, van Hees H, Lemson A, Klijn P, et al. Inter-day test-retest reliability and feasibility of isokinetic, isometric, and isotonic measurements to assess quadriceps endurance in people with chronic obstructive pulmonary disease: A multicenter study. Chron Respir Dis. 2019;16:1479973118816497.
49. Pincivero DM, Gandaio CM, Ito Y. Gender-specific knee extensor torque, flexor torque, and muscle fatigue responses during maximal effort contractions. Eur J Appl Physiol. 2003;89(2):134-41.
50. Frykholm E, Gephine S, Saey D, Lemson A, Klijn P, de Vaate EB, et al. Isotonic quadriceps endurance is better associated with daily physical activity than quadriceps strength and power in COPD: an international multicentre cross-sectional trial. Sci ReP-Uk. 2021;11(1):11557.
51. Gephine S, Frykholm E, Nyberg A, Mucci P, Van Hees HWH, Lemson A, et al. Specific Contribution of Quadriceps Muscle Strength, Endurance, and Power to Functional Exercise Capacity in People With Chronic Obstructive Pulmonary Disease: A Multicenter Study. Phys Ther. 2021;101(6):pzab052.
52. Allaire J, Maltais F, Doyon JF, Noel M, LeBlanc P, Carrier G, et al. Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD. Thorax. 2004;59(8):673-8.
53. Ribeiro F, Oueslati F, Saey D, Lépine PA, Chambah S, Coats V, et al. Cardiorespiratory and Muscle Oxygenation Responses to Isokinetic Exercise in Chronic Obstructive Pulmonary Disease. Med Sci Sports Exerc. 2019;51(5):841-9.
54. van den Borst B, Slot IGM, Hellwig VACV, Vosse BAH, Kelders MCJM, Barreiro E, et al. Loss of quadriceps muscle oxidative phenotype and decreased endurance in patients with mild-to-moderate COPD. Journal of Applied Physiology. 2012;114(9):1319-28.
55. Tornero-Aguilera JF, Jimenez-Morcillo J, Rubio-Zarapuz A, Clemente-Suarez VJ. Central and Peripheral Fatigue in Physical Exercise Explained: A Narrative Review. Int J Environ Res Public Health. 2022;19(7):3909.