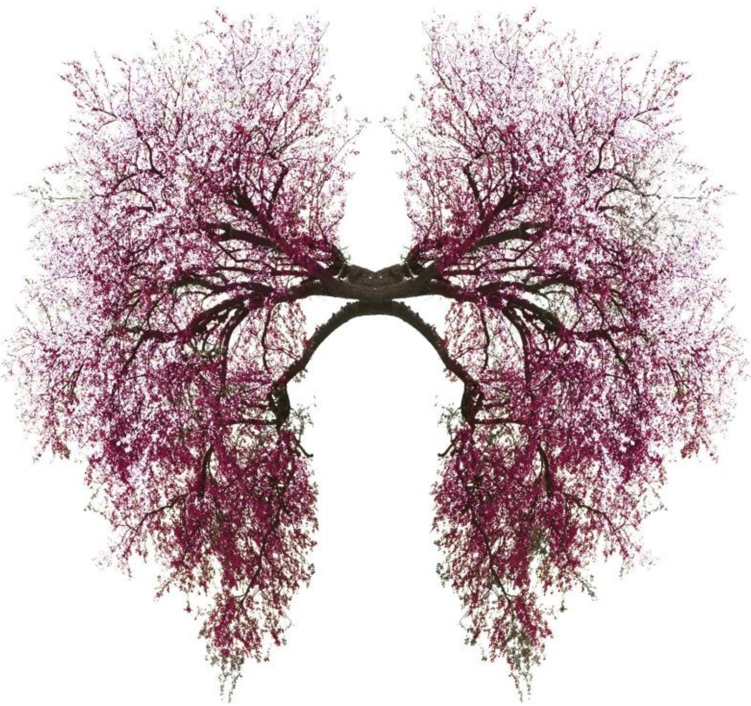
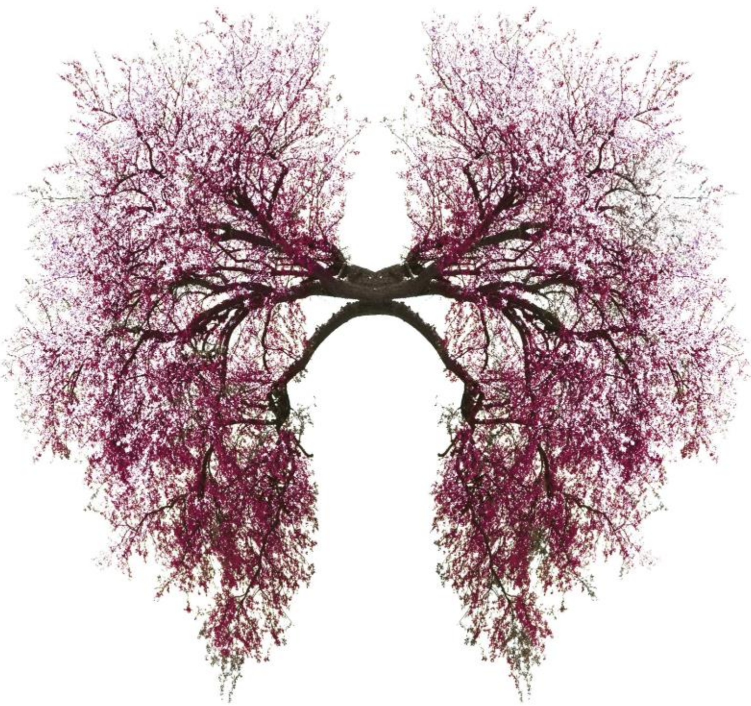
PART 3



Extended applicability of functional exercise capacity assessment (the six-minute walk test)

CHAPTER 5



Course length of 30 metres versus 10 metres has a significant influence on six-minute walk distance in patients with COPD: an experimental crossover study

Emmylou Beekman, Ilse Mesters, Erik J.M. Hendriks, Mariska P.M. Klaassen, Rik Gosselink, Onno C.P. van Schayck, Rob A. de Bie

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ABSTRACT

Questions

Do patients with chronic obstructive pulmonary disease (COPD) achieve a different distance on the six-minute walk test (6MWT) conducted on a 10 m course versus on a 30 m course? When assessing the distance on a 6MWT conducted on a 10 m course, is it valid to use existing reference equations that were generated on longer courses?

Design

A randomised double-crossover experimental study.

Participants

Forty-five patients with COPD in primary physiotherapy care.

Intervention

All patients performed a 6MWT twice over a 10 m course and twice over a 30 m course. The 6MWTs were performed in accordance with the American Thoracic Society guidelines.

Outcome measures

6MWD was assessed and predicted distance was calculated based on a range of reference equations.

Results

The 6MWD on the 10 m course was 49.5 m shorter than on the 30 m course, which was statistically significant (95% CI 39.4 to 59.6). By using existing reference equations for a 6MWT conducted on the 10 m course, the predicted distance is highly overestimated (with a range of 30% to 33%) and the average distance as a percentage of the predicted value is 8%pred lower compared to a 6MWT conducted on the 30 m course, resulting in a worse representation of a COPD patient’s functional exercise capacity.

Conclusion

This study shows that the impact of course length on the 6MWD and on the use of reference equations in patients with COPD is substantial and clinically relevant (based on the most conservative published minimum clinically important difference). Therefore, existing reference equations established for a 6MWT conducted over a 30 m (or longer) course cannot be applied to predict the distance achieved on the 6MWT on a 10 m course, which is frequently used in primary care physiotherapy practices for patients with COPD.

INTRODUCTION

The six-minute walk test (6MWT) is recommended as a reliable, valid, and responsive test to measure functional exercise capacity in adults with chronic obstructive pulmonary disease (COPD) by the American Thoracic Society[1] (ATS 2002) and others.[2,3] Health professionals' preference for the 6MWT may be due to its close relation to activities in daily life, its simplicity, and its broad applicability in frail elderly people or patients who cannot be tested with standard tests like a 12 minute walk test, shuttle walk test, maximal cycle ergometer, or treadmill tests. The 6MWT also takes less time and costs less to perform than more extensive tests.[1,4] It is most suitable to evaluate the effects of medical interventions in people with moderate to severe heart or lung disease.[1] Furthermore, the 6MWT is used as a diagnostic assessment of functional status to justify treatment plans in primary COPD care and as a predictor of morbidity and mortality.[1] Although forced expiratory volume in one second (FEV_1) remains the most important physiological indicator of the severity of airflow obstruction in people with COPD, its predictive value for mortality is weak when FEV_1 is higher than 50% of the age-predicted value .[5] On the other hand, achieving a 6MWT distance (6MWD) of less than 82% of the predicted value can be considered abnormal [6] and a distance of less than 350 m or a fall of 30 m in 12 months is strongly associated with increased mortality in people with COPD.[7,3] As a component of the BODE index (**B**MI, airflow **O**bstruction, **D**yspnoea and **E**xercise), but also as an independent measure, the 6MWD predicts COPD-related mortality better than FEV_1 alone.[5]

The American Thoracic Society guidelines[1] state that the walking course for the 6MWT must be 30 m in a straight line. Normative values have been established for this distance and other distances, mainly exceeding 30 m. An overview of published reference equations for the 6MWT on various course lengths is shown in Table 5.1.

In physiotherapy practices in a primary care setting, a 30 m straight or circular course is often not available, while continuous (oval) courses increase the distance achieved.[8] Space limitations frequently force clinicians and researchers to administer the 6MWT on a 10 m course. Being aware of the space limitation, a COPD guideline for physiotherapists advocates performance of the standardised 6MWT on a course of at least 10 m.[9]

Table 5.1 Overview of published studies with reference equations for MWD involving healthy individuals.[a]

	Track[b], m	Participants	References equations	r^2
548	15	Chinese 21-70 yr	Reference values age and gender specific available in article, No equations	
79	20	Canadian 20-80 yr	♂ 6MWD m = 868.8 - (2.99 *age years) ♀ 6MWD m = 868.8 - (2.99 *age years) – 74.7	0.41 0.41
102	30	Caucasian 20-50 yr	♂ 6MWD m = 518.853 + (1.25 *height cm) - (2.816 *age years) ♀ 6MWD m = 518.853 + (1.25 *height cm) - (2.816 *age years) - 39.07	0.42 0.42
155	30	Tunisian 40-80 yr	♂ 6MWD m = 299.8 – (4.34 *age years) + (342.6 *height m) - (1.46 *weight kg) + 62.5, LLN = calculated value - 124.5 m ♀ 6MWD m = 299.8 – (4.34 *age years) + (342.6 *height m) - (1.46 *weight kg), LLN = calculated value - 124.5 m	0.60 0.60
298	30	Arab 18-50 yr	♂ 6MWD m = (2.81 *height cm) + (0.79 *age years) - 28.5 ♀ 6MWD m = (2.81 *height cm) + (0.79 *age years) - 28.5	0.25 0.25
134	30	Brazilian >13 yr	♂ 6MWD m = 622.461 - (1.846 *age years) + 61.503, SEE = 70.992 m ♀ 6MWD m = 622.461 - (1.846 *age years), SEE = 70.992 m	0.30 0.30
175	30	Chilean 20-80 yr	♂ 6MWD m = 530 - (3.31* age years) + (2.36* height cm) - (1.49* weight kg), SEE = 58 m ♀ 6MWD m = 457 - (3.46* age years) + (2.61* height cm) - (1.57* weight kg), SEE = 53 m	0.55 0.63
132	30	Brazilian 20-80 yr	♂ 6MWD m = 390 + (2.14 *height cm) - (2.37 *age years) - (2.34 *BMI), 5th percentile = 121 m ♀ 6MWD m = 683 + ... 5th percentile = 97 m	0.33 0.71
444	30	Caucasian American 40-80 yr	♂ 6MWD m = 361 - (4* age years) + (2* height cm) + (3 *HR max/HR max%pred) - (1.5* weight kg) ♀ 6MWD m = 361 - (4* age years) + (2* height cm) + (3 *HR max/HR max%pred) - (1.5* weight kg) - 30	0.38 0.38
77	30	Canadian 45-85 yr	♂ 6MWD m = 970.7 + (-5.5 *age years) + 56.3 ♀ 6MWD m = 970.7 + (-5.5* age years)	0.49 0.49
290	30.5	North American 40-80 yr	♂ 6MWD m = (7.57* height cm) - (5.02* age years) - (1.76* weight kg) - 309, LLN = calculated value - 153 m ♀ 6MWD m = (2.11* height cm) - (5.78* age years) - (2.29* weight kg) + 667, LLN = calculated value - 139 m	0.42 0.38
2281	30.5	North American ≥68 yr	♂ 6MWD m = 493 + (2.2 *height cm) - (0.93 *weight pound) - (5.3 *age years) + 17 ♀ 6MWD m = 493 + (2.2 *height cm) - (0.93 *weight pound) - (5.3 *age years)	0.20 0.20
229	40	North African ≥40 yr	♂ 6MWD m = 720.50 - (5.14 *age years) - (2.23 *weight kg) + (271.98 *height m), LLN = calculated value - 89 m ♀ 6MWD m = 720.50 - (5.14 *age years) - (2.23 *weight kg) + (271.98 *height m) - 160, LLN = calculated value - 89 m	0.77 0.77

Study	n
Tsang 2005[10]	
Gibbons et al. 2001[11]	
Chetta et al. 2006[12]	
Masmoudi et al. 2008[13]	
Alameri et al. 2009[14]	
Iwama et al. 2009[15]	
Osses et al. 2010[16]	
Soares & Pereira 2011[17]	
Casanova et al. 2011[18]	
Hill et al. 2011[19]	
Enright & Sherrill 1998[20]	
Enright et al. 2003[21]	
Ben Saad et al. 2009[22]	

Table 5.1 continued

	Track[b], m	Participants	References equations	r^2
35	45	Chinese	♂ 6MWD$_m$ = (5.50 *HR$_{max}$%pred) + (6.94* height$_{cm}$) - (4.49* age$_{years}$) - (3.51* weight$_{kg}$) - 473.27	0.78
		45-85 yr	♀ 6MWD$_m$ = (5.50 *HR$_{max}$%pred) + (6.94* height$_{cm}$) - (4.49* age$_{years}$) - (3.51* weight$_{kg}$) - 473.27	0.78
70	45	Caucasian	♂ 6MWD$_m$ = 64.69 + (3.12* height$_{cm}$) + (23.29 *FEV$_{1, litres}$)	0.34
		Australian	♀ 6MWD$_m$ = 64.69 + (3.12* height$_{cm}$) + (23.29 *FEV$_{1, litres}$)	0.34
		55-75 yr		
109	45	Caucasian	♂ 6MWD$_m$ = 867 - (5.71* age$_{years}$) + (1.03* height$_{cm}$)	0.40
		Australian	♂ 6MWD$_m$ = 748 - (6.32* age$_{years}$) + (0.64* height$_{cm}$) + (2.69* HR$_{max}$%pred)	0.61
		45-85 yr	♀ 6MWD$_m$ = 525 - (2.86* age$_{years}$) + (2.71* height$_{cm}$) - (*BMI)	0.43
			♀ 6MWD$_m$ = 541 - (3.81* age$_{years}$) + (1.80* height$_{cm}$) - (6.22 *BMI) + (*HR$_{max}$%pred)	0.58
51	50	Caucasian	♂ 6MWD$_m$ = 218 + (*height$_{cm}$) – (*age$_{years}$) - (*weight$_{kg}$) + 51.31 RSD = 56 m	0.66
		50-85 yr	♀ 6MWD$_m$ = 218 + (5.14 *height$_{cm}$) – (5.32 *age$_{years}$) - (1.80 *weight$_{kg}$), RSD = 56 m	0.66

[a] Literature searched until October 2012; [b] All tracks were straight and performed indoor, except for Soares and Pereira (2011) who used an outdoor track. All protocols followed standardised encouragement every minute, except for Gibbons et al. (2001), Chetta et al. (2006) and Troosters et al. (1999) who encouraged every 30 seconds, and Ben Saad et al. (2009) where no encouragement was given; [c] Extension of the sample published in 2006 by Camarri et al. (55–75 yr; track length also 45 m).

Abbreviations: $6MWD_m$ = six-minute walk distance in metres, r^2 = the coefficient of determination, the proportion of variability in a dataset that is accounted for by a statistical model, LLN = lower limit of normal, SEE = standard error of the estimate, BMI = body mass index (kg/m^2), HR_{max} = maximal heart rate during the test, HR_{max}%pred = percentage of age-predicted maximal heart rate, with HR_{max} calculated as 220 – age, RSD = residual standard deviation.

Study	n
Poh et al. 2006[23]	
Camarri et al. 2006[24]	
Jenkins et al. 2009[25] [c]	
Troosters et al. 1999[6]	

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Studies on whether course length impacts the performance of patients with COPD are inconclusive. In a cross-sectional study, Sciurba and colleagues[8] compared 6MWDs of different subjects in different centres and reported that course lengths ranging from 17 m to 55 m had no significant effect on walk distance of 761 patients with severe emphysema. However, Enright and colleagues[21] suggested in a narrative review that the greater number of turns with a shorter course length is one of the factors associated with achieving a shorter distance. So far, only one study has published the effects of walkway length comparing 10 m and 30 m in healthy adults.[26] Similarly, only one study has examined this in patients with stroke, who are limited in their walking speed due to abnormal gait and reduced walking endurance.[27] Although these studies concluded that different course lengths have a significant effect on the 6MWD, the question remains whether the same effect occurs in people with COPD, who are limited in their walking speed due to dyspnoea and/or peripheral muscle fatigue. This may invalidate the use of reference equations with results from 6MWTs conducted on different course lengths than the one used to generate the reference equations. No study has described the difference in 6MWD on 10 m versus 30 m courses in patients with COPD. Therefore, the research questions of the present study were:

1. Do patients with chronic obstructive pulmonary disease (COPD) achieve a different distance on a 6MWT conducted on a 10 m course versus on a 30 m course?
2. When assessing the distance on a 6MWT conducted on a 10 m course, is it valid to use existing reference equations that were generated on longer courses?

METHODS

Design

A double-crossover design was used to measure the 6MWD on different course lengths. Patients were instructed to attend the rehabilitation centre twice, with seven days between the visits. This was done to correct for the learning effect that has been reported in patients with COPD[28] and because performance usually reaches a plateau after two tests done within a week.[1] On the first day, patients walked up and down both a 10 m course for six minutes and a 30 m course for six minutes, separated by a rest period of at least 30 minutes. The order in which the different course lengths were tested was randomised. One week later the participants repeated the two tests at the same time of the day but in the reverse order.

Participants

Participants were recruited by the researchers (EB and IM) at a primary care physiotherapy practice specialised in COPD rehabilitation in the south of The

Netherlands. Prior to the 6MWT people attending the physiotherapy practice were screened by the researcher (EB). They were considered eligible to participate if they had a confirmed diagnosis of COPD (by a pulmonologist or general practitioner) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2010)[29]; were clinically stable (no signs of pulmonary exacerbation); were able to execute the 6MWT; and were able to understand the protocol instructions. All participants completed a health status questionnaire to record comorbidities and the results of their most recent lung function test.

On the day of testing all patients confirmed taking their prescribed medication (bronchodilators and medication for co-morbidities). They were required to abstain from short-acting bronchodilators for at least two hours before spirometry and the 6MWTs.[4] Height, body weight, age, sex, and smoking habits were recorded. The intensity and frequency of physical activity in daily life was scored using the Physical Activity Questionnaire, with 0 to 3 being insufficiently active and 4 or above being sufficiently active.[9] Heart rate, resting diastolic and systolic blood pressure were measured twice on both arms with a digital blood pressure monitor[a]. Relative contraindications for the 6MWT were a resting heart rate over 120 beats/min, systolic blood pressure above 180 mmHg, and diastolic blood pressure above 100 mmHg. Spirometry was performed by one researcher (EB) using an electronic spirometer[b] to measure forced vital capacity (FVC), FEV_1, and forced expiratory ratio (FEV_1/FVC) according to the GOLD and ATS/ERS guidelines for spirometry.[29] The results in litres were converted to a percentage of the predicted values reported by Quanjer and colleagues (1993).[30] The severity of COPD was recorded by stage, defined by the GOLD criteria.[29]

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Intervention

Each patient performed the 6MWT four times. All 6MWTs were performed in accordance with the ATS guidelines,[1] except for the course length, which was adjusted as described above. Participants were asked to wear comfortable clothes and shoes and make use of their usual walking aids (e.g., walking stick or rollator) and oxygen supply (if applicable). All tests were performed between 8:00 am and 8:00 pm in a quiet indoor hallway with a flat straight floor with marks at one-metre intervals. Two traffic cones marked the turning points in the hallway. Participants were asked to walk at their own pace, while attempting to cover as much ground as possible within the allotted six minutes.[1] Participants were allowed to turn in whichever direction they preferred because research shows that turning direction seems to have no significant 2013). Every minute, researchers encouraged subjects to continue walking and informed them of the time elapsed, using standardised phrases.[1] Participants were allowed to stop and rest during the test, but were instructed to continue the test as soon as possible.

Outcome measures

Dyspnoea and fatigue were rated by the participant at rest (after sitting for at least 15 minutes, preceding the 6MWT) and directly after exercise, using a laminated modified Borg scale ranging from 0 (nothing at all) to 10 (very, very severe). At the same times, heart rate and oxygen saturation (SpO_2) were measured using a finger pulse oximeter[c]. All tests were supervised by the same researcher (EB). For each participant, the 6MWD was defined as the greater distance achieved on the two tests.[1] The better test was identified for both the 10 m course and the 30 m course.

Data analysis

The number of participants for the study was based on an estimated mean standard deviation of 103 metre,[31,8] an estimated correlation coefficient between 6MWD on a 30 m course versus on a 10 m course of r=0.7, and a predicted mean difference of 35 m, reasoning that a difference in 6MWD larger than the most conservative minimal important difference will justify new reference equations for a 10 m course.[31] Consequentially, the number of patients with COPD needed (with α=0.05 and 1-β=0.80) was 45 subjects. Data were presented as means (SD) for normally distributed variables and medians (5th to 95th percentile) for those with non-normal distribution. Data of all subjects (*n*=45) were checked for missing values, distribution (with the Kolmogorov-Smirnov test of normality), and outliers. Pearson correlation coefficients, Intraclass Correlation Coefficients (ICCconsistency), Standard Errors of Measurement (SEMconsistency) and Bland-Altman plots were produced for the two 6MWTs over the 10 m course, for the better 6MWD over the 10 m and 30 m course, and for the deviation between measured and predicted 6MWD. The difference between 6MWD over the 10 m and 30 m course was analysed using a one-tailed t-test, expecting a onesided effect in favour of the longer course length based on the existing literature.[2,26,27] Deviations of measured 6MWD compared to predicted distances ($\%_{pred}$), based on existing reference equations in similar-aged Caucasian populations and with similar submaximal effort (i.e., comparable to study population) were used to understand the impact of course length on the use of reference equations.[6,11,19,25] The range of differences in $\%_{pred}$ values for the 6MWT over a 10 m course were given as well as the average $\%_{pred}$ 6MWD to compare both course lengths. At a minimal statistical power of 80%, *p* values below 0.05 were considered to be significant.

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RESULTS

Flow of participants

Forty-five patients with COPD, aged 47 to 87 years, were recruited. All participants were familiar with the 6MWT at the time of recruitment. Three patients dropped out of the second 6MWT due to medical reasons (*n*=2, flu and hospitalisation) or private reason (*n*=1, holiday). The first 6MWD in these three patients was used as their best test, based on the remaining 42 participants having a nonsignificant learning effect over both courses of 0% (p>0.1) for the 10 m course and 2% (p>0.1) for 30 m course, high correlations between the first and second tests (r=0.98, p<0.001 for the 10 m course and r=0.92, p<0.001 for the 30 m course), and no substantial offset (i.e., 95% and 90%, respectively, of the difference scores were within the limits of agreement in Bland-Altman plots).

Patient characteristics are summarised in Tables 5.2 and 5.3. All variables were normally distributed, apart from physical activity score, change in heart rate, SpO_2, Borg dyspnoea and Borg fatigue, which were expected to be skewed, since this study population consists of older adults with COPD, disabled in their activity level.

Table 5.2 Characteristics of the participants.

Characteristic	Participants (*n*=45)
Sex, *n* male (%)	26 (58)
Age *(yr)*, mean (SD)	67 (9)
Height *(cm)*, mean (SD)	169 (8)
Weight *(kg)*, mean (SD)	81 (17)
BMI *(kg/m²)*, mean (SD)	28.4 (5.1)
FVC *(L)*, mean (SD)	3.03 (1.03)
(%pred), mean (SD)	92 (21)
FEV_1 *(L)*, mean (SD)	149 (0.54)
(%pred), mean (SD)	56 (19)
FEV1/FVC *(%)*, mean (SD)	49 (15)
GOLD Stage, *n* (%)	
I	6 (13)
II	21 (47)
III	12 (27)
IV	6 (13)
Smoking *(pack-yr)*, mean (SD)	33 (26)
Physical activity level mean (SD)	3.4 (2.3)
median (5th to 95th percentile)	4.0 (0.0 to 8.0)
Sufficient physical activity, n (%)	24 (53)
Systolic blood pressure *(mmHg)*, mean (SD)	134 (21)
Diastolic blood pressure *(mmHg)*, mean (SD)	76 (12)

Abbreviations: BMI = body mass index, FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second, GOLD the Global Initiative for Chronic Obstructive Lung Disease; GOLD stages: I: mild COPD, FEV_1/FVC 0.7, and FEV1 80% of predicted; II: moderate COPD, FEV_1/FVC 0.7, and 50% FEV_1 80% of predicted; III: severe COPD, FEV_1/FVC 0.7, and 30% FEV_1 50% of predicted; IV: very severe COPD, FEV_1/FVC 0.7, and FEV_1 30% of predicted or FEV_1 50% of predicted plus chronic respiratory failure.

Table 5.3 Mean (SD) and median (5th to 95th percentile) cardiorespiratory variables at baseline and changes during the 6MWT on the 10 m and 30 m courses.

Characteristic	Baseline[a]	Change during 6MWT[b]	
		10 m course	30 m course
Heart rate (beats/min)	82 (14)	25 (16)	25 (17)
	83 (58 to 107)	20 (3 to 55)	20 (5 to 64)
SpO_2 (%)	95 (2)	–6 (6)	–6 (5)
	96 (90 to 98)	–5 (–17 to 1)	–5 (–17 to 1)
Borg dyspnoea score (0–10)	2.4 (1.7)	2.4 (1.8)	2.2 (1.8)
	2.5 (0.2 to 5.5)	2.0 (0.0 to 6.0)	2.0 (0.2 to 6.4)
Borg fatigue score (0–10)	1.8 (1.8)	1.7 (1.5)	1.6 (1.4)
	1.8 (0.0 to 5.7)	1.5 (0.0 to 4.0)	1.5 (0.0 to 4.0)

[a]Baseline data for each participant was taken as the mean of the values before all four tests, [b]Change data for each participant was taken from the test in which the greater distance was covered. Abbreviation: SpO2 = transcutaneous oxygen saturation.

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6MWD over 10 m versus 30 m course length

The 6MWDs on the 10 m and 30 m courses were both normally distributed and there were no significant outliers. All participants achieved a shorter 6MWD on the 10 m course than on the 30 m course. The mean difference between the better 6MWD on the 10 m versus 30 m course was 49.5 m (SD 33.6; range 9–143; one-tailed t=–9.9, p<0.001). There was a high Pearson correlation between the better 6MWD on the 10 m and 30 m courses (r=0.96, p<0.01). Furthermore, a high ICCconsistency (0.86, 95% CI 0.76 to 0.92) was revealed between 6MWD on the 10 m and 30 m courses, without substantial offset (SEMconsistency=41.14 and 93% of the difference scores within the limits of agreement: –16.32 m to 115.30 m). Figure 5.1 shows the systematic lower performance on the 10 m course compared to the 30 m course, regardless of test performance.

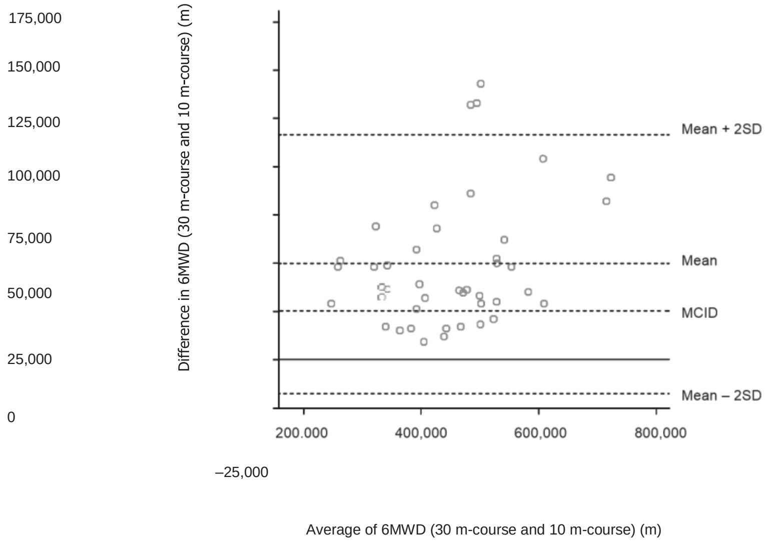

Figure 5.1 Bland-Altman plot showing systematic lower performance on the six-minute walk test over a 10 m-course in patients with COPD.
Abbreviations: 6MWD = six-minute walk distance, MCID = minimum clinically important difference.

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Impact of course length on use of reference equations

Established values to predict the 6MWD were compared with the measured 6MWDs of the participants. Every reference equation that included Caucasian subjects overestimated the measured 6MWDs of the participants, which was to be expected because prediction models are based on healthy subjects. The predicted values compared to the achieved 6MWDs on the 10 m course showed an overestimation ranging from 30% to 33%. However, the predicted 6MWD was based on four prediction models that are all established with walking courses exceeding 10 metres: Gibbons et al (2001)[11] used a 20 m course, Hill et al (2011)[19] used 30 m, Jenkins et al (2009)[25] used 45 m, and Troosters et al (1999)[6] used 50 m. Therefore all participants showed a higher average $\%_{pred}$ 6MWD on the 30 m course than on the 10 m course (mean difference = 8%, $p < 0.001$), with no substantial offset in the variation in the $\%_{pred}$ 6MWD over the range of values (ICCconsistency = 0.81, 95% CI 0.69 to 0.89; SEMconsistency = 6.56 and 93% of the difference scores within the limits of agreement: –2.89 to 18.67 $\%_{pred}$), as presented in Figure 5.2.

On average, patients walked 1.9 m less in the second test on the 10 m course compared with the first (p>0.1) and 9.5 m more in the second test on the 30 m course compared with the first (p>0.1). Regarding the test-retest reliability for the 6MWD on the 10 m course an ICCconsistency of 0.98 was found (95% CI 0.96 to 0.99 and 95% of the difference scores within the limits of agreement: –42.33 m to 41.56 m).

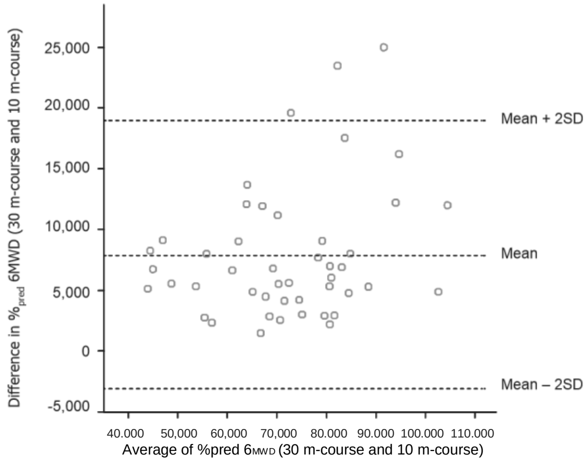

Figure 5.2 Bland-Altman plot showing the difference in $\%_{pred}$ 6MWD using a 10 m versus 30 m course. $\%_{pred}$ 6MWD is based on the average of predicted values from the studies of Gibbons et al (2001), Hill et al (2011), Jenkins et al (2009), and Troosters et al (1999).
Abbreviation: 6MWD = six-minute walk distance.

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DISCUSSION

The results of this study are of considerable importance in physiotherapy settings in which the 6MWT is conducted. Course length substantially influences the performance of patients with COPD in a 6MWT, and the results of the test conducted on a 10 m course versus a course of 30 metres or longer are not interchangeable. Consequently, using existing reference equations to established $\%_{pred}$ values for the 6MWT causes an overestimation of the functional capacity of a COPD patient.

The shorter 6MWD achieved on a 10 m course might be explained by the increased number of turns that are involved in a shorter walking course[2,26,27,]. Moreover, Najafi and colleagues (2009)[32] showed that older people may choose a higher gait speed strategy over a longer walk distance (> 20 m), but a slower gait speed strategy over a shorter walk distance (< 10 m). Finally, patient-specific altered gait mechanisms (e.g., limping, shuffling, shorter step length, and slower walk speed) may contribute to the difference in 6MWDs over the two course lengths.[33,34] Our findings contrasted with those of Sciurba and colleagues (2003)[8] who found no statistically significant effect of course length on 6MWD. However, this study compared different course lengths between different centres retrospectively. The order of the tests was not randomised (ie, each subject was measured on only one course length), only people with severe emphysema were included, and the test courses were all longer than 17 m.[8] The impact of the much shorter 10 m course might be the reason for the statistical significance of the difference. Not only is the difference of 49.5 m statistically significant, this value is also large enough to be of practical relevance. When the difference exceeds the minimum clinically important differences (MCID), concerns are warranted. Recent reported MCIDs for the 6MWD in patients with COPD are 35 m (95% CI 30 to 42) by Puhan and colleagues (2008)[31] and 25 m (95% CI 20 to 61) by Holland and colleagues (2010),[35] both on a 30 m course. Our study shows that the average difference in walk distance, singly depending on the length of the test course, exceeds the MCID (80% of the individual cases, as presented in Figure 5.1). The difference in the distance achieved between a 10 m and 30 m course of 49.5 m allows for the assumption that using a 50 m course compared to a 10 m course would increase this difference even further. A 6MWD obtained on a 10 m course in primary care can therefore not be compared to that obtained on a longer course, eg, a 30 m course at the hospital. For researchers conducting multicentre trials, standardisation of the corridor length across centres is essential. The general thresholds of an absolute 6MWD or change in 6MWD for predicting mortality from the 6MWT do not apply for the 6MWT on a 10 m course. A subsequent step in research should be the development of related 6MWT thresholds for predicting morbidity and mortality and a MCID for the 6MWT on a 10 m course.

It is of great importance for clinicians and researchers to carefully consider the choice of reference equations in clinical tests. The difference of 49.5 m we identified shows the importance of choosing reference models established in accordance with the chosen course length. Using existing models to predict the 6MWD on a 10 m course revealed a significant overestimation (with a range of 30–33% and an average of 8%$_{pred}$ lower compared to a 6MWT executed over 30 m). This overestimation results in a worse representation of a COPD patient's functional exercise capacity. Moreover, achieving a 6MWD of less than 82% of the predicted value can be considered abnormal (Troosters 1999),[6] which may influence the patient's treatment plan.

The test-retest reliability for the 6MWT based on the 10 m course in the fairly homogeneous study population of people with COPD in this study was very high (ICC=0.98), which is consistent with previous studies (ICC=0.93).[28] Future research is needed to study the validity and responsiveness for the 6MWT over a 10 m course. The order in which patients performed on the two test courses would not have affected the results of this study, due to the randomised double-crossover design and because, on average, patients walked about the same distances over the same course lengths. The non-significant learning effect between the two tests on each course may have been due to the fact that patients in this study were familiar with the 6MWT. The learning effect of 0% and 2% in this study cannot be compared to the results obtained by

firsttime performers. Although this study shows a very low learning effect, it still falls within the range 0% to 17% described by the American Thoracic Society.[1]
A limitation of this study is that the significant difference between 6MWDs on a 10 m course versus on a 30 m course was established for a small population of people with COPD. However, the demonstrated difference in walk distance of 49.5 m, and taking into account an alpha error level of 5%, reached statistical power of 89.9%. Considering the low prevalence of patients with COPD GOLD I in primary care practices, the distribution of people over the different GOLD stages in this study (Stage I 13%, Stage II 47%, Stage III 27%, Stage IV 13%) is an adequate reflection of the distribution of COPD disease severity in primary care based on airway obstruction in a cross-sectional population-based study (Stage I 29%, Stage II 48%, Stage III 17%, Stage IV 5%) (Steuten et al 2006).[36] The findings of this study are of particular relevance to practice in The Netherlands. However, there is clear relevance to all settings in which the 6MWT is conducted worldwide. The results of this study apply to individuals who walk 233 m or more on the 6MWT. In order to draw conclusions across different (patient) populations, Ng and colleagues showed a comparable significant impact of different course lengths (10 m versus 30 m) on 6MWD in patients with stroke (41 m) or healthy subjects (59 m) (Ng et al 2013, Ng et al 2011).[27,26] The finding that course length has a substantial impact on the performance, and thus on the use of reference equations, may serve for a variety of chronic diseases like COPD, heart failure, rheumatoid arthritis, and neuromuscular disease.
In conclusion, our randomised double-crossover study in 45 patients with COPD showed that course length (10 m versus 30 m) substantially influences the performance of patients in a 6MWT. The statistical and clinically important difference in 6MWD in patients with COPD, singly depending on the length of the walk course, highlights a practical problem. Existing reference equations cannot be applied to predict the walking distance in the frequently used 6MWT on a 10 m course for people with COPD, due to a substantial overestimation. Unique reference equations for the 6MWT on a 10 m course seem necessary.

Footnotes: [a] UA-767 Plus30, A&D Medical, Toshima Ku, Japan; [b] Spirobank and WinspiroPRO software, Gessate, Italy; [c] Onyx 9500, Nonin Medical Inc, Plymouth MN, USA.

ETHICS

The institutional ethics committee of Maastricht University/Hospital approved the use of the 6MWT in this study, embedded in a cohort-nested randomized controlled trial.

All participants received written and verbal information about the aim of the project and were required to give written informed consent prior to the screening.

SUPPORT

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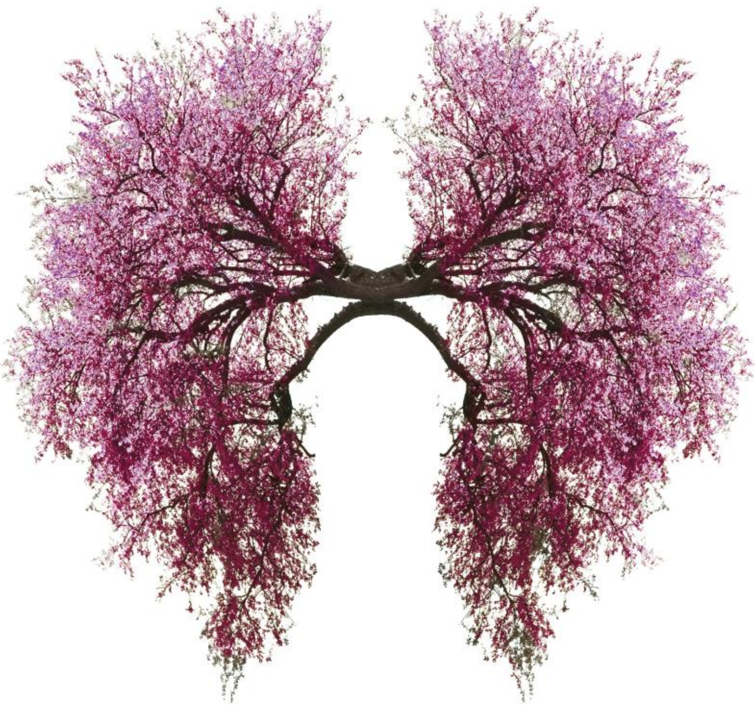
CHAPTER 6



The first reference equations for the six-minute walk distance over a 10 metre course

Emmylou Beekman, Ilse Mesters, Rik Gosselink, Mariska P.M. Klaassen, Erik J.M. Hendriks, Onno C.P. Van Schayck, Rob A. de Bie

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What determines which six-minute walk test is conventional?

Emmylou Beekman, Ilse Mesters, Rik Gosselink, Onno C.P. Van Schayck, Rob A. de Bie

Thorax 2015; 70(1): 86-87

ABSTRACT

Rationale

As primary care practice space is mostly limited to 10 m, the 6-minute walk test (6MWT) over a 10 m course is a frequently used alternative to evaluate patients' performance in COPD. Considering that course length significantly affects distance walked in 6 minutes (6MWD), this study aims to develop appropriate reference equations for the 10 m 6MWT.

Methods

181 healthy subjects, aged 40-90 years, performed two standardised 6MWTs over a straight 10 m course in a cross-sectional study.

Results

Average distance achieved was 578±108 m and differed between males and females ($p<0.001$). Resulting sex-specific reference equations from multiple regression analysis included age, body mass index and change in heart rate, explaining 62% of the variance in 6MWD for males and 71% for females.

Conclusion

The presented reference equations are the first to evaluate 6MWD over a 10 m course and expand the usefulness of the 6MWT.

THE FIRST REFERENCE EQUATIONS FOR THE SIX-MINUTE WALK DISTANCE OVER A 10 METRE COURSE

RATIONALE

The 6-minute walk test (6MWT) is used to evaluate functional exercise capacity in patients with COPD.[1] Reference equations for the 6MWTwere established over courses ranging from 20 to 50 m,[2] with 30 m being the recommended length by the American Thoracic Society (ATS).[1] However, space limitations in primary care force professionals to execute the 6MWT over a 10 m course. Until now, no matching reference equations were established while current studies revealed a significant impact of course length on 6-minute walk distance (6MWD) and risk of clinical interpretation errors.[2,3] We aimed to develop reference equations for the 10 m 6MWT.

METHODS

A total of 194 healthy Caucasian subjects were recruited. After health screening, 181 remained (Table 6.1). Subjects' characteristics are summarised in Table 6.2.

Table 6.1 Reasons for exclusion from the healthy study population (*n*=194), resulting from the screening.

Variable	*n* excluded
FVC and/or FEV_1 was <80% of predicted	4
A diagnosis of asthma and FVC and/or FEV_1 <80% of predicted	1
Non-controlled blood pressure (216/122 and 200/107 respectively)	2
Using anti-arrhythmic medication	2
Using long acting bronchodilator without a medical diagnosis	1
History of TIA with neurological impairment in one leg, influencing walking	1
speed History of myocardial infarction and heart surgery Having a pacemaker	1
	1

Abbreviations: FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second, TIA = transient ischemic attack.

The 6MWTs were performed in accordance with the ATS guidelines over a 10 m course.[1] Univariate Pearson correlation coefficients and hierarchical/ stepwise multiple regression analysis were used to evaluate variables explaining the variance in the 6MWD and to create a model predicting 6MWD. Included variables were sex, age, height, weight, body mass index, FVC, expiratory volume in one-second (FEV1), smoking pack-years, physical activity level, baseline heart rate (HR), change HR, baseline transcutaneous oxygen saturation (SpO_2), change SpO_2, baseline dyspnoea, change dyspnoea, baseline fatigue and change fatigue. A sex-specific lower limit of normal was calculated. Detailed information on methods is available in the published Supplement 6.1.

Table 6.2 Demographic and functional characteristics of study subjects.

Characteristics (*n*=181)	*n* (%) or mean±SD and	median (5^{th}-95^{th} percentile)
Sex (M)	62 (34)	
Age (years)	63.5±11.6	
40-49, sex (M)	25 (14), 6 (24)	
50-59, sex (M)	42 (23), 23 (55)	
60-69, sex (M)	60 (33), 17 (28)	
70-79, sex (M)	39 (22), 11 (28)	
80-90, sex (M)	15 (8), 5 (33)	
Height (cm)	168.2 ± 98.5	167.4 (153.4-185.9)
Weight (kg)	74.4 ± 12.7	72.5 (57.0-99.0)
BMI (kg/m^2)	26.2 ± 3.4	25.7 (21.6-32.7)
FVC (L)	3.9 ± 1.2	
FEV_1 (L)	2.9 ± 0.9	
Smoking (pack years)	7.4 ± 12.6	0.6 (0.0-33.0)
Physical activity^ level (0-8)	4.1 ± 2.0	4.0 (1.0-8.0)
sufficient	123 (68)	
Systolic blood pressure (mmHg)	140.2 ± 20.5	137.0 (113.1-176.0)
Diastolic blood pressure (mmHg)	79.8 ± 10.4	79.0 (66.0-99.8)
Baseline heart rate (bpm)	80.8 ± 12.0	80.0 (60.0-102.0)
Change* heart rate (bpm)	39.9 ± 20.8	35.0 (13.1-78.9)
Baseline SpO2 (%)	97.4 ± 1.3	98.0 (95.0-99.0)
Change* SpO2 (%)	-1.0 ± 2.6	-1.0 (-4.0-1.0)
Baseline Borg dyspnoea (0-10)	0.3 ± 0.6	0.0 (0.0-2.0)
Change* Borg dyspnoea (0-10)	1.3 ± 1.3	1.0 (0.0-3.5)
Baseline Borg fatigue (0-10)	0.5 ± 0.9	0.0 (0.0-3.0)
Change* Borg fatigue (0-10)	1.0 ± 1.2	1.0 (0.0-3.0)

Abbreviations: M = male, BMI = body mass index, FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second, SpO_2 = transcutaneous oxygen saturation.

^ Physical activity was measured by two questions assessing the frequency of 20 minutes vigorous and 30 minutes moderate intensity physical activity in a "usual" week resulting in a total score (0-8). A score of ≥4 is considered to represent sufficient physical activity (see reference 6 in published supplement 6.1). *Change scores are based on the better walk test over a 10m-course.

RESULTS

We found that 6MWD in male and female was respectively 625±120 m and 554±94 m, with a significant difference (p<0.0001). 6MWD was significantly independently correlated with age, height, body mass index (BMI), FVC, FEV1, smoking, physical activity and changes in HR, experienced dyspnoea and fatigue (Table 6.3).

Table 6.3 Univariate correlation coefficients (Pearson's *r*) between 6MWD and continuous subject variables.

Variable	6MWD (m)	*p*-value
Age (years)	-0.704	0.001
Height (cm)	0.378	0.001
Weight (kg)	0.074	0.320
BMI (kg/m^2)	-0.265	0.001
FVC (L)	0.614	0.001
FEV_1 (L)	0.641	0.001
Smoking (pack years)	-0.169	0.023
PA (level)	0.333	0.001
Baseline HR (bpm)	0.002	0.980
Change HR (bpm)	0.645	0.001
Baseline SpO_2 (%)	0.083	0.268
Change SpO_2 (%)	-0.007	0.924
Baseline Borg dyspnoea	-0.099	0.186
Change Borg dyspnoea	0.164	0.027
Baseline Borg fatigue	-0.333	0.655
Change Borg fatigue	0.152	0.041

Abbreviations: 6MWD = six-minute walk distance, BMI = body mass index, FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second, PA = Physical Activity, HR = heart rate; SpO2= transcutaneous oxygen saturation.

Based on a clear difference between the directions of the slopes for male versus female (Figure 6.1), sex-specific reference equations were calculated (Table 6.4).

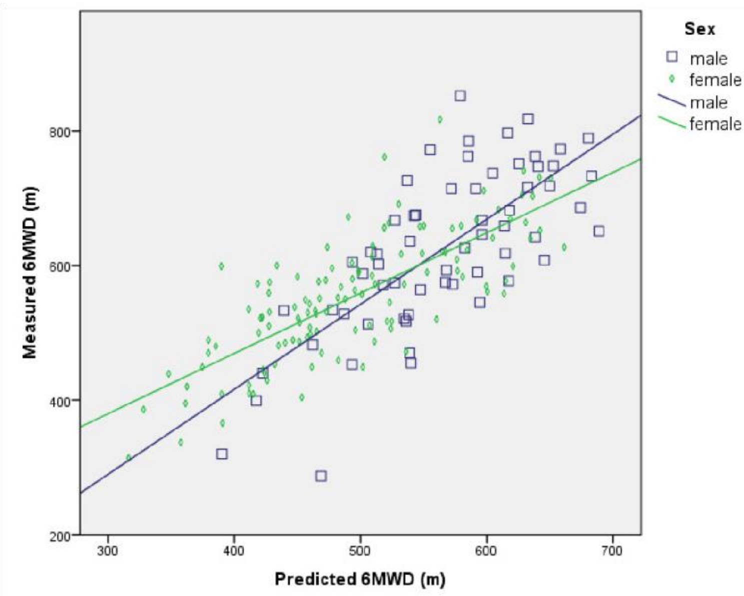

Figure 6.1 Comparison of measured and predicted 6MWD by the overall regression model (n=181), differentiated by sex. The difference between the directions of the slopes for male versus female was statistically significant (p<0.001).

The amount of variation in 6MWD that was accounted for by the basic and extended model was respectively 52% and 62% for male and 59% and 71% for female. Assumptions of multiple regression analysis were met, and the models appeared to be reliable. Additional information on statistical analyses is available in the published Supplement 6.1.

Table 6.4 Reference equations for 6MWD over a 10 m course.

Basic equation	
♂ 6MWD = 1266 − (7.80*age) − (5.92*BMI)	$r^2 = 0.52$
LLN = 6MWDpredicted − 163	$r^2 =$
♀ 6MWD = 1064 − (5.28*age) − (6.55*BMI)	0.59
LLN = 6MWDpredicted − 119	
Extended equation*	
♂ 6MWD = 1073 − (6.03*age) − (5.79*BMI) + (1.86*HRchange)	$r^2 = 0.62$
LLN = 6MWDpredicted − 146	
♀ 6MWD = 878 − (3.60*age) − (6.42*BMI) + (1.95*HRchange)	$r^2 = 0.71$
LLN = 6MWDpredicted − 101	

*The choice whether the extended model can be used should depend on the considerations of the healthcare provider.

Abbreviations: 6MWD = 6-minute walk distance in m, age in years, BMI = body mass index in $kg/m^{2,}$ HRchange = change in heart rate in beats per minute (heart rate measured directly after the test minus heart rate measured at rest before the test), LLN = lower limit of normal, r^2 = the coefficient of determination, the proportion of variability in a dataset that is accounted for by a statistical model.

6

DISCUSSION

Our data provide healthcare professionals with suitable reference equations for the 10 m 6MWT. The significant association of 6MWD with age, gender and either BMI or 'weight and height' corresponds with previous studies.[4] This is the first study to show a significant contribution of absolute HR values. However, HR is not always an adequate predictor for 6MWD due to lack of submaximal cardiac performance, other reasons for performance limitation, deviation of standardised HR measurement or use of β-adrenergic blocking agents. Although both models explained more variance than previous studies with Caucasian subjects (ranging from r^2=0.20 to 0.66),[2] other variables, such as psychological characteristics, may improve explained variance in 6MWD.[4] Elaboration on the discussion is available in the published Supplement 6.1.

We conclude that unique reference equations for the 6MWT are essential when professionals use a 10 m course. The presented equations solve a practical problem and apply to subjects in various healthcare settings.

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PUBLISHED SUPPLEMENT 6.1

METHODS

Study population

Healthy Caucasian subjects who volunteered to participate (n=194) in a cross-sectional study were recruited by the researchers (EB and IM) in southern and central regions of The Netherlands. The population in this study was recruited by means of snowball sampling: the researcher sampled an initial group of people relevant to the research question, and these sampled participants proposed other participants from among their colleagues (at Maastricht University), family members of colleagues, inhabitants of homes for the elderly and participants of exercise and cycle teams for people aged 50+, who had characteristics relevant to the research.[1] Subjects who were free from injury and who had no history of hospitalization or chronic disease, influencing their exercise capacity during the 6MWT, were asked to participate.

Both sedentary as well as (highly) active subjects, smokers, non-smokers and ex-smokers were asked to participate. All subjects performed the 6MWT for the first time in their lives. The number of subjects, included after screening, needed to achieve reliable prediction in this study is at least 170 (in this study the rule of thumb for regression models is considered to give the minimum number of subjects needed: *N = 10* number of independent factors = 10*17 = 170*).[2,3] All subjects were required to give written informed consent prior to the screening.

Any necessary ethics committee approval was secured for the study reported, checked with the institutional ethics committee (METC Atrium-Orbis-Zuyd, 13-N-91) and all healthy volunteers received written and verbal information about the aim of the project and were required to give written informed consent prior to the screening.

Screening

Prior to the 6MWT all participants were screened by one researcher (EB) during intake. Participants completed a health status questionnaire to ensure good health, defined as: having no walking problems and no history of lung cancer, any respiratory disease (apart from seasonal allergic rhinitis at other moments than the test moment), lung surgery, stroke, angina pectoris, myocardial infarction, any heart disease, heart surgery and not using the following medication: anti-arrhythmic, any long-acting or short-acting bronchodilator, inhaled corticosteroids, mucolytica or antibiotics. Heart rate, resting diastolic and systolic blood pressure were measured twice on both arms with a digital blood pressure monitor (A&D Medical, UA-767 Plus30). Subjects with hypertension were allowed to participate in the case of a stable and medically controlled condition and no blood pressure over 180/100 mmHg or resting heart rate over 120. All subjects who did not meet former criteria were excluded. Spirometry was performed by one researcher (EB) using a Spirobank and WinspiroPRO software to measure forced vital capacity (FVC), expiratory volume in one second (FEV_1) and Tiffeneau index (FEV_1/FVC) according to the GOLD and ATS/ERS guidelines for spirometry.[4] The results in litres were referred to the predicted litres as reported by Quanjer and colleagues.[5] If FVC or FEV_1 was <80% of the predicted value, subjects were excluded from further testing and referred to a pulmonologist.[4]

Sex, age, height and body weight were measured. Variables that were noted to record smoking history were number of cigarettes, years of smoking and current smoking. To score intensity and frequency of physical activity in daily life the Physical Activity Questionnaire was used, scoring 0-3 = insufficiently active, 4 ≥ = sufficiently active.[6,7]

Six-minute walk test

Participants were asked to wear comfortable clothes and shoes. All tests were performed between 08:00 and 20:00 hours in a quiet indoor hallway with a flat and straight floor with marks at one metre intervals. Subjects were instructed to walk up and down over a straight 10metre course. Two traffic cones marked the turning points at nine metre, allowing for a circular turn of one metre. To achieve familiarisation and to allow for the learning effect, the test was repeated after a rest period of at least 15 minutes.[8,9] Participants were asked to walk at their own pace, while attempting to cover as much ground as possible within the allotted six minutes.[10] Participants were allowed to turn in either direction, whatever they preferred, because research shows that turning direction seems to have no significant influence on the distance coverd.[11,12] Researchers encouraged subjects every minute to continue walking and informed them of the time elapsed, using standardised phrases.[10] Participants were allowed to stop and rest during the test, but were instructed to continue the test as soon as possible. Transcutaneous oxygen saturation (SpO_2), heart rate, dyspnoea and fatigue were assessed at rest (after sitting for at least 15 minutes, preceding the 6MWT) and directly after testing, with a finger pulse oximeter (Onyx 9500) and the modified Borg scale ranging from zero (nothing at all) to ten (very, very severe).[13] All tests were supervised by the same researcher (EB). 6MWD was defined as the greatest distance achieved from the two tests, i.e. the better test.[10]

Statistical analysis

Data were presented as means±SDs and medians (5^{th}-95^{th} percentiles). At a minimal statistical power of 80%, p-values below 0.05 were considered to be significant. Univariate correlation coefficients between 6MWD and continuous subject characteristics and between subject characteristics were calculated by Pearson single correlation coefficients. Variables that were significantly independently associated with the 6MWD (two-tailed, α=0.05) were entered into a hierarchical and stepwise (backward) multiple regression analysis to evaluate independent variables explaining the variance in the 6MWD and to create a model predicting 6MWD.[14] Change scores (change HR, change SpO_2, change Borg dyspnoea, change Borg fatigue) were determined as the score directly after the test minus the score at rest before the test (preceded by a resting period of minimal 15 minutes). Pack years, to equally determine lifetime tobacco exposure with one value, were calculated as: number of cigarettes per day / 20 cigarettes (one pack) * number of years smoking. One cigarette contains one gram tobacco, one pack pipe tobacco (of 50 grams) will therefore be substituted by 50 cigarettes and one cigar (of approximately 4 grams) by 4 cigarettes.[15] The habit that cigars and pipe tobacco are sometimes not inhaled is left out of consideration in these calculations. When a subject gave an estimate of the amount of cigarettes smoked, the highest value mentioned by the person was noted.

A sex-specific lower limit of normal (LLN) was calculated as the 5th percentile of the data. In the absence of predefined cut-offs for 6MWD on clinical grounds and the utilization of the 5th percentile in previous studies on 6MWD reference equations, the statistical delineation of normal is assumed to fall within 1.64 standard errors of the estimate.[16,17]

RESULTS

Additional statistical comments

Subjects' characteristics, summarised in Table 6.2, were comparable to healthy people (the majority was sufficiently physical active, had normal blood pressure and showed no substantial increase in dyspnoea and fatigue). Age was distributed normally, as well for the 181 participants as for male and female separately. The FVC and the 6MWD were distributed normally. All other variables were slightly skewed to the left. On average, subjects walked 578±108m on the better 6MWT. Walk distance varied 287 to 852m. Most subjects (86%) performed better on the second test, which was on average 30±33m or 6±6% better than the first test (p<00.1). The 6MWD in male was 625±120m in contrast to 554±94m in female, with a statistically significant difference of 70±16m (t=4.34, p<0.001).

In multiple regression analysis all significantly independently correlating variables were entered. Variables were added by hierarchical method and stepwise backward method combined, based on the substantive theoretical importance of these variables. The variables age, gender and either BMI or "weight and height" were added in their order of importance by means of blockwise entry, based on previous studies.[17] The remaining variables lung functions, smoking, physical activity, and changes in HR, experienced dyspnoea and fatigue were added stepwise backward to check their influence on 6MWD prediction in an explorative way. In the overall regression model (N=181) age alone explained 50% of the variance in 6MWD. Sex and BMI explained an additional 6.1% and 3.2%, respectively. Apart from these demographic and anthropometric factors that were retained in the model on a theoretical and statistical basis, three additional variables contributed significantly to the variance in 6MWD: change in heart rate (10.2%), physical activity (2.7%) and FEV_1 (2.3%).

Apart from change in heart rate, the additional variables were considered but not retained in the model due to lack of theoretical basis in combination with the small contribution to explained variance. Figure 6.1 shows a comparison of measured and predicted 6MWD determined by the following overall model (N=181): 6MWD (m) = 1,158.68 – (6.10*age) – (5.86*BMI) – (59.61*sex), where males = 0 and females = 1. A clear difference exists between the directions of the slopes for male versus female. Since the number of participants per sex-group is still sufficient (male: N=62, female: N=119), based on the variables that were retained in the model, sexspecific reference equations were calculated.

Residual statistics showed no cause for concern; no significant outliers and the sample appeared to conform to what was expected for a fairly accurate model (*highest standardised residual of 2.818<3, only 1% of the sample had a value greater than 2.5 and only 3% had a value greater than 2*).[14] No influential cases were identified according to Cook's distance (*highest value of Cook's distance of 0.271<1*). Although, with respect to the cut-off for the Mahalanobis distances[18] and the average leverage values (2* 0.022), one influential case seemed problematic. However, when running the regression analysis without the potential influential cases the differences between the *b*-coefficients in the regression equations were small enough not to exclude one of the cases from the final analysis (*all standardised DFBeta values <1*). Overall, the models appear to be fairly reliable without undue influence of any subset of cases.[14,18] None of the assumptions of multiple regression analysis was violated. Based on a correlation matrix, there was little chance for multicollinearity (*all r<0.69*), except for the correlation between FVC and FEV_1 (*r=0.933*). Therefore only one of the two variables was entered in the model based on a theoretical basis, yet was not retained in the final model. Furthermore, lung function variables were expressed in absolute numbers (litres) and not in percentages of predicted, because the calculation of predicted lung functions already incorporates sex, age and height. In accordance with the correlation matrix, the eigenvalues or the variance inflation factor showed no concern for biased regression (*largest VIF of 1.430<10 and smallest value of tolerance of 0.699 > 0.2*). The standardised residuals in the model were independent (*Durbin-Watson 2.5>1.602>1.5*) and random, normally distributed with a mean of zero (*D(181)=0.05, p>0.2*). Finally plots of standardised residuals against standardized

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predictive values seemed to justify the assumptions of linearity and homoscedasticity. Consequently, the models generalise very well, because the cross-validity of these models is very good, both in male (*adjusted* r^2*=0.521 versus observed* r^2*=0.537* for the basic model and *adjusted* r^2*=0.616 versus observed* r^2*=0.635* for the extended model) and in female (*adjusted* r^2*=0.579 versus observed* r^2*=0.586* for the basic model and *adjusted* r^2*=0.699 versus observed* r^2*=0.707* for the extended model).[14] For generalisability, the range of each factor in the study population should be taken into account (Table 6.2). For people with an extreme low or high BMI (5th and 95th percentiles: 21.6-32.7) or high age (>90 years), the outcome of the reference equation should be interpreted with caution.

In the multiple regression analysis, the variables age, gender and either BMI or "weight and height" were added by means of a hierarchical method, based on the substantive theoretical importance of these variables,[17,19] whereas the other variables were added exploratively by means of a stepwise backward method. When, in an additional analysis, all variables were added stepwise to create a complete explorative model, age, gender and BMI were still retained as most prominent variables. This indicates that the theoretical assumptions that were made in this study, regarding the importance of predictors, were in agreement with our dataset.

When adding "weight and height" to the basic model instead of BMI, only slight, but no statistically significant changes were noted ($r^2=0.540$, $F=22.70$, $p<0.001$ versus $r^2=0.537$, $F=34.17$, $p<0.001$ for male and $r^2=0.585$, $F=53.93$, $p<0.001$ versus $r^2=0.586$, $F=81.99$, $p<0.001$ for female), meaning either can be used. Here the single variable BMI was chosen.

ELABORATION ON DISCUSSION ITEMS

The significant contribution of HR was in line with three previous studies.[20-22] However, because these studies used a percentage of age-predicted maximal heart rate (HR_{max}%predicted), there may be double correction for the variable age. Therefore, our study included only absolute values.

Some considerations need to be made regarding the use of HRchange as a predictor in the reference equation. Firstly, change in heart rate does not only depend on age ($r=-0.503$, $p<0.001$) but also on the participant's motivation to perform well on the test. However, all participants confirmed that they had given everything they could during the tests and all participants were equally motivated by the researcher according to the ATS-standard.[10] In addition, the maximum heart rate achieved in the healthy subjects in this study was on average 77%±14% of predicted HR_{max} (220-age) during the better test of two. This confirms that the 6MWT was actually received as a submaximal test. These results show similarity to the percentage of age-predicted HR_{max} reported by Troosters and colleagues (77% during the better test of two).[23] They are somewhat lower than the percentages by Camarri and colleagues (87% during the better test of three)[24] and by Kervio and colleagues (86% during the better test of two),[25] but higher than the percentage by Enright and colleague (<65% during the first and only test).[17]

Secondly, the explained variance of 6MWD in the extended equations (including HRchange) should be interpreted with some caution when symptoms, such as dyspnoea in patients with COPD, fatigue in peripheral muscles or musculoskeletal pain, limit test performance.

Thirdly, because a change score of heart rate (the difference between HR directly after the test minus the score at rest before the test) was used in the equations, standardisation of the measurement should be maintained. Here, baseline HR measurement was preceded by a resting period of minimal 15 minutes (sitting) and subjects drank water only, no coffee or tea, within two hours before the test.

Fourthly, the extended equations should be used with some caution in patients with chronic illness using medication that affects the relation between external physical load and HR, like beta-adrenergic blocking agents. In such cases, the equation including HRchange will be unreliable. Medication for anxiety disorders or beta-adrenergic bronchodilators are more likely to influence resting HR than HRchange, but in the case of chronic use of beta-adrenergic bronchodilators that can cause ventricular tachycardia one should better avoid the extended equation.

All subjects using beta-adrenergic blocking agents or bronchodilators were excluded from this study. Those subjects who had stable hypertension, used diuretic, anticoagulant or antihypertensive medication and had no blood pressure over 180/100 mmHg. Consequently, these participants showed a decreased baseline HR and end HR. However, HRchange corrected for the absolute increased values and was not significantly different from HRchange in the subset of subjects without hypertension and/or related medication (*$t=1.484$, $p=0.139$*). These findings correspond with a study by Kervio and colleagues where HR at the start and at the end of the 6MWT also was decreased in patients with chronic heart failure under optimal drug treatment compared to healthy subjects, whereas HRchange showed no difference between the groups.[26]

The small significant association of 6MWD with absolute resting pulmonary functions was in agreement with a recent study in patients with COPD.(27) FEV_1 was not retained in the final model because it's predictive value for 6MWD (2.3% explained variance) lacks evidence in the literature. Other studies suggested that part of the unexplained variance in 6MWD could be contributed to patient characteristics like physical activity in daily life or the effects of smoking.[20,24] The present study added these variables in an explorative way in regression analysis. Although a negative association between pack years and 6MWD was hypothesised, no statistically significant association was supported by the data. This finding is consistent with other studies that failed to show an association between carboxyhaemoglobin (COHb) levels or pack years and 6MWD,[23,24] probably because the participants had lung functions within the normal range (FVC ≥80% and FEV_1 ≥80% of predicted). Physical activity was a significant predictor of 6MWD, but was not retained in the final model because it explained only 2.7% of the variance in 6MWD. Other studies support the lack of influence of self-reported daily physical activity.[8,20,23,24]

Not all predictors in the equation were normally distributed (BMI and HRchange). The most important assumption of multiple regression analysis is that the residuals in the model are random, normally distributed variables with a mean of zero. This assumption was met in the analysis.[14]

The expectation that the predicted 6MWD in this study is lower than the predicted 6MWD from reference equations in other studies, using longer walking courses, was confirmed. For example a woman 70 years of age, 65kg, 168cm, HRchange of 30 bmp, a HR_{max} of 116 bpm and a HR_{max}%predicted of 77%, has a predicted 6MWD of 544 m (according to the basic model in Table 6.4). As expected, the predicted walk distances increased when calculated with the prediction models by Gibbons and colleagues (+41m), Hill and colleagues (+42m), Troosters and colleagues (+48m) and Jenkins and colleagues (+93m).[8,22,23,28] But, there was a decrease when compared to the prediction models by Casanova and colleagues (-249 m) and Enright and colleague (-76m), which might be explained by race difference or a reduced maximum heart rate achieved in the study subjects.[17,20] The decrease compared to the model by Chetta and colleagues (-51m) can probably be explained by the much younger subjects included in that study (20-50 yr) compared to this study (40-90yr).[29]

This study had some limitations. Firstly, participants were not a pure random sample from the population of adults. The non-probability sampling technique to recruit healthy study subjects was necessary to locate potential subjects, because especially older people without any heart or lung complaints and no walking disabilities are a relatively small subgroup of Western populations. However, the subjects represented all age groups with age as a normally distributed factor, balanced by sex. Geographic variations in normal 6MWD appear to exist. Although, the skewed distribution of sex (66% female) represents the current male-female ratio in elderly in western countries, gender-specific reference-equations were provided.[30,31] Secondly, about 45% of the variance in 6MWD remained unexplained by the basic model and 34% remained unexplained by the extended model. Other potential variables not included in this study may improve the variance in 6MWD. For example mood, attitude, motivation and psychological characteristics, as these also seem to affect 6MWD in older people.[32,33]

This study aimed for a practical solution to provide health care providers with a reference equation for the 6MWT over a 10m-course that is simple, efficient and easy to implement in clinical practice. As it stands, both models in this study explain more variance than most previous studies with Caucasian subjects (ranging from $r^2=0.20$ *to* *0.66*[8,17,20,22,23,28,29,32]) and include all the factors that have shown a strong and independent association with the 6MWD.

Since the majority of patients with cardiopulmonary pathologies and other chronic diseases are over 40 years of age, the prediction models may be applicable to a wide range of patients with diseases like COPD, heart failure, rheumatoid arthritis and neuromuscular disease and is generalisable to different countries.
Finally, urgency of reference equations for the 6MWT over a 10m-course does not only represent the Dutch situation, as it also applies to other countries such as Germany, England, the United States of America, Australia and Scandinavian countries.[34,35]

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THE SIX-MIN WALK TEST IN PATIENTS WITH COPD: WALK THIS WAY!

Sally J Singh, Martijn A Spruit, Thierry Troosters, Anne E Holland
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As the co-chairs of the joint American Thoracic Society/European Thoracic Society (ATS/ERS) task force on field exercise testing we noted with interest the work by Beekman et al.,[1] who describe reference values for a 6-min walk test (6MWT) performed around a 10 m course. These authors have previously shown that walk distances on this track provoke a significantly shorter distance than on the course consistently recommended in guidelines in patients with COPD.[2] This protocol deviation does not represent a conventional 6MWT,[3] and we suggest should be renamed to avoid confusion. Importantly, it remains unclear whether other important 'benchmark values' such as the minimal important difference (MID) and the distance below which survival is affected can simply be transposed to the 10 m-6MW. We appreciate that space is an important constraint in many clinical settings, including primary care environments, however we believe there are robust tests of walking performance that are conducted over a course shorter than 30 m, such as the incremental shuttle walking test,[4–6] and the 4 m gait.[7–10] It is currently unclear what this variant adds to this existing repertoire of field based exercise tests.

While we appreciate the test is conducted within 6 min, it does not accurately reflect current guidance on standard performance of the 6MWT in terms of track length. We would encourage researchers and clinicians to conduct the 6MWT as indicated in international guidelines.[3] For clarity, we would propose to label this test as 10 m-6MW or comparable alternative. In addition we want to alert readers to the fact that for this version of the test little is known about the validity, reliability, responsiveness and its place in an endpoint model of outcomes.

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WHAT DETERMINES WHICH SIX-MIN WALK TEST IS CONVENTIONAL?

We thank the co-chairs of the joint American Thoracic Society (ATS) and the European Respiratory Society (ERS) task force for their comments on our paper and interest in our article on reference values for the 6-min walk test (6MWT) performed over a 10m course (Box 6.1). In their correspondence, the shorter course length is considered as one specific protocol deviation from the ATS statement[1] that does not represent a conventional 6MWT. What is the 'conventional' 6MWT? Fourteen years ago, the ATS guidelines were published with the advice to test on a 30m course. However, at that time some studies used other course lengths, as was mentioned in the statement.[1] Since then, more studies[2–4] and healthcare providers have used a shorter course length due to space limitations. Moreover, 14 reference equations have been established for the 6MWT since 2002, of which 6 are for course lengths other than 30 m, ranging from 10 m to 45 m.[5,6] Obviously, it is incorrect to only rename the 6MWTover a 10 m course as 10 m 6MWT (as the writers purpose). In that case, we suggest to rename all variants (20 m 6MWT, 45 m 6MWT, 50 m 6MWT) and to refer to specific reference values obtained at similar course length. We do militate for a clear methodological description of the 6MWT, including course length.

Other tests, such as the incremental shuttle walk or the 4 m gait serve different goals then the 6MWT,[7,8] whereas the 6MWT is a very practical comparison with walking in everyday life in contrast with the incremental shuttle walk (a non-self-paced test).[7] The 6MWT is a sensitive indicator of clinical change in most cardiopulmonary conditions, especially in COPD where it demonstrates functional responses with improvement of the 6-min walk distance (6MWD).[9,10] The other tests amplify the test battery but cannot fully replace the 6MWT as a functional capacity test.[8] The perceived need for the 10 m reference equations in everyday practice was confirmed by the many requests for the norm values we received after the article was published.

The test-retest reliability for the 6MWD over 10 m has an intraclass correlation coefficient (ICC) consistency of 0.98 (95% CI 0.96 to 0.99 and 95% of the difference scores within the limits of agreement: −42.33 to 41.56 m).[5] The number of subjects needed to achieve reliable prediction models were used and the models appeared to be reliable without undue influence of any subset of cases.[6] The test-retest reliability in patients with COPD was very high (ICC=0.98) and consistent with previous studies.[5] As was mentioned in our previous article, future research is needed to study the validity and responsiveness of the 6MWT over a 10 m course.[5]

Whether absolute 'benchmark values', established in research using 30 m or larger courses, are suitable for a test conducted over 10 m is indeed not clear yet, neither is it for a test over 50 m (on which reference equations were conducted by Troosters et al.[11]), and should be studied. Relative benchmark values, such as achieving a 6MWT distance of less than 82% of the predicted value considering abnormal,[11] still apply.

In accordance with Singh et al, we encourage researchers and clinicians to use published reference equations for the 6MWT related to the length of the test course.[6] Moreover, an update of the ATS guidelines is timely. New literature was published since 2002 and there is a need for adaptations of functional exercise tests in different clinical settings, especially in primary care.

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