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## The 2- and 6-Minute Walk Tests in Neuromuscular Diseases: Effect of Heart Rate Correction on the Learning Effect

Kirsten Lykke Knak<sup>#</sup>, Linda Kahr Andersen<sup>#</sup>, Nanna Witting and John Vissing

Department of Neurology, University of Copenhagen, Denmark

<sup>#</sup>These authors contributed equally to this work.

\*Corresponding author: Kirsten Lykke Knak, Department of Neurology, University of Copenhagen, Copenhagen Neuromuscular Center, Copenhagen, Denmark, Tel: +45-35458976; E-mail: [kirsten.lykke.knak@regionh.dk](mailto:kirsten.lykke.knak@regionh.dk)

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### Abstract

**Objective:** The 2- and 6-minute walk tests are common measures for evaluating walking ability, but reliability is weakened by a well-documented learning effect. Since heart rate is related to workload, any change in walking distance, which is unrelated to change in clinical function, should be reflected in a change in heart rate during walking. Therefore, the aim of the present study was to investigate test-retest reliability of the 2- and 6-minute walk tests with and without heart rate correction.

**Methods:** Ninety-three adult patients (mean age of 53 years, range; 22-83 years) with 12 different neuromuscular diseases (myotonic dystrophy type 1, limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy type 1, Charcot-Marie-Tooth disease, mitochondrial myopathy, Becker muscular dystrophy, spinobulbar muscular atrophy, sporadic inclusion body myositis, spinal muscular atrophy, myotonia congenita Thomsen disease, congenital myopathy, polymyositis) were recruited in the study. One 2- and 6-minute walk test was performed on two occasions, 1-2 weeks apart. Heart rate was monitored by a pulse-watch.

**Results:** The distance walked increased significantly with repeated 2- and 6-minute walk tests (2-minute walk test increased by  $4 \pm 9$  m and 6-minute walk test by  $11 \pm 26$  m,  $p < 0.001$ ). Heart rate correction eliminated the learning effect in the 6-minute walk test ( $+0.01$  m/heartbeat,  $p = 0.84$ ), but not in the 2-minute walk test ( $+0.03$  m/heartbeat,  $p = 0.018$ ). The same pattern of heart rate-correction in the 6-minute walk test was observed in all subgroup diagnoses. There was no difference in the learning effect between disease severities.

**Conclusion:** Both the 2- and 6-minute walk tests are associated with a learning effect. The learning effect is eliminated when correcting for heart rate in the 6-minute walk test, but not in the 2-minute walk test. The results suggest using a heart rate corrected 6-minute walk test to weed out day-to-day variations that are not due to a real change in the patient's clinical condition.

**Keywords:** Walk test; Neuromuscular diseases; Reproducibility of results; Psychometrics

### Introduction

The 2-minute walk test (2MWT) and 6-minute walk test (6MWT) are submaximal exercise tests that are easy to administer and require no expensive equipment [1]. Both tests are used in the clinic and in clinical trials for evaluating walking ability in patients with neuromuscular diseases (NMDs). The 6MWT is by many considered the gold standard to assess walking capability. However, variability due to a learning effect, motivation, fatigue and other day-to-day variations is well documented in the literature in patients with NMDs and non-NMDs in the 6MWT [1-4] and in non-NMDs in the 2MWT [5-9]. A learning effect is a better performance at retest, which is not due to improvement of the clinical condition, but instead a result of familiarization. A pilot study in 16 patients with neuromuscular diseases indicated that the variability of the 6MWT can be eliminated by correcting for heart rate (HR) during the test [2]. The rationale for eliminating variation in walking distance in the walk tests that is not due to a real change in the patient's clinical condition, by HR-

correction is that HR is directly related to the level of physical exertion [10]. So, any change in walking distance, which is not related to changes in the physical condition of the test subject, should be paralleled by changes in HR as an indicator of the level of physical effort.

This study investigated test-retest reliability of the 2- and 6MWTs with and without HR-correction in patients with NMDs.

### Methods

#### Subjects

Ninety-three adult patients (mean age of 53 years, range; 22-83 years) with neuromuscular diseases were recruited from Copenhagen Neuromuscular Center, Rigshospitalet. Inclusion criteria were biopsy or genetically confirmed neuromuscular disease, age  $\geq 18$  years and ability to walk more than 60 meters in the 6MWT to avoid large variations in performance related to near loss of ambulation. Exclusion criteria were heart arrhythmias, use of drugs affecting heart rate and other medical conditions, which could significantly impact on walking

ability, such as arthritis, generalized pain and some diseases in the central nervous system.

**Procedures**

The patients performed one 2MWT and one 6MWT separated by 30 minutes in a block randomized order. The 2- and 6MWTs were repeated after 1-2 weeks with the same procedure. In the 6MWT, a patient walks as far as possible in 6 minutes with standard encouragement by walking back and forth on a 30-meter walk lane marked by cones. The same applies for the 2MWT. The 6MWT was performed according to the American Thoracic Society (ATS) guideline [11], and the 2MWT was comparable to the ATS guideline regarding equipment and test lane, but the instruction and encouragement were modified to the shorter duration of the 2MWT. The patients' heart rate was monitored during the walking tests with a Suunto Quest pulse-watch, and the time was recorded for each 30 meters. To avoid confounding factors for interpretation, the patients were asked to refrain from ingesting caffeine and performing strenuous exercises from the evening before the test days. Testing was performed in quiet surroundings and at the same time of the day to minimize intraday variability. It was the same investigator at test and retest to avoid inter-rater variability. Data from the walking distance in these patients has been presented in previous studies [12,13], but Andersen et al. [12] investigated the validity of the 2MWT compared to the 6MWT, and Knak et al. [13] investigated the absolute- and relative reliability of the 2- and 6MWTs. In contrast, the present paper targets a different aspect of reliability by investigating if the variability of 2- and 6MWTs can be eliminated by heart rate correction. At retest, the

patients and investigators were not allowed to check the results from the first test day to avoid any influence on motivation. To calculate heart rate correction in the 2- and 6MWTs, the following formula was used:

$$\text{Heart rate correction (meter walked/heart beat)} = \frac{\text{walking distance (m)}}{\text{average heart rate}}$$

The walking distance was the total distance walked in the walk test. The average heart rate was of the total duration of the walk test.

The study is approved by the Regional Committee on Health Research Ethics in Denmark (H-4-2014-FSP). Informed consent was obtained from all patients.

**Statistical analysis**

Results are presented as mean ± 2 standard deviations of the mean. Correlation between walked distance and average HR was assessed by Pearson product-moment correlation coefficient (r). Reliability was assessed by a two-sided Student's paired t-test to check for systematic differences between tests. Statistical significance was defined by p ≤ 0.05. For HR-correction the total walked distance was divided with the average heart rate during the test.

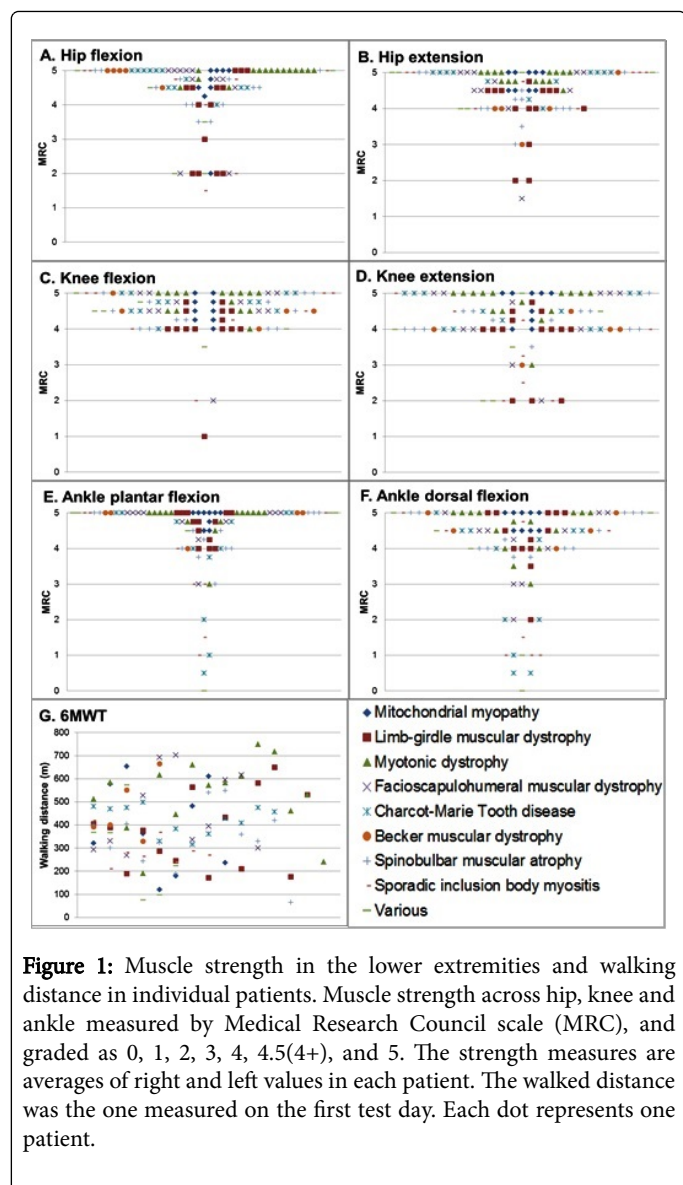
**Results**

Characteristics of patients are shown in Table 1 and Figure 1. At the 2MWT retest, 60 patients walked longer, 27 walked shorter, and six walked the same distance.

	Sex (f/m)	Age	Height (m)	Weight (kg)	BMI	MRC	MRC
						Ankle (d/p)	Hip (f/e)
DM1 (15)	4/11	44 ± 15	1.74 ± 0.12	70.5 ± 16.5	23 ± 3.5	4.5 ± 0.6/4.8 ± 0.5	4.9 ± 0.0/4.9 ± 0.2
LGMD (14)	5/9	59 ± 12	1.74 ± 0.09	83.8 ± 15.9	27.5 ± 4.5	4.3 ± 0.9/4.6 ± 0.4	3.7 ± 1.2/3.9 ± 0.9
FSHD1 (11)	6/5	49 ± 18	1.74 ± 0.07	70.4 ± 12.3	23.5 ± 4.5	4.1 ± 1/4.7 ± 0.6	4.3 ± 1.2/4.4 ± 1.0
CMT (12)	5/7	54 ± 16	1.71 ± 0.10	80.5 ± 20.8	27.6 ± 6.2	3.1 ± 1.8/3.7 ± 1.6	4.7 ± 0.3/4.8 ± 0.3
MM (9)	5/4	48 ± 15	1.67 ± 0.14	68.3 ± 18.1	25 ± 8.4	4.8 ± 0.3/4.9 ± 0.2	4.4 ± 1/4.8 ± 0.3
BMD (5)	0/5	35 ± 7	1.79 ± 0.05	87.8 ± 14.6	27.5 ± 5.4	4.6 ± 0.4/4.8 ± 0.4	4.9 ± 0.2/4 ± 0.7
SBMA (13)	0/13	61 ± 10	1.78 ± 0.06	82.3 ± 10.3	25.9 ± 3.1	4.4 ± 0.5/4.4 ± 0.6	4.4 ± 0.5/4.2 ± 0.6
IBM (8)	5/3	76 ± 4	1.68 ± 0.10	63.4 ± 11.4	22.4 ± 2.7	2.9 ± 1.9/3.4 ± 1.6	4 ± 1.4/4.7 ± 0.5
Various (6)	2/4	48 ± 21	1.81 ± 0.10	80.9 ± 8.7	24.8 ± 4	3.3 ± 2.2/4.1 ± 2.0	3.7 ± 1.4/4.7 ± 0.5
All (93)	32/61	53 ± 17	1.74 ± 0.10	76.2 ± 16.3	25.2 ± 5	4 ± 1.6/4.4 ± 1.1	4.4 ± 1/4.5 ± 0.7

**Table 1:** Patient characteristics. Values are mean ± 2 standard deviations. DM1: Myotonic Dystrophy type 1; LGMD: Limb-Girdle Muscular Dystrophy; FSHD1: Facioscapulohumeral Muscular Dystrophy type 1; CMT: Charcot-Marie-Tooth disease/Hereditary Motor and Sensory Neuropathy; MM: Mitochondrial Myopathy; BMD: Becker Muscular Dystrophy; SBMA: Spinobulbar Muscular Atrophy/Kennedy Disease; IBM: Sporadic Inclusion Body Myositis; Various: Spinal Muscular Atrophy (3), myotonia congenita (Thomsen disease) (1), congenital myopathy (1), polymyositis (1). Gender: f=female, m=male. BMI: Body Mass Index (BMI: Bodyweight in kg/height in m<sup>2</sup>). MRC: Medical Research Council scale (graded as 0, 1, 2, 3, 4, 4.5(4+), and 5), d=dorsal flexion, p=plantar flexion, f=flexion, e=extension. The strength measures are averages of right and left values in each patient.

Similarly in the 6MWT, 67 patients walked longer at retest, 24 walked shorter, and two walked the same distance.



**Figure 1:** Muscle strength in the lower extremities and walking distance in individual patients. Muscle strength across hip, knee and ankle measured by Medical Research Council scale (MRC), and graded as 0, 1, 2, 3, 4, 4.5(4+), and 5. The strength measures are averages of right and left values in each patient. The walked distance was the one measured on the first test day. Each dot represents one patient.

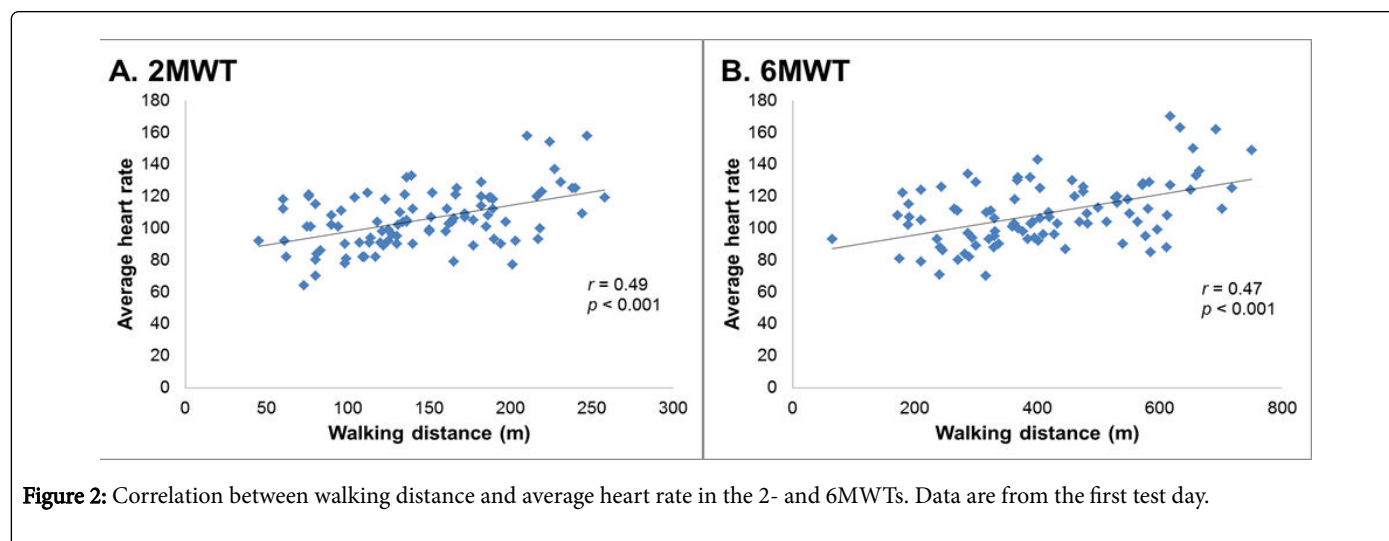
Twenty-eight patients used assistive devices. The total walked distance in the 2- and 6MWTs correlated with average HR during the walk tests ( $r=0.47$  and  $r=0.49$  respectively,  $p<0.001$ ) (Figure 2). The mean walked distance in the 6MWT increased from the first test day to the second test day by  $11 \pm 26$  m (2.7%) from 412 to 423 m ( $p<0.001$ ). When correcting for HR, the learning effect was abolished ( $3.79$  vs.  $3.80$  m/heartbeat,  $p=0.84$ ) (Figure 3). The mean walked distance in the 2MWT increased by  $4 \pm 9$  m (2.9%) from 145 to 149 m ( $p<0.001$ ). HR-correction did not abolish the learning effect ( $1.38$  vs.  $1.41$  m/heartbeat,  $p=0.018$ ) (Figure 3). The same pattern of HR-correction in the 6MWT was observed in all subgroup diagnoses.

There was no difference in the learning effect between disease severities (difference in walking distance from the first test day to the second test day in patients who walked  $<250$  m compared to those who walked  $>350$  m in the first 6MWT: 6MWT  $p=0.959$ , 2MWT  $p=0.759$ ).

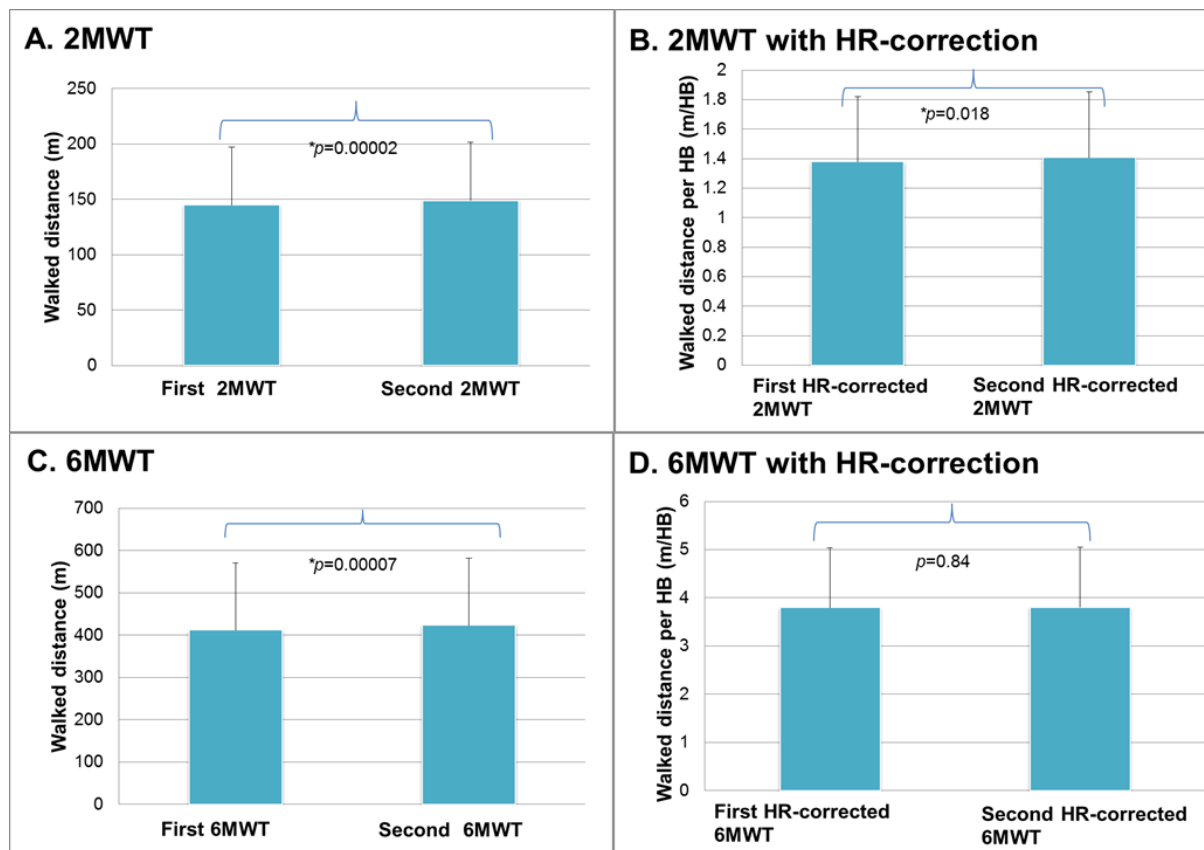
## Discussion

The present study shows that correcting for average HR during walking can rectify variations in the 6MWT. This is so, because HR is directly related to the level of physical exertion [10]. Thus, increments in walking distance, which are unrelated to clinical improvements, are paralleled by increases in HR. Similarly, reductions in walking distance, which are unrelated to clinical deteriorations, are paralleled by decreases in HR. Thus, the HR-corrected 6MWT is a more reproducible measure than the standard 6MWT in patients with NMDs. This finding has important implications for defining a robust endpoint for clinical follow-up and outcome measure in clinical trials. It is not surprising that HR-correction did not alter the learning effect in the 2MWT, as HR during this short test does not reach steady state.

The notion that variations in the 6MWT, which are unrelated to changes in the patient's disease status, can be resurrected by correcting for HR has previously been suggested in neuromuscular diseases [2]. However, this pilot trial [2] was weakened by a small sample of only 16 patients with five different neuromuscular diseases and by only representing the mildly affected patients. In contrast, the present study is strengthened by: (i) The large cohort studied (ii) The HR-correction finding across all disease severities and subgroup diagnoses and (iii) 5-15 patients in most of the NMD groups.



**Figure 2:** Correlation between walking distance and average heart rate in the 2- and 6MWTs. Data are from the first test day.



**Figure 3:** Walking distance for the 2- and 6MWTs. The left column is the walking distance without heart rate correction and the right column is the walking distance with heart rate correction for the 2- and 6MWTs.

The correlation between average HR and total walking distance ( $r=0.49$  in the 6MWT and  $r=0.47$  in the 2MWT,  $p<0.001$ ) was lower than the significant  $r=0.73$  reported in a pilot trial [2]. Prahm et al. [2] suggested that the lack of a stronger correlation might be due to non-compliance of refraining from tobacco and caffeine. However, even when patients who did not refrain from caffeine, were excluded, the fair relationship was maintained in the present study ( $r=0.46$  in the 6- and 2MWTs,  $p<0.001$ ). Though, self-reporting might be confounded by social-desirability bias. The difference in the magnitude of the correlation coefficients between Prahm et al. [2] and the present study might be due to different samples regarding sample size, specific neuromuscular diseases, mix of patients and healthy controls and group heterogeneity.

The present study showed a learning effect in both the 2- and 6MWTs when the tests were repeated after 1-2 weeks. The distance increased by 4 m in the 2MWT, which is comparable to studies in participants with non-NMDs [5-9], but a learning effect in the 2MWT has never been investigated before in patients with NMDs. The increase of 11 m in the 6MWT from test to retest is a little lower than the 17-24 m reported in other NMD-studies [4-15]. The difference in walking variability across studies might be due to different sample sizes, neuromuscular diseases, disease severity and methods. Although the walking distance increased significantly, several patients walked shorter at retest, which is consistent with findings from a study of Duchenne muscular dystrophy [14,15]. This reflects that variability

among repeated tests is not only caused by a learning effect, but also unpredictable random effects such as motivation, fatigue, and other day-to-day variations. This study indicates that both upward and downward variations in walked distance among 6MWTs can be corrected by heart rate. The learning effect in the 6MWT can last for several months [1].

Previous studies have recommended to use the best of 2-3 6MWTs to eliminate the learning effect [1,4]. However, multiple tests are not always feasible to perform, and are time-consuming and fatiguing for patients. Therefore, the HR-corrected 6MWT is an alternative to the standard 6MWT.

HR-corrected 6MWT is useful in patients without cardiac arrhythmias who do not take drugs affecting the HR. It is primarily suitable in clinical trials with a drug intervention. It is not suitable if the intervention is physical training, since increased fitness by itself changes heart rate responses to exercise. Patients should also refrain from caffeine intake 12 hours before testing to avoid influence on HR responses. When comparing two walk tests, retests should optimally be performed within one year as maximal heart rate decreases by one beat per minute every year of life after age 25.

The present study was only limited by few protocol violations, such as not refraining from caffeine or physical exhausting activities close to the time of testing. However, patients with these minor protocol

violations showed similar results compared to other patients. Therefore, the patients were not excluded from the study.

This study shows that a learning effect is also present in the 2MWT in patients with NMDs, which is known, and also shown in this study, for the 6MWT. The learning effect is eliminated when correcting for HR in the 6MWT, but not surprisingly, this was not the case in the 2MWT, and since a steady-state heart rate response is not reached in this short time. The results suggest using a HR-corrected 6MWT to weed out day-to-day variations that are not associated with changes in the patient's clinical condition.

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